CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214429Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 17, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214429
Product Name and Strength:	Fexinidazole Tablets, 600 mg
Applicant/Sponsor Name:	Drugs for Neglected Diseases initiative (DNDi)
OSE RCM #:	2021-1031
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Valerie Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

On May 18, 2021, DNDi submitted their Class 1 Resubmission to provide their response to the deficiencies included in the Agency's Complete Response Letter (CRL), dated November 12, 2020.[a] Thus, the Division of Anti-Infectives (DAI) requested that we review the proposed prescribing information (PI), container labels (blistercards), and carton labeling (wallet) for Fexinidazole (Appendix A) to determine if they are acceptable from a medication error perspective.

2 BACKGROUND/REGULATORY HISTORY

The original NDA was submitted by Sanofi-aventis U.S. LLC (Sanofi) on March 12, 2020.

The Agency provided their CRL to Sanofi on November 12, 2020.

DNDi assumed sponsorship of the Fexinidazole NDA on May 4, 2021.[b]

[a] Rodgers, A. Communication: Complete Response Letter for Fexinidazole. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2020 NOV 12. NDA 214429. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805ac568&_afrRedirect=1793461751228487.

[b] Acceptance of Sponsorship of NDA: Transfer of Sponsorship for Fexinidazole (NDA 214429). Geneva (Switzerland): Drugs for Neglected Diseases initiative; 2021 MAY 04. Available from: \\CDSESUB1\evsprod\nda214429\0034\m1\us\cover.pdf.

DNDi submitted their Class 1 Resubmission, dated May 18, 2021,[c] to supply their response to the deficiencies included in the Agency's CRL.

3 DISCUSSION

Prior to the issuance of the November 12, 2020 CRL, we reviewed the proposed Fexinidazole PI, container labels (blister cards), and carton labeling (wallet) and we previously found the proposed container labels (blister cards) and carton labeling (wallet) acceptable.[d,e] Included in their resubmission, dated May 18, 2021, DNDi cross-references container labels (blister cards) and carton labeling (wallet) submitted on September 2, 2020 and August 18, 2020, respectively. We determined that the container labels (blister cards) and carton labeling (wallet) are identical to those previously submitted apart from the following text changes:

(b) (4)

was replaced with:

Manufactured for:
Drugs for Neglected Diseases initiative
15 Chemin Camille-Vidart
1202 Geneva, Switzerland

Distributed by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

We find the above proposed changes to the container labels (blister cards) and carton labeling (wallet) to be aligned with the change in sponsorship and acceptable from a medication error perspective.

Additionally, we note that our previous recommendations to DAI[f] have been implemented in the PI received on May 18, 2021.

4 CONCLUSION

Our evaluation of the proposed Fexinidazole PI, container labels (blister cards), and carton labeling (wallet) included in the resubmission dated May 18, 2021, did not identify additional areas of vulnerability that may lead to medication errors. Therefore, we have no additional recommendations at this time.

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[c] Resubmission to a Complete Response Letter received on May 18, 2021 (Fexinidazole NDA 214429) Geneva (Switzerland): Drugs for Neglected Diseases initiative; 2021 MAY 18. Available from: \\CDSESUB1\evsprod\nda214429\0035\m1\us\cover.pdf.

[d] Myers D. Label and Labeling Review Memo for Fexinidazole (NDA 214429). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 18. RCM No.: 2020-483-1.

[e] Myers D. Label and Labeling Review Memo for Fexinidazole (NDA 214429). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 02. RCM No.: 2020-483-2.

[f] Myers, D. Label and Labeling Review for Fexinidazole (NDA 214429). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 21. RCM No.: 2020-483.

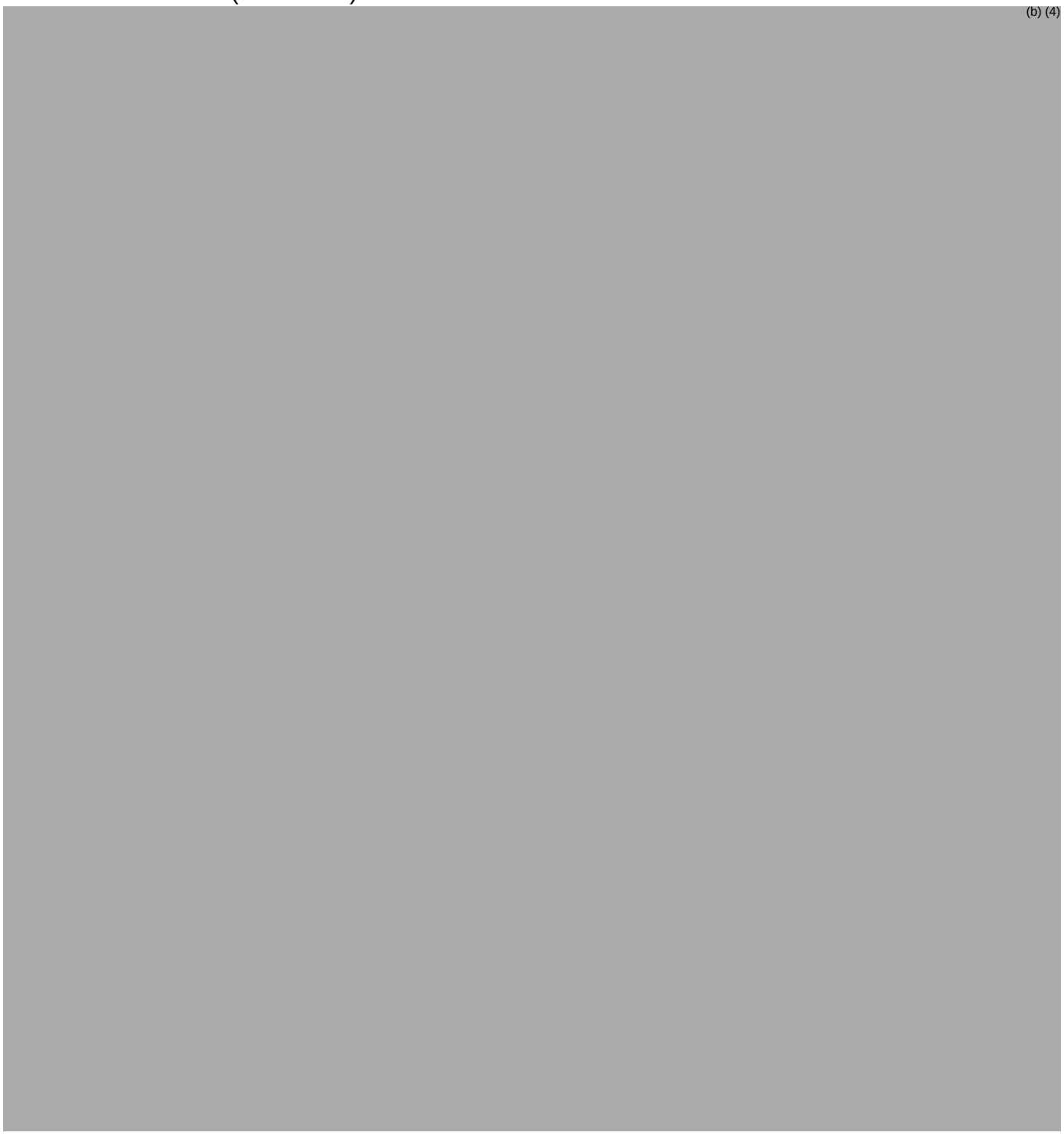
APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 18, 2021

Prescribing Information (PI) (image not shown):

- Clean proposed (Draft) PI available at the following link: \\CDSESUB1\evsprod\nda214429\0035\m1\us\proposedpi.doc.
- Annotated PI available at the following link: \\CDSESUB1\evsprod\nda214429\0035\m1\us\annotatedpi.doc.

Container labels (blistercard)

(b) (4)



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/s/

DEBORAH E MYERS
06/17/2021 10:00:00 AM

VALERIE S VAUGHAN
06/17/2021 10:52:51 AM

Clinical Inspection Summary

Date	10/7/2020
From	Christian Shenouda, M.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Shrimant Mishra, MD, Clinical Reviewer Edward Weinstein, MD, Clinical Team Leader Alison Rogers, Regulatory Project Manager Division of Anti-Infectives (DAI)
NDA	214429
Applicant	Sanofi-Aventis
Drug	Fexinidazole
NME	Yes
Proposed Indication(s)	The treatment of both first-stage (hemolymphatic) and second-stage (meningoencephalitic) of human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense.
Consultation Request Date	4/28/2020
Summary Goal Date	10/12/2020
Action Goal Date	10/30/2020
PDUFA Date	11/15/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Helene Mahenzi Mbembo, Medard Ilunga Wa Kyhi, and Steven Lumeya Vuvu underwent remote regulatory assessments of the clinical investigator's practices and procedures to determine compliance with applicable regulations in support of this NDA. Based on the results of these investigations, the study DNDiFEX004 appears to have been conducted adequately, and the data generated by these clinical investigators generally appear reliable in support of the proposed indication. However, it should be noted that Dr. Vuvu's site enrolled six possibly ineligible subjects (all randomized to the fexinidazole group). Only two of the six events (i.e., the two subjects that lacked confirmatory LP) were reported as protocol deviations, and all six subjects were included in the final analysis. The review division should exclude the six subjects (all of whom were randomized to the fexinidazole group) who lacked confirmatory LP (Subject #'s (b) (6) and (b) (6) and with BMI exclusionary criteria (Subjects #'s (b) (6) and (b) (6) from the per protocol analysis set. The review division may wish to perform a sensitivity analysis to assess the robustness of the results, taking the protocol deviations for these six subjects into account.

II. BACKGROUND

Fexinidazole is an oral formulation of a 2-substituted 5-nitroimidazole compound that has been shown to be a broad-spectrum antiprotozoal, and the sponsor is seeking approval for its use in the treatment of both first-stage (hemolymphatic) and second-stage (meningoencephalitic) human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense.

The applicant, Sanofi Aventis, submitted the data from Protocol DNDiFEX004, a randomized, open-label, active control (Nifurtimox Eflornithine Combination Therapy [NECT]) study in support of this indication. This study was conducted throughout 10 sites in the Democratic Republic of the Congo (DRC) and the Central African Republic. The following briefly describes the protocol.

Protocol DNDiFEX004

Title: "Efficacy and safety of Fexinidazole compared to nifurtimox-eflornithine combination therapy (NECT) in patients with late-stage human African trypanosomiasis (HAT) due to *T. b. gambiense*: a pivotal, non-inferiority, randomised, open-label, multicentre study"

Subjects: 390 adults

Sites: 9 sites in the Congo and 1 site in the Central African Republic

Study Initiation and Completion Date: 10/2/2012 - 11/29/2016

Summary: Subjects above age 15 were enrolled following confirmation of late-stage HAT diagnosis and were randomized to Fexinidazole or NECT. Subjects were excluded if they had medical instability or complications (Karnofsky score <50, severe malnutrition as defined by a body mass index [BMI] of <16, prior treatment of HAT or other comorbidity). The Karnofsky Performance Score is an ordinal scale (0-100) that assesses functional impairment. A score of 50 indicates that an individual is unable to work but requires considerable assistance and has frequent medical care needs.

Mobile medical teams were able to assess and enroll subjects in the field, or subjects could present themselves to designated study sites. Criteria for diagnosis of HAT included testing for T.b. gambiense in the blood, lymph, and cerebral spinal fluid (CSF) or an elevated WBC in CSF suggestive of infection. Late stage HAT diagnosis relies on diagnosis of trypanosomes visualized in the CSF. Individuals without trypanosomes visualized in the CSF but with mildly elevated CSF WBC count (19, 20, 21, or 22/microliter) were to have a second examiner perform the WBC count or have a repeat LP prior to enrollment.

Those enrolled were given 10 days of treatment and were then followed for a total of 24 months. Study visits were at baseline, Day 5, Day 8, Day 11 (End of Treatment), Day 13 to Day 18, Week 9, 3 months, 6 months, 12 months, 18 months (Primary Efficacy Time Point) and 24 months. Enrolled subjects had testing for evidence of trypanosome presence in the

blood, lymph, or CSF at baseline and repeat testing at 6, 12, and 18 months to detect signs of continued infection.

The *primary efficacy endpoint* was the outcome (i.e., "success" or "failure") of treatment as assessed at 18 months. Subjects were classified as "success" (including the subcategories of "cure" or "probable cure") if alive, no evidence of trypanosomes in any body fluid, with a CSF white blood cell (WBC) count of <20 per microliter (designation of "cure"). If no lumbar puncture was performed, a designation of "probable cure" was if there were no lymphocytes in the blood. "Failure" was designated if there was evidence of trypanosomes in the blood or death, regardless of the cause.

Rationale for Site Selection
The following clinical investigator (CI) sites were chosen for routine inspection primarily based on numbers of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history.

III. INSPECTION RESULTS

Sites 01, 02, and 04 were located in the Democratic Republic of the Congo (DRC). Due to travel restrictions to the DRC, remote regulatory assessments (in lieu of full GCP site inspections) were conducted at the sponsor (Sanofi-Aventis) headquarters located at: 255 Corporate Drive, Bridgewater, New Jersey, 08807. Certified hardcopies of study documents were scanned into the electronic master file (eTMF). Video conferencing via WebEx, document sharing via an online platform (b) (4), and read-only access to the online trial master file were used in these remote investigations.

1. **Helene Mahenzi Mbembo**
   Site 01
   Av. WAMBA N°1
   C.Mayoyo Bandundu Ville
   Bandundu
   Democratic Republic of Congo
   Remote Regulatory Assessment dates: 6/23/2020-7/7/2020

At this site for protocol DNDiFEX004, 103 subjects were screened and 53 were randomized into the study. Fifty-one of these subjects were dosed, and 48 subjects completed the study (i.e., made it to 18 months). All three subjects who were discontinued from the study were randomized to the fexinidazole group: Subject (b) (6) ied during follow-up due to a neoplastic submandibular mass with metastasis, Subject (b) (6) died during follow-up reportedly due to alcohol intoxication, and Subject (b) (6) died during the treatment period due to "intoxication of indigenous products." All these deaths were reported to the sponsor per protocol (i.e., within 24 hours).

Documents reviewed included, but were not limited to, IEC approvals, investigator agreements, lab reports, Informed Consent (ICFs), clinical assessments, and adverse events (AEs). The review team was able to verify eligibility for all subjects dosed.

The primary efficacy endpoint which is white blood cell count in the cerebrospinal fluid at 18 months for all subjects dosed was verifiable. However, presence of trypanosomes in the CSF was not available for this investigation; this data for trypanosome visualization was noted to be contained in hospital laboratory notebooks that also included non-study patient data that could not be redacted due to time constraints. Instead, data from the eCRF entries related to CSF trypanosome visualization were compared against the data line listings provided by the sponsor; no discrepancies with noted. Of note, for the investigations of the other two CIs, CSF trypanosome data was able to be redacted and was provided for verification.

There was no evidence of underreporting of adverse events. There were at total of eight SAEs at this site, which included the three deaths described above. Of the eight SAEs, six occurred within those assigned to fexinidazole (the above three deaths, one inguinal hernia, and two incidences of malaria) and two were in those assigned to the control (one instance of severe hyperkalemia and one episode of severe dehydration following a head injury). All SAEs were reported to the sponsor per protocol, and details of the SAE were provided in the NDA submission.

2. Steven Lumeya Vuvu
Site 02
Mission Protestante Vanga
Bandundu
Democratic Republic of Congo
Remote Regulatory Assessment dates: 6/23/2020 - 7/16/2020

At this site for protocol DNDiFEX004, 118 subjects were screened, 69 were enrolled, and 66 subjects were dosed. Of the 66 subjects dosed, 61 subjects completed the study. There were five deaths, one death in the control group due to malnutrition (Subject (b) (6) and four deaths in the fexinidzaole group (Subject (b) (6) had severe pneumonia, Subject (b) (6) had "intoxication with indigenous substances," Subject (b) (6) had pulmonary tuberculosis/starvation, and Subject (b) (6) had aspiration pneumonia). There were two subjects who were classified as treatment failures due to relapse (Subject #'s (b) (6) relapsed at 6 and 12 months, respectively); both were assigned to the fexinidazole group. All SAEs were reported per protocol (i.e., within 24 hours).

Documents reviewed included, but were not limited to, IEC approvals, investigator agreements, lab reports including CSF WBC and trypanosome visualization, Informed Consent documents (ICFs), clinical assessments, and adverse events (AEs).

The ORA investigators were able to verify the primary efficacy endpoint of white blood cell count and trypanosome presence in the cerebrospinal fluid at month 18 for all 66 subjects enrolled and dosed. The data for presence of trypanosomes was obtained from laboratory notebooks that had non-study subject information redacted. There were no discrepancies noted in this data.

There were 17 SAEs in 13 subjects reported at this site, including the five deaths listed above. Additional SAEs reported for the fexinidazole group included psychiatric manifestations (n=4;

e.g., suicide attempt, personality change), respiratory complications (n=3, e.g. aspiration pneumonia), and relapse (n=2). Other events included splenomegaly, diabetes, and gastroenteritis. Additional SAEs reported for the control group including suspected seizure, closed tibial fracture, and severe hypoglycemia. The site reported the SAEs to the sponsor per protocol (i.e., within 24 hours), and all these SAEs were in the NDA submission.

A review of the adverse event reporting showed two instances of underreporting adverse events, i.e., in Subject (b) (6) (back pain) and Subject (b) (6) (leg pain), both of whom were assigned to the fexinidazole group.

Reviewer's comment: These two underreported adverse events should be considered when evaluating the safety profile of the study drug.

Six subjects who did not meet enrollment requirements criteria. Body Mass Index (BMI) requirements in four subjects and absence of confirmatory lumbar puncture testing in two subjects were noted to be deficient by the ORA investigators.

- Regarding the BMI eligibility criteria, the OA investigators noted that changes (when comparing source documents to the eCRF) were made to the height of Subject #'s (b) (6) (b) (6) and (b) (6) and to the weight of Subject (b) (6) which resulted in their BMI changing from ineligible to eligible based on the exclusion criterion of BMI<16. All of these subjects were randomized to receive fexinidazole. A review of the audit trails for the eCRF did not show that any changes were made to the original entries, but it was unclear if the EDC had instances of edit checks firing that were not recorded in the audit trails.

- The protocol specified that if trypanosomes were not visualized in CSF and CSF WBC was between 19 and 22/µl inclusive, results would be reviewed by a second study examiner, a confirmatory LP would be performed, or the subject would not be enrolled. A second lumbar puncture was not assessed before enrollment for Subject #'s (b) (6) and (b) (6) whose CSF was negative for trypanosomes and both with a white cell count of 22/µl. Both of these subjects were randomized to the fexinidazole group.

Reviewer's comment: Only two of the six events (i.e., the two subjects that lacked confirmatory LP) were reported as protocol deviations, and all six subjects were included in the final analysis. The review division should exclude the six subjects (all of whom were randomized to the fexinidazole group) who lacked confirmatory LP (Subject #'s (b) (6) and (b) (6) and with BMI exclusionary criteria (Subjects #'s (b) (6) and (b) (6) from the per protocol analysis set.

3. Medard Ilunga Wa Kyhi
Site 4
Av de lhopital n1 Quartier Tubondo
C. de la Kanshi Mbujimayi
Kasaï Oriental
Democratic Republic of Congo
Remote Regulatory Assessment dates: 7/20/2020 - 8/7/2020

There were 126 subjects screened, 63 were consented, and 56 were dosed. All 56 subjects completed the study. Documents reviewed included, but were not limited to, IEC approvals, investigator agreements, lab reports including CSF WBC and trypanosome visualization , Informed Consent (ICFs), clinical assessments, and adverse events (AEs).

The review team was able to verify eligibility, general protocol adherence, and the primary efficacy endpoint of white blood cell count and trypanosome presence in the cerebrospinal fluid at month 18 for all 56 subjects enrolled and dosed. There was no evidence of underreporting of adverse events.

There were three SAEs reported at this site, all in subjects randomized to fexinidazole. Subject (b) (6) had infected wound of the left leg with lymphangitis, Subject (b) (6) had acute respiratory tract infection, and Subject (b) (6) had angina and hypoglycemia. All SAEs occurred after the 10-day dosing period and within 90 days of the last fexinidazole dose. All SAEs were reported to the sponsor per the protocol (i.e., within 24 hours) and were included in the NDA submission.

{See appended electronic signature page}

Christian N. Shenouda, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Lead
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm. NDA 214427
DAI Review Division /Division Director/Sumathi Nambiar
DAI Review Division /Medical Team Leader/ Edward Weinstein
DAI Review Division /Project Manager/ Alison Rodgers
DAI Review Division/MO/ Shrimant Mishra
OSI/Office Director/ Ni Khin
OSI/DCCE/ Division Director/ David Burrow
OSI/DCCE/Branch Chief/ Kassa Ayalew
OSI/DCCE/Team Leader/ Phillip Kronstein
OSI/DCCE/GCP Reviewer/ Christian Shenouda
OSI/ GCP Program Analysts/ Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 6, 2020

TO: Sumathi Nambiar, MD
Director
Division of Anti-Infective Products (DAIP)
Office of Antimicrobial Products
Office of New Drugs

FROM: Sripal Reddy Mada, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly Benson, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Remote Record Review (RRR) of [redacted] (b) (4)

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of the method validation supporting Study DNDiHATFEX008 (NDA 214429, Fexinidazole [redacted] (b) (4) IR Tablet, 600 mg) conducted at [redacted] (b) (4) An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic.

I did not observe any objectionable findings during the RRR that impact reliability of study data.

1.1. Recommendation

Based on my review of the RRR findings, I conclude the data from the audited studies are reliable.

2. Reviewed Studies

Validation Report #0058-2009: "Validation of an Analytical Method for the Determination of Fexinidazole and its Metabolites Fexinidazole-sulfoxide and Fexinidazole-sulfone in Human Plasma by LC-MS-MS"

Validation Period: 02/11/2009 – 05/29/2009

Validation Report #0058-2009: "Long-Term Stability Assessment of Fexinidazole and its Metabolites Fexinidazole-sulfoxide and Fexinidazole-sulfone in Human Plasma Stored at -80°C up to 3 months"
Validation Period: 04/20/2009 – 08/06/2009

3. Scope of RRR

OSIS scientist, [redacted] Pharmacologist, reviewed the validation portions of the above method validations conducted at [redacted] This RRR was conducted after an RRR with [redacted] During RRR at [redacted] it was brought to my attention that the method validation supporting Study DNDiHATFEX008 (NDA 214429, Fexinidazole [redacted] IR Tablet, 600 mg) was conducted at [redacted]. As such, an RRR with [redacted] was conducted relative to NDA 214429. An RRR recommendation memorandum for the [redacted] was finalized on September 14, 2020, therefore this is one of two RRR recommendation memoranda for NDA 214429.

The RRR included an examination of study records for method validation, as well as interviews with the firm's management and staff. I reviewed portions of the raw data for method validation, e.g., stock/working solution, bench-top, freeze-thaw and long-term stabilities.

4. RRR Findings

At the conclusion of the RRR for [redacted] I observed no issues that might impact reliability of study data.

5. Conclusion

After reviewing the RRR findings, I conclude that validation data generated at [redacted] are reliable.

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Choi/Skelly/Au/Mada

Draft: SRM 10/06/2020
Edit: YMC 10/06/2020; KB 10/06/2020

ECMS:http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8839daeed
OSIS File: BE 8919

Sripal Reddy Mada, Ph.D.
Pharmacologist, OSIS, OTS

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/s/

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YOUNG M CHOI
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10/06/2020 04:17:54 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 17, 2020

To: Alison Rodgers, Regulatory Project Manager
Division of Regulatory Operations for Infectious Diseases (DRO-ID)

Abimbola Adebowale, Associate Director for Labeling
Office of Infectious Diseases (OID)/Division of Anti-Infectives (DAI)

From: Puja Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for FEXINIDAZOLE tablets, for oral use

NDA: 214429

In response to DAI's consult request dated April 17, 2020, OPDP has reviewed the proposed patient product labeling (PI) and carton and container labeling for the original NDA submission for FEXINIDAZOLE tablets, for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRO-ID (Alison Rodgers) on September 11, 2020, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 18, 2020, and September 2, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Puja Shah at (240) 402-5040 or puja.shah@fda.hhs.gov.

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/s/

PUJA J SHAH
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 14, 2020

TO: Sumathi Nambiar, MD
Director
Division of Anti-Infective Products (DAIP)
Office of Antimicrobial Products
Office of New Drugs

FROM: Sripal Reddy Mada, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly Benson, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Remote Record Review (RRR) of [redacted]

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of the analytical portion of Studies DNDiHATFEX008 (NDA 214429, Fexinidazole [redacted] IR Tablet, 600 mg) and DNDiHATFEX006 (NDA 214429, Fexinidazole [redacted] IR Tablet, 600 mg) conducted at [redacted] An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic.

I observed two items that impact reliability of study data. At the close out meeting of the RRR, I discussed the items with the firm's management. The firm submitted their response on 9/11/2020.

It should be noted that I was not able to review a portion of the raw data for method validation, e.g., stock/working solution, bench-top, freeze-thaw and long-term stabilities because the raw data of these studies were not available at [redacted] The data for these experiments were generated at [redacted]

1.1. Recommendation

Based on my review of the RRR findings and the firm's response, I conclude the data from the audited studies are reliable provided that there is no issue on the stock/working solution, bench-top, freeze-thaw and long-term stabilities generated at (b) (4) OSIS will initiate a separate RRR for (b) (4) specifically for these stability studies.

2. Reviewed Studies

Study DNDiHATFEX008 (NDA 214429): "A bioequivalence study of the reference clinical fexinidazole tablet versus the test marketed formulation (600 mg tablet) in healthy male volunteers of African sub-Saharan origin: an open-label, randomized, two-treatment, single dose, replicate design under fed condition"
Sample Analysis Period: 05/27/2015 – 08/14/2015

Study DNDiHATFEX006 (NDA 214429): "Efficacy and safety of fexinidazole in children at least 6 years old and weighing over 20 kg with Human African Trypanosomiasis (HAT) due to *T. b. gambiense*: a prospective, multi-centre, open study, plug-in to the pivotal study"
Sample Analysis Period: 06/19/2014 – 05/09/2016

3. Scope of RRR

OSIS scientist, (b) (4) Pharmacologist, reviewed the analytical portions of the above studies conducted (b) (4)

The RRR included an examination of study records, method validation, and sample analysis, and interviews with the firm's management and staff.

Note: I was not able to review the raw data for method validation of stock/working solution, bench-top, freeze-thaw and long-term stabilities because the data for these experiments were generated at (b) (4) (b) (4) OSIS will initiate a separate RRR for (b) (4) to cover these experiments and submit as an addendum.

4. RRR Findings

At the conclusion of the RRR for (b) (4) I observed issues that might impact reliability of study data. I discussed the issues with the firm's management during the RRR close-out meeting. The firm's management submitted their written responses to the issues on 9/11/2020.

My evaluation of the findings that were discussed and the firm's response dated 09/11/2020 (**Attachment 1**) are presented below.

4.1. Findings discussed at the close-out of RRR

4.1.1. In study DNDiHATFEX008, the firm did not record the real time of the events for sample extraction and instrumental analysis. Therefore, it was not possible to reconstruct the study, and to evaluate whether there would be any impact of bench-top stability and auto sampler stability.

Firm's Response: In their response to RRR findings, (b) (4) (b) (4) said the original method validation was conducted at (b) (4) and the method was transferred from (b) (4) to (b) (4) conducted the partial validation. (b) (4) also performed autosampler stability covering 120 hours at 4°C. (b) (4) also said, in the study DNDiHATFEX008, the sample processing sheets presented the date of processing and re-injection, and Analyst software recorded the time stamp of fist injection and re-injection during the sample analysis.

(b) (4) confirmed that (b) (4) has demonstrated benchtop stability in plasma for 24 hours at room temperature (RT).

As a corrective action, (b) (4) will update the procedures effective (b) (4) for incorporating the time stamps in the sample processing sheets.

OSIS Evaluation: I reviewed the records of sample processing sheets and the audit trails of the Analyst software for the respective date of sample processing and analysis. I found that the sample storage at RT after extraction was within 24 hours, and the sample storage time at the autosampler was within 120 hrs. Therefore, the firm's response is acceptable, and the issues of discussion would not impact on the study reliability provided that there is no issue regarding the data generated at (b) (4)

The firm's corrective action will provide the traceability of events from extraction till the last sample analysis in the respective runs.

4.1.2. In study DNDiHATFEX008, the firm employed the sample selection for reanalysis inconsistently. Specifically, the firm reanalyzed the samples potentially impacted by inversion along with the positive control samples, i.e., before and after the samples of inversion suspicion for the run ID 14. However, for the run ID 16, the firm did not reanalyze all the positive control samples.

Firm's Response: [redacted] responded that the information of suspicion of sample inversion was presented in sample processing sheets for Run ID 14 and Run ID 16. To allow consistency of the process of reanalysis of "samples inversion suspicion", [redacted] will update their SOP [redacted]-SOP013". Per the new procedures, they will reanalyze all samples from the impacted subject or subject period in duplicates. The new SOP will be effective [redacted]

OSIS Evaluation: The five samples in Run ID 14 were selected and reanalyzed due to "samples inversion suspicion" including three additional adjacent samples as positive control. However, the firm did not use additional samples as controls for a similar issue observed in Run ID 16.

In Run ID 16, the subsequent sample after the suspected sample was a QC sample and this sample was not picked for reassay of samples. The firm said they evaluated plasma concentration time profile for the rest of the subject samples analyzed in Run ID 16. I discussed that the reassay of the sample should not be selected based on pharmacokinetic profile and should be based on prior criteria written in the SOP to avoid any inconsistency in reassay of the selected samples. After reviewing the raw data of the QC sample, I am of the opinion that the lack of the reassay of the QC sample should not have impact on the data reliability.

The firm updated the procedure for reassay of samples due to 'samples inversion suspicion'. The updated procedures will be implemented in the future studies. This corrective action of the firm is acceptable.

5. Conclusion

After reviewing the RRR findings and the firm's response, I conclude that data from the audited studies generated at [redacted]

(b) (4) are reliable provided that there is no issue with the stock/working solution, bench-top, freeze-thaw and long-term stabilities generated at (b) (4)

OSIS will initiate a separate RRR for (b) (4) (b) (4) to cover additional validation experiments.

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Choi/Skelly/Au/Mada

Draft: SRM 09/11/2020; 9/14/2020
Edit: YMC 09/12/2020; 9/14/2020; KB 09/14/2020

ECMS:http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8839daeed
OSIS File: BE 8919

Sripal Reddy Mada, Ph.D.
Pharmacologist, OSIS, OTS

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YOUNG M CHOI
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
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Division of Pediatric and Maternal Health Review

Date: 8/28/20 **Date consulted:** 6/22/20

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Anti-Infectives (DAI)

Drug: Fexinidazole tablets for oral use

NDA: 214429

Applicant: Sanofi-Aventis U.S. LLC (Sanofi)

Subject: Pregnancy and Lactation Labeling Recommendations

Indication: Treatment of both first-stage and second-stage human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense in adults and children

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214429
- DPMH consult request dated 3/10/20, DARRTS Reference ID 4631937

(b) (4)

(b) (4)

- June 30, 2020, DPMH review for Lampit (nifurtimox), Carrie Ceresa, Pharm D., MPH, DARRTS Reference ID 4633593[2]

Consult Question: "We are seeking advice and labeling recommendations for pregnancy and lactation. There is evidence of maternal toxicity and secondary fetal toxicity in rat and rabbit dams. The drug is distributed into milk and transiently retards growth in suckling rat pups."

INTRODUCTION AND BACKGROUND

On March 12, 2020, Sanofi submitted a new drug application (NDA) for Fexinidazole for the treatment of both first-stage and second-stage human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense (g-HAT) in children ≥ 6 years old and adults. On June 22, 2020, DAI consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Fexinidazole (formerly known as HOE239) is not currently approved in the United States. In 2018, Fexinidazole was approved by the European Medicine Agency (EMA) for the treatment of g-HAT (under Article 58) which supports its registration in endemic countries and distribution by the World Health Organization.[3] It has been approved in the Democratic Republic of Congo and distribution started in January 2020.
- In addition to treatment of g-HAT, fexinidazole is currently under development for treatment of visceral Leishmaniasis and Chagas disease.
- Fexinidazole was jointly developed by the Drugs for Neglected Diseases initiative (DNDi) and Sanofi.
- April 4, 2016: Fexinidazole received Orphan Drug Designation (ODD) for the treatment of HAT.
- March 12, 2020: The applicant submitted NDA 214429 and requested Priority Review and request for a Tropical Disease Priority Review Voucher (PRV)

Fexinidazole Drug Characteristics[4]

- Drug class: Fexinidazole is an antiprotozoal that is a 5-nitroimidazole derivative belonging to a wider class of nitroimidazole anti-infective agents. Other drugs in this class include benznidazole and metronidazole.
- Mechanism of action: Fexinidazole has activity against *Trypanosoma cruzi*, *Leishmania donovani*, *Leishmania infantum*, *Trypanosoma brucei (T. b.) rhodesiense*, *T. b. gambiense*, and *Entamoeba histolytica*.[5] Fexinidazole generates reactive amine species that are indirectly toxic and mutagenic to trypanosomes, although its exact mechanism of action has not been assessed.[6]
- Fexinidazole is the first and currently only all-oral treatment regimen for g-HAT.

[2] The nifurtimox review was part of the material reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[3] Deeks ED. Fexinidazole: First Global Approval. *Drugs*. 2019;79(2):215-220. doi:10.1007/s40265-019-1051-6
[4] Refer to proposed labeling, 3/12/20
[5] Refer to proposed labeling, section 12, 3/12/20.
[6] Deeks, E., & Lyseng-Williamson, K. (2019). Fexinidazole in human African trypanosomiasis: a profile of its use. *Drugs & Therapy Perspectives: for Rational Drug Selection and Use.*, *35*(11), 529–535.

- Dose and administration: Fexinidazole is proposed to be available as a 600 mg tablet for oral use given once daily for 10 days with food. The dosing regimen for adults is as follows: 1800mg (600 mg tablet x 3) once daily for 4 days followed by 1200 mg (600 mg tablet x 2) once daily for 6 days.
- Molecular weight: 279.3 g/mol
- Terminal half-life: 14 hours, 23 hours for its metabolite M2
- Plasma protein binding: 95.4% (in vitro)
- Contraindications: (b) (4)
- Warnings and precautions (proposed): QT interval prolongation, psychiatric related events, risk of infection, hepatotoxicity
- Adverse reactions (proposed): vomiting, nausea, asthenia, decreased appetite, headache, insomnia, tremor, dizziness.

REVIEW

PREGNANCY

Human African trypanosomiasis (HAT) and Pregnancy

- HAT, also known as sleeping sickness, is a parasitic infection endemic in sub-Saharan Africa. The infection is transmitted through the bite of an infected tsetse fly. There are two subspecies of the fly that lead to different clinical features of infection.[7]
    - Infection with Trypanosoma brucei gambiense (g-HAT) occurs in western and central Africa (currently 98% of cases) and causes a slowly progressing form of the disease. Fexinidazole is indicated for this form.
    - Infection with T.b. rhodesiense (r-HAT) occurs in eastern and southern Africa and causes a more acute form of the disease.
- HAT is categorized into two disease stages
    - First stage (hemolymphatic stage): the parasites multiply in the lymph and blood causing nonspecific symptoms such as headache, fever, weakness, joint pain, muscle pain, and lymphadenopathy.
    - Second stage (meningoencephalitic stage): brain involvement leads to various neurological disturbances, including sleep and sensory disturbances, psychiatric disorders, abnormal tone, ataxia, seizures, progression to coma, and ultimately death.
    - HAT is curable with medication but can be fatal if left untreated.
- *Epidemiology*
    - There is an overall downward trend for g-HAT, and the disease is targeted for elimination by WHO by 2030.[8] In 2018, historically low number of cases worldwide (<1000) were reported. Cases occurred predominantly in central Africa and in limited areas of West Africa.[9] HAT cases are occasionally diagnosed in non-endemic countries, typically in travelers returning from endemic areas and migrants. From 2000-2011, three g-HAT cases were

[7] https://www.cdc.gov/parasites/sleepingsickness/epi.html

[8] https://www.who.int/health-topics/human-african-trypanosomiasis#tab=tab_1

[9] WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

diagnosed in the United States, all in young male adults.[10] From 2009-2018, 19 g-HAT cases were diagnosed and reported in non-endemic countries. In 2017-2018, only two cases of g-HAT were reported in non-endemic countries and neither of these cases were in the United States.[11]

- *Pregnancy complications of g-HAT*
    - Trypanosomes can cross the placenta and infect the fetus (i.e., vertical transmission) and the duration of pregnancy is sufficient to allow progression to second stage disease in utero. Risk of vertical transmission is unknown.[12]
    - Since 1933, 13 published reports of cases of congenital transmission diagnosed within 5 days of birth have been described.[13] Three infants died soon after birth before treatment was initiated.[14] Additional cases of HAT diagnosed in neonates and infants have been reported where congenital transmission is assumed but not confirmed.
- *Interim treatment guidelines for g-HAT (WHO 2019)*[15]
    - In contrast to other available treatments for g-HAT, fexinidazole is an all oral regimen and does not require disease staging via lumbar puncture because it can be used to treat both stages of disease. Fexinidazole may also be administered to selected patients in an outpatient setting (i.e., patients who are likely to adhere, patients who do not have psychiatric disorders).
    - Treatment for g-HAT in pregnancy depends on clinical severity:
        - If a pregnant woman's general condition allows for watchful waiting, regular clinical assessment (at least monthly) is advised. Fexinidazole or pentamidine should be administered after the first trimester, with the main objective of reducing the risk of vertical transmission of the disease. Nifurtimox-eflornithine combination therapy (NECT) should generally be administered after delivery.
        - If the general condition of the pregnant woman is moderately or severely altered, treatment with fexinidazole, eflornithine alone or NECT must be administered with the main objective of saving her life.
    - Patients are typically followed 24 months after treatment to assess for relapses.

Nonclinical Experience

In embryo-fetal toxicity studies, pregnant rats were exposed through gestation day (GD) 6 to GD 17. There was no effect on prenatal development in the rat up to the daily dose of 200 mg/kg, about 0.4 times the clinical dose based on AUC comparisons.

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[10] Simarro PP, Franco JR, Cecchi G, et al. "Human African trypanosomiasis in non-endemic countries (2000-2010). J Travel Med. 2012; 19(1): 44-53.
[11] Franco, José R et al. "Monitoring the Elimination of Human African Trypanosomiasis at Continental and Country Level: Update to 2018." *PLoS neglected tropical diseases.* 14.5 e0008261–18. Web.
[12] Lindner AK, Priotto G (2010) The Unknown Risk of Vertical Transmission in Sleeping Sickness—A Literature Review. PLoS Negl Trop Dis 4(12): e783. doi:10.1371/journal.pntd.0000783
[13] WHO. Control and surveillance of human African trypanosomiasis. *World Health Organ Tech Rep Ser* 2013; 1–237.
[14] Lindner AK, Priotto G (2010) The Unknown Risk of Vertical Transmission in Sleeping Sickness—A Literature Review. PLoS Negl Trop Dis 4(12): e783. doi:10.1371/journal.pntd.0000783
[15] WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

At a dose of 800 mg/kg, maternal toxicity effects led to significantly reduced body weight gain, delayed ossification of some bones (sternum, metacarpals and caudal vertebrae) and reduced fetal and placental weights.

In the rabbit prenatal development study, pregnant rabbits were exposed from GD 6 to GD 20. Fexinidazole resulted in abortions in the presence of maternal toxicity (reduced food consumption and reduced body weight gain) at doses of 20 mg/kg/day and above.

Reviewer comment: The Pharmacology/Toxicology review by Owen McMaster, Ph.D., is pending.

Pharmacovigilance (PV) Database

Across the fexinidazole clinical program, a total of 1055 subjects have been exposed to fexinidazole for g-HAT and additional indications (visceral Leishmaniasis and Chagas disease) in 12 studies (completed and ongoing).[16] Post-marketing exposure data are not available because fexinidazole was not supplied in any countries at the time of the search.[17]

A total of four cases of exposure to fexinidazole during pregnancy were noted in an ongoing study (DNDi-FEX-09-HAT) in g-HAT patients. Patients were permitted to participate once they had reached the second trimester of pregnancy. Fexinidazole exposure occurred in the 2nd trimester (n=2) and 3rd trimester (n=2). The four pregnancies include follow up information of four healthy live births. See Appendix A.

The applicant also summarized cases of fexinidazole exposure before pregnancy that occurred during the clinical studies. The summary included 25 cases, with the interval from the end of treatment with fexinidazole and the start of pregnancy ranging from 27 to354 days after the end of treatment.[18]

Reviewer comment: None of the cases of fexinidazole exposure prior to pregnancy were within six times the half-life prior to pregnancy (i.e., six days) and are therefore unlikely related to fexinidazole.

Applicant's Review of Literature

The applicant conducted a general literature search for fexinidazole and products within the class with a cut-off date of September 7, 2019 using the PubMed online database over the last 12 years. The applicant limited the search to oral and IV formulations, active controlled studies, and case reports with a focus on safety concerns. The applicant did not identify any publications related to pregnancy.

DPMH review of literature

DPMH conducted a search of published literature search for "fexinidazole" and "pregnancy," "fexinidazole" and "congenital defects/congenital anomalies/teratogenicity/prematurity/stillbirth/ spontaneous abortion" and did not identify any publications.

[16] Applicant's Summary of Clinical Safety, page 19
[17] Applicant's Summary of Clinical Safety, page 27
[18] Applicant's Summary of Clinical Safety, page 273

Fexinidazole is not referenced in Micromedex,[19] REPROTOX,[20] or Teris.[21]

LACTATION

Nonclinical Experience

In the prenatal and postnatal development study, female rats were exposed from GD 6 to lactation day 21. Lower body weights were reported in F1 pups from dams treated at 600 mg/kg/day (approximately 0.7 times the clinical exposure based on AUC comparisons) throughout lactation. Sexual maturity showed a minimal delay for both males and females. Post-weaning development for behavior and reproductive performance did not indicate any late adverse effect on the progeny. In lactating rats given a single oral dose of 800 mg/kg 14C-fexinidazole, drug was identified milk 48 hours after dosing.

Reviewer comment: The Pharmacology/Toxicology review by Owen McMaster, Ph.D., is pending.

Pharmacovigilance Database

In the ongoing study (DNDi-FEX-09-HAT), patients with g-HAT were permitted to breastfeed. The applicant submitted 17 case reports of exposure during lactation. Among them, three serious adverse events (SAEs) were reported among two infants during the post-treatment follow up of the mother and were determined by the Investigator and Sponsor as not related to fexinidazole.

The cases are described by the applicant as follows:[22]

- Patient (b) (6) (mother): 10-month-old female was exposed to fexinidazole via breastfeeding during ten days of study treatment of the mother. During the post-treatment follow up period, a SAE of malaria complicated by anemia was reported, leading to the child's death 17 days after the end of treatment.

- Patient (b) (6) (mother): 8-month-old child was exposed to fexinidazole during 10 days of treatment for the mother. During the follow period, 2 SAEs of malaria and anemia occurred in the child 5 months after the mother's last study drug dose, leading to the child's death.

Reviewer comment: This reviewer agrees that the SAEs summarized by the applicant are likely not related to fexinidazole.

Applicant's Review of Literature

The applicant did not identify any publications related to lactation.

[19] https://www.micromedexsolutions.com, accessed 6/9/20.
[20] Truven Health Analytics information. Reprotox, accessed 8/6/20.
[21] Truven Health Analytics information. Teris, accessed 8/6/20.
[22] Applicant's summary of clinical safety, page 191

DPMH review of literature:
DPMH conducted a search in PubMed and Embase using the search terms "fexinidazole" AND "lactation" and "fexinidazole" AND "breastfeeding" and did not identify any articles.

Fexinidazole is not referenced in ReproTox, TERIS, LactMed, or Thomas Hale's Book (*Medications and Mothers' Milk*[23]*).*

Updated WHO interim guidelines for treatment of gambiense HAT[24] recommend that breastfeeding should continue during HAT treatment

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience
Fexinidazole and the M2 metabolite were mutagenic in the Ames test. Fexinidazole was negative in the *in vitro* micronucleus test in cultured human peripheral blood lymphocytes, the rat liver unscheduled DNA synthesis (UDS) assay and the *in vivo* mouse micronucleus assay. No carcinogenicity study was performed with fexinidazole due to the short duration of treatment.

In the fertility and early embryonic development study, male rats were treated for 28 days prior to start of cohabitation with treated females and throughout the cohabitation period until sacrifice. Female rats were treated for 14 days prior to start of cohabitation with treated males throughout cohabitation until copulation occurred and up to GD7. Fexinidazole showed no effect on fertility parameters and no evidence of impairment of reproductive performance up to the dose of 600 mg/kg/day.

Reviewer comment: The clinical relevance of the positive Ames test and negative micronucleus test is not clear. DPMH reached out to Pharmacology/Toxicology for input and their response is pending. The Pharmacology/Toxicology review by Owen McMaster, Ph.D., is pending.

Review of Pharmacovigilance Database
The applicant did not report any cases related to infertility.

Applicant's Review of Literature:
The applicant did not identify any publications related to fexinidazole and infertility.

DPMH review of literature:
DPMH conducted a search of published literature using the search terms "fexinidazole" AND "fertility," "fexinidazole" AND "reproduction" and did not identify any relevant publications.

Fexinidazole is not listed in Micromedex, REPROTOX, or Teris.

Reviewer's comment: Overall, the applicant performed an adequate literature search and summary of their clinical trial database regarding fexinidazole use in females and males of

[23] Hale TW. Hale's medications and mother's milk. 2019. Springer Publishing Co. NY, New York.
[24] WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

reproductive potential. The reader is referred to the Discussion and Conclusions section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Very limited data human pregnancy outcome data from a clinical study of fexinidazole treatment for g-HAT (n=4 pregnant patients) are insufficient to determine a drug-associated risk of miscarriage, major congenital anomalies, or maternal or fetal adverse effects. There is one positive test for mutagenicity, but other tests were negative. The clinical relevance of this finding is not clear. While animal data shows some adverse effects in the setting of maternal toxicity, there are no data regarding potential adverse findings in the absence of maternal toxicity.

Given the overall downward trend of g-HAT (<1,000 cases worldwide in 2018), and that cases of g-HAT outside of endemic countries including in the United States are increasingly rare, a pregnancy study is not feasible. (b) (4)

The primary goal of treatment during pregnancy is to prevent vertical transmission to the fetus. The WHO recommends treating g-HAT during pregnancy but after the first trimester if the pregnant woman is clinically stable. Labeling will include language in 8.1, Risk Summary and Clinical Considerations to provide the risk/benefit considerations for the provider.

Lactation

There is limited clinical experience (n=17 cases) of fexinidazole use during lactation based on clinical trials. The three reported serious adverse events that occurred during lactation (i.e., malaria with concurrent anemia) are unlikely related to the effects of fexinidazole and there were otherwise no reports of any adverse outcomes in the other infants exposed to fexinidazole during lactation. There are no data on the presence of fexinidazole in human milk. Fexinidazole is present in rat milk so it is likely that the drug will be present in human milk.

Given the downward trend of g-HAT (<1,000 cases worldwide in 2018), and that cases of g-HAT outside of endemic countries, including in the United States, are increasingly rare, a lactation study is not feasible. DPMH recommends using the standard risk/benefit language in subsection 8.2 of fexinidazole labeling.

(b) (4)

Females and Males of Reproductive Potential

There are no data on fexinidazole and the effects of fertility or contraception in humans. Animal data do not appear to affect fertility. Subsection 8.3 Females and Males of Reproductive Potential will be omitted in the labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DAI on August 24, 2020. DPMH recommendations are below and DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

(b) (4)

Risk Summary

There are risks to the mother and fetus associated with untreated HAT due to *T. b. gambiense* during pregnancy (*see Clinical Considerations*). Available data from clinical trials with fexinidazole use in pregnant women are insufficient to evaluate for a drug- associated risk of major birth defects or miscarriage.

(b) (4) effects of fexinidazole on embryo-fetal development were observed in the rat and in the rabbit at doses harmful to the dams only. (b) (4)

Reviewer comment: Final labeling edits for nonclinical including human dose equivalents are pending.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

There are adverse effects on maternal and fetal outcomes associated with untreated HAT due to *T. b. gambiense* in pregnancy. Disease progression may occur during pregnancy. Pregnant women should be treated for HAT due to *T. b. gambiense* during pregnancy to prevent vertical transmission.

Data

Animal Data

In the embryo-fetal toxicity studies, pregnant rats were exposed through gestation day (GD) 6 to GD 17. There was no effect on prenatal development in the rat up to the daily dose of 200 mg/kg, about 0.4 times the clinical dose based on AUC comparisons.

In the pre-natal and postnatal development study, female rats were exposed from GD 6 to lactation day 21. Lower body weights were reported in F1 pups from dams treated at (b) (4) (approximately (b) (4) times the clinical exposure based on AUC comparisons) throughout lactation. Sexual maturity showed a minimal delay for both males and females. Post-weaning development for behavior and reproductive performance did not indicate any late adverse effect on the progeny.

Maternal toxicity was evidenced by the significantly reduced body weight gain observed at 800 mg/kg. Delayed ossification (b) (4) (sternum, metacarpals and caudal vertebrae) and reduced fetal and placental weights were observed in the presence of maternal toxicity.

In the rabbit (b) (4) development study, pregnant rabbits were exposed from GD 6 to GD 20. Fexinidazole resulted in abortions in the presence of maternal toxicity (reduced food consumption and reduced body weight gain) at doses of 20 mg/kg/day and above.

8.2 Lactation

Risk Summary

There are no data on the presence of fexinidazole in human milk or the effect on milk production. There are no reports of adverse effects associated with fexinidazole exposure through breastmilk based on a limited number of reported cases. Fexinidazole is present in rat milk *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk..

The developmental and health benefits of breastfeeding should be considered along with the mother's clincal need for fexinidazole and any potential effects on the breastfed infant from fexinidazole or from the underlying condition.

Data

In lactating rats given a single oral dose of 800 mg/kg 14C-fexinidazole, radioactive drug was detected in the milk.

Reviewer comment: Final labeling edits for nonclinical including human dose equivalents are pending.

Appendix A

Table 1: Pregnancy outcome data from clinical study DNDi-FEX-09-HAT[27]

Patient ID/ g-HAT stage	Medical history of pregnancies	Treatment	Estimated pregnancy start	Exposure during pregnancy	SAEs during pregnancy	Delivery date (weight)	Outcome
DNDi-FEX-09-HAT							
(b) (6)	1 alive child	Fexinidazole	141 days before exposure	Yes (2nd T)	No	126 days after EOT (3.5 kg)	Normal female newborn
	3 previous pregnancies with 1 living child and 2 abortions	Fexinidazole	206 days before exposure	Yes (3rd T)	No	23 days after EOT (2.5 kg)	Normal female newborn
	NA	Fexinidazole	237 days before exposure	Yes (3rd T)	No	4 days after EOT (3.0 kg)	Normal male newborn
	3 previous pregnancies with 2 living children, 1 dead child and no abortion	Fexinidazole	146 days before exposure	Yes (2nd T)	No	150 days after EOT (3.1 kg)	Normal female newborn

[27] Applicant's summary of clinical safety, excerpt from Table 68

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LYNNE P YAO
09/04/2020 08:58:20 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 2, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214429
Product Name and Strength:	Fexinidazole Tablets, 600 mg
Applicant/Sponsor Name:	Sanofi-aventis U.S. LLC (Sanofi)
OSE RCM #:	2020-483-2
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels (blistercards) received on September 2, 2020, for Fexinidazole. The Division of Anti-Infectives (DAI) requested that we review the revised container labels (blistercards) for Fexinidazole (Appendix A) to determine they are acceptable from a medication error perspective. The revisions are in response to the Agency's August 26, 2020, information request recommending revising the storage statement on the container labels (blistercards) to read, "Store below 30°C (86°F)" versus (b) (4)

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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09/02/2020 02:05:55 PM

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09/02/2020 09:23:10 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 18, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214429
Product Name and Strength:	Fexinidazole Tablets, 600 mg
Applicant/Sponsor Name:	Sanofi-aventis U.S. LLC (Sanofi)
OSE RCM #:	2020-483-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels (blistercards) and carton labeling (wallet) received on August 18, 2020 for Fexinidazole. The Division of Anti-Infectives (DAI) requested that we review the revised container labels (blistercards) and carton labeling (wallet) for Fexinidazole (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Myers D. Label and Labeling Review for Fexinidazole (NDA 214429). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 21. RCM No.: 2020-483.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DEBORAH E MYERS
08/18/2020 04:35:19 PM

OTTO L TOWNSEND
08/18/2020 05:04:31 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214429
Submission Number	001
Submission Date	3/12/2020
Date Consult Received	4/6/2020
Drug Name	Fexinidazole (HOE239)
Indication	Treatment of human African trypanosomiasis
Therapeutic dose	The proposed dosing regimen includes body-weight based loading and maintenance doses with once daily dosing for 10 days under fed condition (see Section 3.1)
Clinical Division	DAI

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 4/6/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Sponsor's clinical study reports #PH16052 and #PH17016 (link)
- Sponsor's clinical study # DNDiFEX001 Part I (link)
- Sponsor's clinical study # DNDiFEX001 Part II (link)
- Sponsor's clinical study # DNDiFEX001 Part III (link)
- Sponsor's clinical study # DNDiFEX003 (link)
- Sponsor's clinical study # DNDiFEX004 (link)
- Sponsor's clinical study # DNDiFEX005 (link)
- Sponsor's clinical study # DNDiFEX006 (link)
- Sponsor's clinical study # DNDi-CH-FEXI-001 (link)
- Sponsor's clinical study # DNDi-VL-FEXI-001 (link)
- Summary of clinical safety (link);
- Sponsor's propose product label (link); and
- Sponsor's cardiac-safety-report (link)

1 SUMMARY

Fexinidazole administration was associated with a dose and concentration-dependent increases in the QT interval over the range of doses evaluated in this QT assessment. The QTc prolongation appears to be associated with concentrations of fexinidazole's M2 metabolite. Based on the exposure-response relationship, significant QT prolongation is expected at the maximum therapeutic dose (under fed condition) with the mean ΔΔQTcF

of 17.2 (90% CI upper: 20.0) msec. The expected high clinical exposure scenario has not been identified during the development, and the intrinsic and extrinsic factors that can increase the concentrations of M2 metabolite are expected to further increase the QTc interval.

The effect of fexinidazole was evaluated in healthy subjects using data from 2 clinical studies (Studies # DNDiFEX001 and DNDiFEX003). Study # DNDiFEX001 was a randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and pharmacokinetics following single- (Part-I) and multiple (Part-III) ascending doses of fexinidazole under fasting condition. Study # DNDiFEX003 was a randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and pharmacokinetics following multiple ascending doses of fexinidazole under fed condition. The highest dose that was evaluated was 2400 mg once daily (Day 1 to 4), which covers the therapeutic exposures.

The data were analyzed using exposure response analysis as the primary analysis, which suggest that fexinidazole is associated with significant QTc prolonging effect (refer to section 4.5) – see Table 1 for overall results. The reviewer's analysis indicated that QTc prolongation was associated with concentrations of M2 metabolite (section 4.5). This finding is also supported by the sponsor's non-clinical evaluation, which indicated that M2 has higher potential for blocking the hERG channel compared to the parent and its M1 metabolite. The central tendency analysis of QTcF also indicates that the administration of fexinidazole is associated with an increase in QTcF in both healthy subjects. Thus, the findings of exposure response analysis are further supported by the available nonclinical data (section 3.1.2), by-time analysis (section 4.3), and categorical analysis (section 4.4).

Because the highest concentrations are expected on Day 4 during the proposed 10-day dosing regimen, the predicted QT effects are presented for the peak M2 concentrations on Day 4 following maximum therapeutic dose of 1800 mg once daily under fed condition (Section 3.1.1).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Concentration* (ng/mL)	ΔΔQTcF (msec)	90% CI (msec)
QTc	1800 mg	19700	17.2	(14.3 to 20.0)

Administered as 1800 mg once daily for 4 days followed by 1200 mg once daily for 6 days.
**Peak concentrations of M2 metabolite on Day 4; For further details on the FDA analysis please see section 4.*

In a pooled analysis of trials conducted in the g-hat population (DNDiFEX004 and DNDiFEX006), 2 patients had QTc >500 msec and 7 patients had an increase from baseline >60 msec (Table 4). There were no adverse events suggesting arrhythmia per ICH E14 guidelines (i.e., torsades, significant ventricular arrhythmias or sudden cardiac death).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

- We request the IRT-QT team to review the abovementioned three reports. We request the IRT-QT feedback on the adequacy and acceptability of Applicant's proposed language related to QT findings in product labeling.

  Response: The sponsor submitted substitution request for thorough QT study and provided data from 4 clinical studies – 2 studies in healthy subjects (Studies # DNDiFEX001 and DNDiFEX003) and 2 studies in patients with human African trypanosomiasis (Studies # DNDiFEX004 and DNDiFEX006). Our exposure-response assessment included both studies conducted in healthy subjects (Studies # DNDiFEX001, P-I & P-III and DNDiFEX003). In addition, we did include all studies for categorical outlier analysis. Please refer to Section 2 for our recommendations to the proposed label.

- We request the IRT-QT input on need for conducting a thorough QT study, if the QT data from the aforementioned reports are deemed to be not sufficient for purposes of cardiac safety and/or labeling.

  Response: Submitted clinical studies (healthy as well as patient) indicate a dose and concentration-dependent increase in the QT interval. These studies are adequate to characterize the QTc prolongation potential of fexinidazole and can serve as an alternative to the thorough QT study. The results indicate that the QT prolongation is associated with concentration of M2 metabolite of fexinidazole and it is unclear if the intrinsic and extrinsic factors affects the concentration of M2 metabolite of fexinidazole. Potentially higher QT effects are anticipated at the exposures higher those observed at therapeutic doses.

- **Additional Comment:**

  Our analysis indicates that there is the concentration dependent increase in heart rate and the magnitude of mean effect on heart rate at the proposed therapeutic doses is below 10 bpm (see Section 4.5).

  We had difficulties reproducing the sponsor's analysis (see e.g., eCTD 0018 Table 2 vs Table 4 in the review) and several IRs were issued in an attempt to resolve this issue. Inspection of the provided datasets suggests that the differences were potentially due to the use of different datasets and that the sponsor's analysis was likely based on centrally read data vs the reviewer's analysis based on automatic ECG data (section 4.4.1). Because the analysis results are similar, we recommend reporting the results as reported by the sponsor, which is based on centrally-read ECGs.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

The sponsor proposed QT labeling language for Section 5, 6, 7 of the product label submitted to SDN001 (link). However, no QT labeling language was proposed by the

sponsor in the section 12.2. Below are proposed edits from the IRT. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

5.2 QT Interval Prolongation

(b) (4) been shown to prolong the QT interval in a concentration-dependent manner [Clinical Pharmacology (12.2)]. Treatment with (b) (4) caused an average increase of 19 ms in the QTcF interval. In clinical studies, (b) (4) patients (b) (4) fexinidazole (b) (4) had a QTcF >500 msec (b) (4)

Avoid (b) (4) in patients who have:

- QTcF interval is greater than 470 msec
- a history of Torsades de pointes, congenital long QT syndrome, cardiac arrhythmias, uncompensated heart failure, or family history of sudden death
- (b) (4)

(b) (4)

If patients are, or need to be, treated with drugs known to prolong QTcF interval or to induce bradycardia either do not initiate fexinidazole until such drugs are eliminated from the body (allow a washout period of 5 half-lives), or do not start such drugs until fexinidazole is eliminated from the body (allow a washout period of 7 days).

Outlier analysis was based on data from studies DNDiFEX004 and DNDiFEX006. Please see additional comment under section 1.2 and section 4.4.1 for additional details.

6 ADVERSE REACTIONS

(b) (4)

QT interval prolongation

(b) (4)

(b) (4)

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions

Drugs that ~~May~~ Prolong the QT Interval and/or Induce Bradycardia

(b) (4) with drugs (b) (4) known to block potassium channels (such as antiarrhythmics, neuroleptics, fluoroquinolones, imidazole and triazole antifungals, pentamidine), prolong the QT interval (such as antimalarials, phenothiazines, tricyclic antidepressants, terfenadine and astemizole, IV erythromycin, and quinolone antibiotics) and/or induce bradycardia (such as β-blockers) (b) (4) [see Warnings and Precautions (5.2) (b) (4)

In general, we have not routinely included drugs that induce bradycardia in this section.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Concentration-dependent QTcF prolongation was observed with (b) (4) administration of (b) (4). Based on the exposure-response relationship, the mean (upper 90% confidence interval) increase in QTcF is predicted to be 19.0 msec (23.3 msec) at the (b) (4) recommended (b) (4). The observed increase in QTcF appears to be associated with the M2 metabolite of fexinidazole.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance. The predicted mean increase in QTcF is based on a linear-mixed effects model of the healthy subject studies (Studies # DNDiFEX001, P-I & P-III and DNDiFEX003) using the M2 metabolite exposure as the only concentration covariate as it appears to be the driver of the observed QTcF prolongation. Using this model, we predicted the effect using the expected Cmax on day 4 as we expect peak M2 concentration at that day (Table 1). Since the sponsor's model predicted QT effects of similar magnitude, we propose to use those numbers on the product label.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Sanofi-Aventis is developing fexinidazole for the treatment of human African trypanosomiasis (NDA-214429). Human African trypanosomiasis is a tropical diseases caused by infection of two subspecies of Trypanosoma brucei - T.b.gambiense and T.b.rhodesiense and it has 2 clinical stages (1: hemo-lymphatic and 2: meningo-encephalitic). Fexinidazole (HOE239; MW: 279.31) is antiprotozoal (5-nitroimidazole derivatives, antiparasitics) drug. It is believed that fexinidazole acts through bioactivation by nitroreductase enzymes generating reactive amines leading to toxic and mutagenic effects. The product is formulated as immediate-release uncoated tablet formulation (b) (4) containing 600 mg fexinidazole for oral administration. The sponsor also utilized suspension formulation during the early clinical development.

The proposed dosing regimen includes loading and maintenance doses with once daily dosing for 10 days under fed condition (1800 mg once daily for 4 days followed by 1200 mg once daily for 6 days in adults patients ≥ 35 kg; and 1200 mg once daily for 4 days followed by 600 mg once daily for 6 days in pediatric patients age ≥ 6 years and weight ≥ 20 kg and < 35 kg). Fexinidazole undergoes (oxidative) metabolism forming - fexinidazole sulfoxide (M1), which is further metabolized to fexinidazole sulfone (M2). Data from in vitro studies indicated that these metabolites (i.e., M1 and M2) have equivalent pharmacological activity compared to the parent drug. The mean peak concentrations of 836 ng/mL for fexinidazole (Tmax: ~4 h; half-life ~14 h), 8036 ng/mL for M1 (Tmax: ~4 h; half-life ~13 h) and 19580 ng/mL for M2 (Tmax: ~6 h; half-life ~24 h) are expected at steady-state (Day 4) with the anticipated therapeutic dose (Study # DNDiFEX003; Cohort 1). Studies indicate that M1 and M2 exhibit non-linear pharmacokinetics with relatively lower exposures at higher doses. The product exhibits a positive food effect with 3 to 4-fold increase in exposure (fexinidazole, 4-fold; M1, 3-fold; and M2, 2.5-fold for Cmax) was observed following its administration with a standard high-fat meal compared to that under fasting condition (Study # DNDiFEX001-Part II). In clinical studies (DNDiFEX004, DNDiFEX005, DNDiFEX006), it was recommended to administered fexinidazole under fed condition.

The sponsor claims that fexinidazole is mainly metabolized to M1 by several CYP450 enzymes (CYP3A4 fm: ~12%) and FMOs (fm: ~5%) (Study # EIH0019). The studies indicate that M1 is also metabolized by several CYP450 enzymes (CYP3A4 fm: ~30%; minor: CYP1A1, -1A2, -2B6, -2D6, -2E1) and FMOs (~19%; FMO1, -3 and -5). The sponsor highlights that M1 metabolized mainly to M2 and M2 is not significantly metabolized. No formal clinical drug interaction studies have been conducted by the sponsor. Expected high clinical exposure scenario was not identified during the development and clinical pharmacology studies characterizing potential worst-case scenario for the parent drug and metabolites due to drug interaction or organ impairment (severe renal impairment or hepatic impairment) were not performed.

The sponsor conducted 2 clinical studies in healthy subjects (sub-Saharan male) evaluating the safety, tolerability, and PK of oral fexinidazole (Studies # DNDiFEX001 and

DNDiFEX003). In addition, the sponsor conducted 2, phase 2/3, pivotal, randomized, open-label, multi-center, clinical studies evaluating safety and efficacy of fexinidazole in target population (Studies # DNDiFEX004 and DNDiFEX006). The sponsor included available PK/ECG data from these clinical studies conducted in healthy subjects (ΔQTcF; Studies # DNDiFEX001 and DNDiFEX003) and patients with human African trypanosomiasis (ΔQTcSS; Studies # DNDiFEX004 and DNDiFEX006) in their exposure response analysis. The sponsor's QT assessment plan was not previously evaluated by the IRT (see Appendix, section 5).

Study # DNDiFEX001 was a randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and pharmacokinetics following single- (Part-I) and multiple (Part III) ascending doses of fexinidazole (as extemporaneous suspension) under fasting condition. The study also evaluated comparative bioavailability between oral suspension and tablet (Part II) and included exploratory assessment of food effect using a 3-way crossover design.

Part I of the study was a randomized, double-blind, placebo-controlled, parallel group, single ascending dose study which included 9 dosing cohorts (100, 200, 400, 800, 1200, 1800, 2400, 3000, and 3600 mg; n=72; 6 active + 2 placebo per dose cohort) under fasting condition. Since the maximum tolerated dose was not reached, study included 2 additional cohorts (i.e., 3000 and 3600 mg; per protocol). ECGs (12-lead) were collected at pre-dose, 1, 2, 3, 4, 6, 8, 12, and 24 h post-dose on Day 1. PK samples for determination of fexinidazole and its metabolites (M1 & M2) were collected on Day 1 through Day 7 (using a validated LC-MS/MS method). PK samples were planned at pre-dose (baseline) and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, and 24 h post-dose. In addition, samples were planned on Days 3 (48 h), 4 (72 h), 5 (96 h), 6 (120 h), 7 (144 h), and 8 (168 h).

Part III of the study was a randomized, double-blind, placebo-controlled, parallel group, multiple ascending dose study which included 3 dosing cohorts (1200, 2400, and 3600 mg; n=27) under fasting condition. ECGs (12-lead) were collected at pre-dose, 1, 2, 3, 4, 6, 8, 12, and 24 h post-dose on Day 1 and at 2 and 24 h on Day 7. PK samples for determination of fexinidazole and its metabolites (M1 & M2) were collected on Day 1, Day 7, Day 14 including pre-dose samples on Days 3, 4, 9, 11, and 13 (using a validated LC-MS/MS method). PK Samples were planned at pre-dose (baseline) and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, and 24 h post-dose on Day 1, 7 and 14. In addition, samples were planned on Days 17 (48 h), 18 (72 h), 19 (96 h), 20 (120 h), 21 (144 h), and 22 (168 h) following last dose.

Study # DNDiFEX003 was a double-blind, placebo controlled, randomized multiple ascending study. Since fexinidazole exhibits a positive food effect with 3 to 4-fold increase in exposure under fed condition compared to that under fasting condition (Study # DNDiFEX001), the sponsor conducted multiple ascending dose study under fed condition (a light standard breakfast) using 2 dose cohorts (n=36; 24 active + 12 placebo). Subjects received 1800 mg (3 × 600 mg tablets or matching placebo) once daily for 4 days (Days 1 through 4), followed by 1200 mg (2 × 600 mg tablets or matching placebo) once daily for 6 days (Days 5 through 10) under fed condition in dosing cohort 1 (n=18; 12 active + 6 placebo). Similarly, subjects received 2400 mg (4 × 600 mg tablets or matching placebo) once daily for 4 days (Days 1 through 4), followed by 1200 mg (2 × 600 mg tablets or matching placebo) once daily for 6 days (Days 5 through 10) under fed condition in dosing cohort 2 (n=18; 12 active + 6 placebo). PK samples for determination of fexinidazole and

its metabolites (M1 & M2) were collected on Day 1, Day 4, Day 7, and Day 10 (using a validated LC-MS/MS method). PK samples were planned at pre-dose (baseline) and at 0.5, 1, 2, 3, 4, 6, 9, 12, 16, and 24 h post-dose. In addition, samples were planned on Day 12 (48 h), 13 (72 h), 14 (96 h), 15 (120 h), 16 (144 h), and 17 (168 h) following last dose. Continuous ECG monitoring was performed on Day -1, Day 4, Day 7, and Day 10.

Study # DNDiFEX004 was conducted in late stage 2 patients (age ≥ 15 years; n=394; 264 on fexinidazole and 130 on NECT). Subjects received 1800 mg (3 × 600 mg tablets) once daily for 4 days (Days 1 through 4), followed by 1200 mg (2 × 600 mg tablets) once daily for 6 days (Days 5 through 10) under fed condition. Study included active comparator nifurtimox-eflornithine combination therapy (three times daily at a dose of 15 mg/kg/day for 10 days). Study included pre-screening, screening, treatment period (10 days, hospitalization), 18-month follow-up until the primary efficacy endpoint assessment, additional 6-month follow-up until the end of the study. Pharmacokinetic samples were collected for the measurement of fexinidazole and its metabolites, M1 and M2, in the whole blood (using DBS) for all patients in the fexinidazole group. Samples were collected on Day 8: 3 hours, 15 minutes post-dose, Day 9: 3 hours post-dose; Day 10: 3 hours, and 7 hours, 15 minutes post-dose; Day 11: 24 hours post-dose (relative to last dose on Day 10); Day 12: 48 hours post-dose (relative to last dose on Day 10). ECGs (triplicate) were recorded at: baseline; Day 4 (4 hours and 23 hours post-dose); and Day 10 (between 2 and 3 h post-dose). The ECG measurements on Day 4, at 23 hours post-dose (i.e., 1 hour before study treatment administered on Day 5) were also used as a safety assessment; if QTcF was >500 ms, a second ECG was performed after a 10- to 20-minute rest. If the value was confirmed, the patient was withdrawn from the study, and no further doses of fexinidazole were administered.

Study # DNDiFEX006 was conducted in children with HAT (age ≥ 6 years over 20 kg and < 15 years; n=394; single arm). Subjects received body-weight based dosing: 1) ≥ 35 kg group: 1800 mg (3 × 600 mg tablets) once daily for 4 days (Days 1 through 4), followed by 1200 mg (2 × 600 mg tablets) once daily for 6 days (Days 5 through 10) under fed condition and 2) ≥ 20 kg and < 35 kg: 1200 mg (2 × 600 mg tablets) once daily for 4 days (Days 1 through 4), followed by 600 mg (1 × 600 mg tablets) once daily for 6 days (Days 5 through 10) under fed condition. Study included pre-screening, screening, treatment period (10 days, hospitalization), 12-month follow-up until the primary efficacy endpoint assessment, additional 6-month follow-up until the end of the study. Pharmacokinetic samples were collected for the measurement of fexinidazole and its metabolites, M1 and M2, in the whole blood (using DBS). Samples were collected on Day 10: 3 hours, and 7 hours, 15 minutes post-dose; Day 11: 24 hours post-dose (relative to last dose on Day 10); Day 12: 48 hours post-dose (relative to last dose on Day 10). ECGs (triplicate) were recorded at: baseline; Day 4 (4 hours and 23 hours post-dose); and Day 10 (between 2 and 3 h post-dose). The ECG measurements on Day 4, at 23 hours post-dose (i.e., 1 hour before study treatment administered on Day 5) were also used as a safety assessment; if QTcF was >500 msec, a second ECG was performed after a 10- to 20-minute rest. If the value was confirmed, the patient was withdrawn from the study, and no further doses of fexinidazole were administered.

The sponsor included data from all 4 clinical studies for the evaluation of QT effects of fexinidazole using exposure response analysis. In addition, the sponsor utilized ECG data

from studies # DNDiFEX005 (no PK), DNDi-CH-FEXI-001, and DNDi-VL-FEX-001 for summary. In both patient studies (Studies # DNDiFEX004 and DNDiFEX006), the concentrations fexinidazole and its metabolites (M1 and M2) were determined using dry blood sampling techniques and the POP-PK model was used to predict the concentrations at the ECG collection time. Moreover, these studies were not placebo control.

The reviewers included clinical studies conducted in healthy subjects (Studies # DNDiFEX001 and DNDiFEX003) for concentration-QT analysis (see Section 4.5) and data from studies # DNDiFEX004 and DNDiFEX006 were utilized for conducting categorical analysis and safety analysis.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's summary of clinical pharmacology studies (m2.7.2) and non-clinical overview (m2.4). The sponsor claims that no significant changes in hERG peak tail current were observed at the highest studied concentrations for fexinidazole (~11% at 30 μM i.e., 8380 ng/mL; PPB: 90.7 to 95.4%; mean peak Cmax, free: ~78 ng/mL) and its M1 metabolite (~2% at 30 μM i.e., 8860 ng/mL; PPB: 25.9 to 33.9%; mean peak Cmax, free: ~5955 ng/mL). However, significant changes in hERG peak tail current were observed at the highest studied concentrations for M2 metabolite (~33% at 30 μM i.e., 9340 ng/mL; PPB: 33.7 to 41.6%); mean peak Cmax, free: 13000 ng/mL). Thus, the sponsor's analysis indicate that M2 has a significant higher potential of hERG inhibition compared to the parent and its M1 metabolite (Study # 0507-2007; link).

HEK 293 cells stably transfected with hERG cDNA were used for patch clamp experiments in voltage clamp configuration. Onset and steady state blockade of the hERG channel current (IKr) due to the test items were monitored using a pulse pattern with fixed amplitudes (first depolarization: -50 mV for 500 ms; second depolarization: +20 mV for 2 seconds; hyperpolarization: -50 mV for 7 seconds). The current amplitude at the onset of the second step to –50 mV ("peak tail current") was monitored until a steady state was obtained in vehicle solution and then the test item was applied to the bath solution at 37°C. At the end the reference item was applied to block 100% of the current for determination of the current "leak" response to the stimulation protocol. The effect of the test items was ascertained by calculating the residual current as percentage of control (% control). All data were corrected for "leak" current by subtracting the response in presence of 300 nM of the positive control E4031. Each test item was tested at three concentrations: 1, 5, and 30 μM.

Exposure to fexinidazole and fexinidazole sulfoxide (metabolite M1) did not reduce hERG residual tail current at any of the doses tested. Only the highest dose (30 μM, 9.34 μg/mL) of fexinidazole sulfone (metabolite M2) showed a decrease on hERG peak tail current to 67.41 ± 2.24% of control, which was considered significant.

Each of 4 male Beagle dogs received a single oral administration of the vehicle and of fexinidazole at escalating doses of 100, 300 and 1000 mg/kg (Study # 0506-2007). The interval between each dose was 4 days. Oral administration of fexinidazole at doses of 100, 300 and 1000 mg/kg to Beagle dogs did not have any meaningful effect on blood pressure, HR and ECG intervals, including the QT interval. Body temperature was moderately increased between 2 and 5 hours after administration at doses of 300 and 1000 mg/kg (+0.6 and +1.0°C, respectively).

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The sponsor's primary analysis is based on concentrations-QTc analyses. Please see section 3.2.3 for additional details.

Reviewer's Comments: *The sponsor presented by-time central tendency analysis --- mean changes from baseline --- in Table 6 (link) and figure 6 (link) within the appendix of report Ph16052, which consists of analyses for studies DNDIFEX001 and DNDIFEX003. However, due to the small sample size, the FDA statistical reviewer used non-parametric method (Hodges-Lehman Estimate, median). Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

Sponsor's categorical analysis are based on dosed-cohorts and results are presented as table below:

Population	Healthy Volunteers		Patients	
Studies	DNDIFEX001	DNDIFEX003	FEX004	FEX006
QTcF > 500 msec	0	0	2	0
ΔQTcF > 60 msec	0	0	3	3
QTcSS > 500 msec			1	0
ΔQTcSS > 60 msec			1	3

Source: Sponsor's cardiac safety report, Table 3 and Table 4, page 33.

Reviewer's Comments: *The results of the reviewer's analysis (section 4.4.1) are marginally different than the sponsor's results. There were more ΔQTcF observations greater than 60 msec in reviewer's analysis (6 vs 14). As noted in section 4.4.1, the sponsor's analysis appears to be based on overread ECGs whereas the analysis by the reviewer is based on datasets that appear to include automatic ECG measurements. Combination of the datasets results in 7 patients with QTcF > 60 msec vs sponsor's reported 6.*

3.2.3 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between concentration of fexinidazole (and its metabolites) and ΔQTcF (change from baseline in QTcF) using PK/ECG data from clinical studies conducted in healthy subjects (Studies # DNDiFEX001 and DNDiFEX003) and patients with human African trypanosomiasis (ΔQTcSS; Studies # DNDiFEX004 and DNDiFEX006).

The sponsor's model included a treatment specific intercept, a slope for M2 concentrations and a random subject specific intercept. In addition, a specific intercept was estimated for

digitalized paper ECGs. The sponsor claims that the ECG collection methodology (paper vs. digital) did not impact the assessment significantly. However, the precision for intercept with paper ECGs (digitalized; RSE=71%, p=0.16) were lower compared to digital ECGs. The sponsor highlighted that following Tmax, fexinidazole concentrations rapidly decreased whereas ΔQTcF continued to increase. A similar observation was made for the metabolite M1 but not for metabolite M2. Only a positive slope estimated at 0.00138 msec per ng/mL was found significant thus suggesting that changes in QTcF after single dose increased with M2 concentrations. The 90% CI upper bound was above the threshold of 10 msec at doses of 2400 and 3600 mg given in fasted condition and at a dose of 1200 mg administered under fed condition. Similarly, the increase in ΔQTcF appeared significantly related to M2 concentrations following multiple dosing. The sponsor highlights that the concentration-response models developed using M2 concentrations described – 1) the cumulative effect on ΔQTcF resulting from the accumulation of M2 following multiple-dosing; and 2) the dissipation of effects on ΔQTcF with decreasing M2 concentrations following the last dose.

Based on the sponsor's model, the predicted ΔΔQTcF values at geometric mean Cmax (90% CI, lower and upper) for the proposed maximum dosing regimen (i.e., 1800 mg once daily for 4 days and 1200 mg once daily for 6 days) were between 15 and 23 msec. Similarly, the estimated ΔΔQTcF and 90% CI (using bootstraps) at the proposed therapeutic dose (under fed condition) were 19.0 ms (90% CI = 15.1, 23.3) (Study # DNDiFEX003). Similarly, the estimated ΔQTcSS at highest exposure GM for DNDiHATFEX004 study was 19.1 ms (90% CI 17.5; 20.7) and 16.0 ms (90% CI 13.8; 18.2) for DNDiHATFEX006 study. Since concentrations data for fexinidazole ant its (M1 and M2) metabolites were not determined at all time points of ECG measurement, the sponsor used predicted concentrations using POP-PK model. Nevertheless, the magnitude of QTc increase observed in the patient studies agrees with the above described studies in healthy subjects at the therapeutic doses (Studies # DNDiFEX001 and DNDiFEX003).

Reviewer's comment: Concentration (metabolite M2) dependent increase in QTc interval was observed. The conclusion of the reviewer's analysis agreed with the sponsor's analysis. Please see section 4.5 for additional details.

3.2.4 Safety Analysis

In the pooled safety analysis of 3 clinical trials in the g-hat population, 39/619 (6%) patients treated with fexinidazole experienced a total of 44 cardiac disorders TEAEs: palpitations (22/619 [4%] patients; 26 TEAEs), tachycardia (4/619 [<1%] patients; 4 TEAEs) and sinus tachycardia (1/619 [<1%] patients; 1 TEAE). None of the cardiac disorders TEAEs were severe in intensity.

The sponsor reports no adverse events of clinical importance per ICH E14 guidelines (i.e., significant ventricular arrhythmias or sudden cardiac death) in the development program in patients receiving fexinidazole.

Reviewer's comment: While, no adverse events of clinical importance was observed significant concentration-dependent QTc prolongation was observed (section 4.5) including observations of >500 msec together with an increase over baseline of 60 msec (section 4.4.1). Moreover, electrolyte abnormalities were also observed in fexinidazole treated patients.

4 REVIEWERS' ASSESSMENT

The reviewer's assessment is based on the datasets listed below in Table 2.

Table 2: Datasets used in reviewer's analysis

Study	Dataset[a]
DNDiFEX001 parts 1 - 3	rootpath\0007\m5\datasets\fex001pt1\analysis\adam\datasets\adeg.xpt
DNDiFEX001 part 3	rootpath\0007\m5\datasets\fex001pt1\analysis\adam\datasets\adegholt.xpt
DNDiFEX003	rootpath\0006\m5\datasets\fex003\analysis\adam\datasets\adegholt xpt
DNDiFEX004	rootpath\0006\m5\datasets\dndifex004\analysis\adam\datasets\adeg xpt
DNDiFEX006	rootpath\0006\m5\datasets\dndifex006\analysis\adam\datasets\adeg xpt

[a]: rootpath is \\cdsesub1\evsprod\nda214429

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 bpm) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

ECGs of all three parts of Study # DNDiFEX001 were captured in paper ECGs, while Holter ECGs were also used in Part III. Digital ECGs from Study # DNDiFEX001 (Part III), 003, 004, 006 were uploaded to the ECG warehouse. Paper ECGs were read automatically (machine read), digital ECGs were read blindly and semi-automatically by a core lab. Both data from paper and digital ECGs were used in our review. Overall ECG acquisition and interpretation in these studies appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

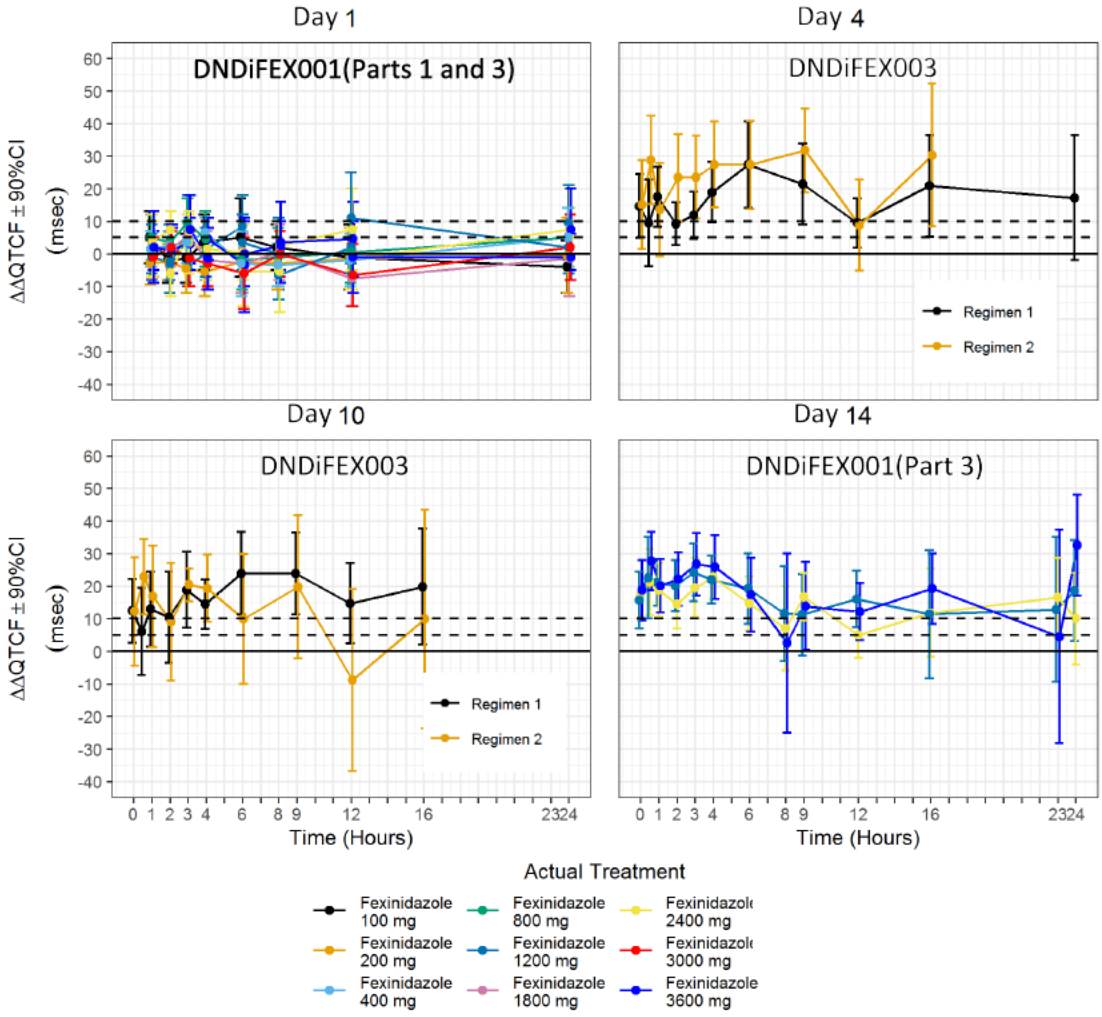
Sponsor submitted studies DNDiFEX001 and DNDiFEX003 which enrolled healthy volunteers, and HEX004 and FEX006 which enrolled patients. By-time analysis are based on DNDiFEX001 and DNDiFEX003.

Given the smaller sample size for all dose cohorts (n=6 to 12), the statistics reviewer applied non-parametric statistics (e.g. Hodges-Lehman Estimate, median) and its 90% CI interval of ΔΔQTcF by time. No positive control group included in both studies. All figures present the time points up to 24 hours.

4.3.1 QTcF

Figure 1 displays the time profile of ΔΔQTcF for different dose groups showing a greater increase in ΔΔQTcF where M2 metabolite concentrations are also higher, which is consistent with the findings of the exposure-response analysis (section 4.5).

Figure 1: Median and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).



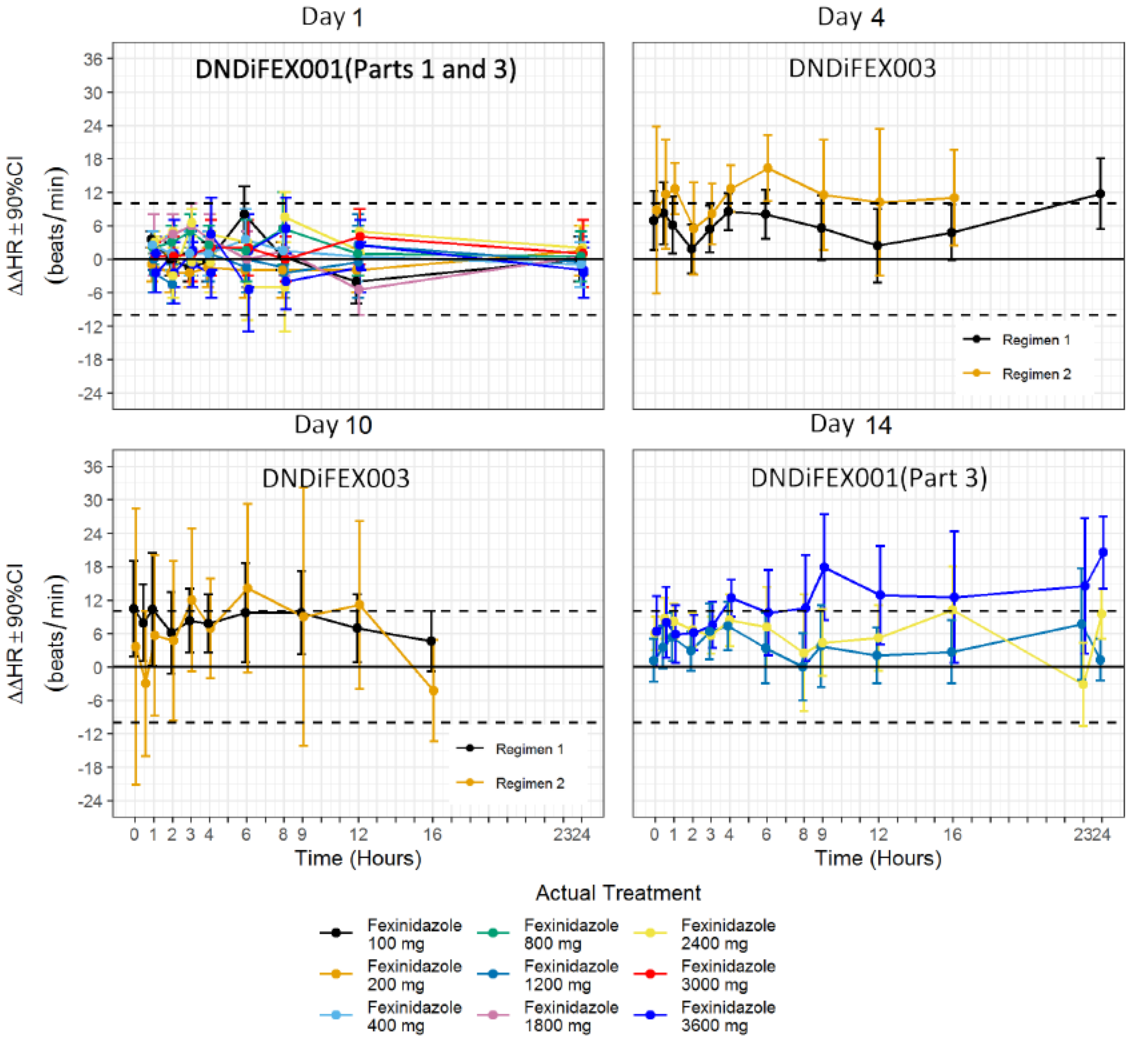
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different dose cohorts. Large estimated median ΔΔHR were observed at Day 4 and Day 10 for sequence regimen 2 (which has higher dosage then regimen 1 at Day 4) in study DNDiFEX003 and at Day 14 for treatment Fexinidazole 3600 mg (which is the highest dose level in the repeated dosing study) in study DNDiFEX001 Part 3.

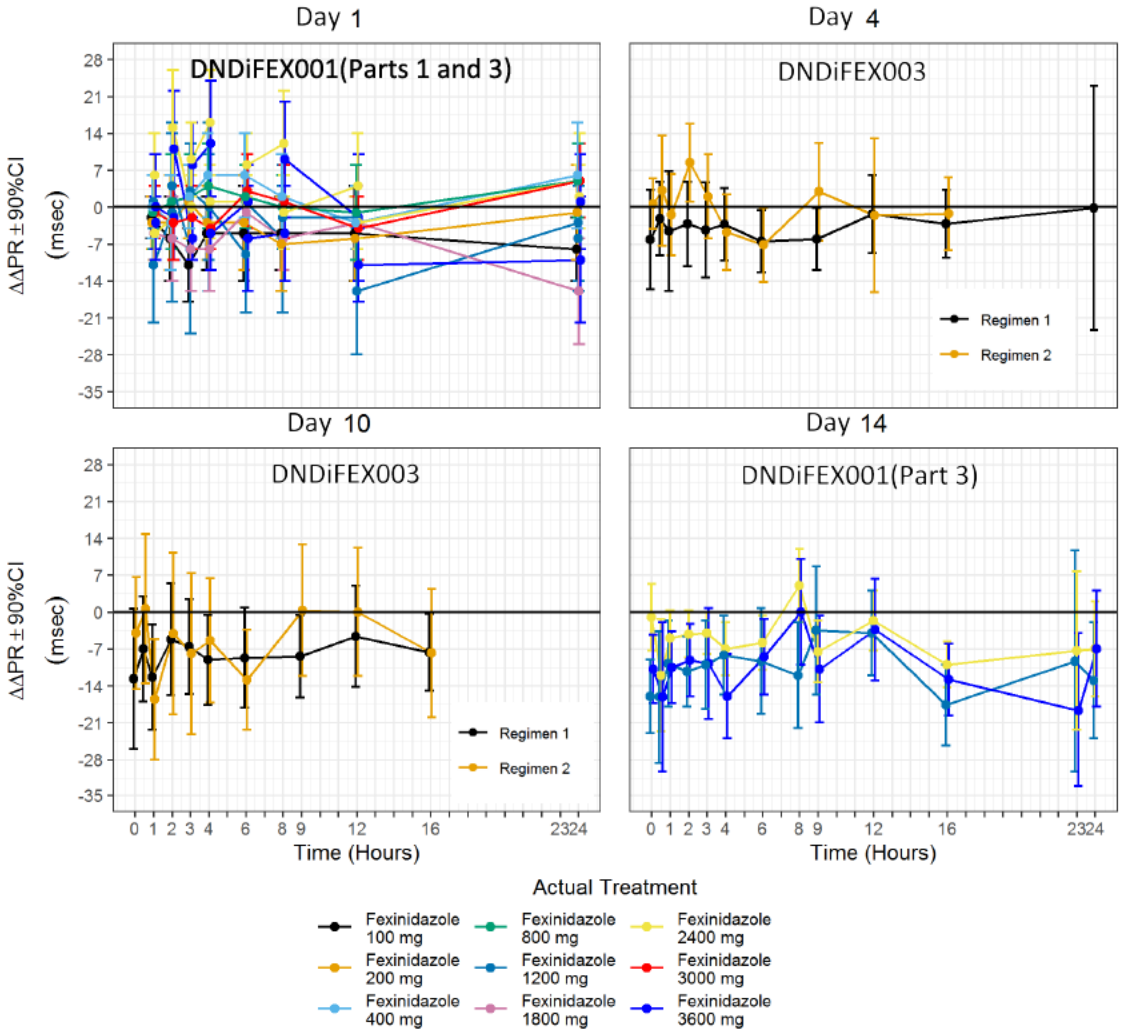
Figure 2: Median and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different dose groups. The ΔΔPR profile does not suggest drug-induced increase in the PR interval.

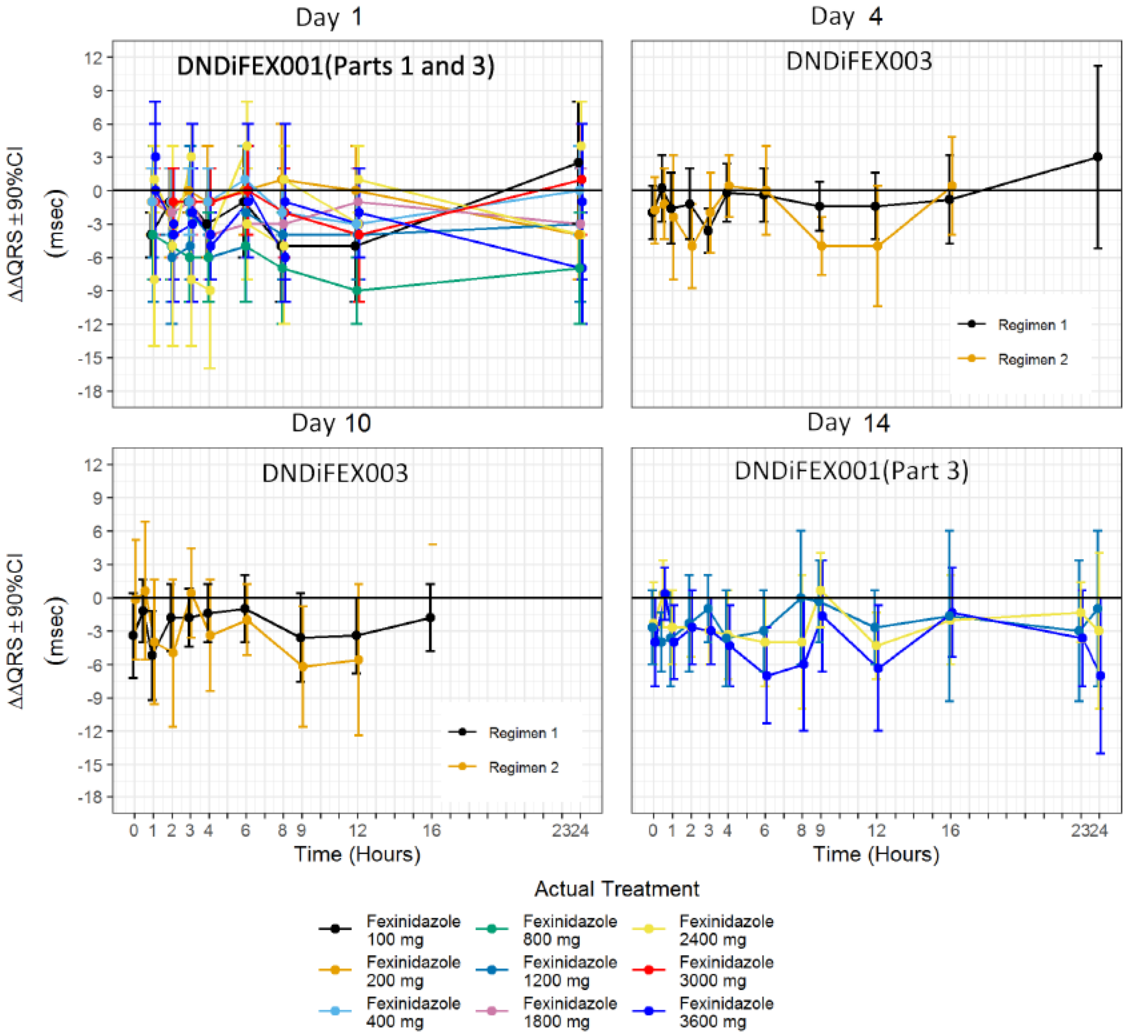
Figure 3: Median and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different dose groups. The ΔΔQRS profile does not suggest effects on the QRS duration.

Figure 4: Median and 90% CI of ΔΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

Categorical analysis is based on (i) healthy subjects from DNDIFEX001 and DNDIFEX003 and (ii) patients from FEX004 and FEX006. For FEX004 and FEX006, the categorical analysis was limited to the first 11 days.

4.4.1 QTc

Table 3 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 msec, between 450 and 480 msec, between 480 and 500 msec and > 500 msec with or without ΔQTcF > 60 msec. Two subjects had QTcF > 500 msec and ΔQTcF > 60 msec, which was confirmed at several time-points consistent with the increase in QTc

observed in the by-time analysis (Figure 1) and concentration-dependent analysis (Figure 7).

Table 3: Categorical Analysis for QTcF

Population	Total (N)		Value <= 450 msec		450 msec < Value <= 480 msec		480 msec < Value <= 500 msec		Value > 500 msec & < 60 msec		Value > 500 msec & >= 60 msec	
	# Subj	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Healthy volunteers	134	2160	134 (100.0%)	2160 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Patients	509	2674	466 (91.6%)	2596 (97.1%)	38 (7.5%)	71 (2.7%)	2 (0.4%)	3 (0.1%)	1 (0.2%)	2 (0.1%)	2 (0.4%)	2 (0.1%)

Table 4 lists the categorical analysis results for ΔQTcF (≤ 30 msec, between 30 and 60 and > 60 msec). One subject from healthy volunteers and 14 subjects from patients had ΔQTcF > 60 msec.

Table 4: Categorical Analysis for ΔQTcF

Population	Total (N)		Value <= 30 msec		30 msec < Value <= 60 msec		Value > 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Healthy volunteers	134	2160	107 (79.9%)	2024 (93.7%)	26 (19.4%)	135 (6.2%)	1 (0.7%)	1 (0.0%)
Patients	509	2674	330 (64.8%)	2266 (84.7%)	165 (32.4%)	380 (14.2%)	14 (2.8%)	28 (1.0%)

Reviewer's comment: *The results presented above differ from the sponsor's analysis presented in eCTD 0018 (link, Table 2), which shows 6 patients with a ΔQTcF > 60 compared to the 14 above. Using the dataset analysis dataset provided for the patient studies (submitted to eCTD 0008 as adpkpd), the number of outliers is 5. Inspection of one patient meeting the criteria in the reviewer's analysis, but not the analysis dataset (FEX006 (b) (6) reveals that the ECG meeting the criteria (Day 4 – pre-dose) measured 504 msec in the adeg dataset used by the reviewer but was reported as 425 msec in the analysis dataset consistent with the QT value in the ECG warehouse (link). The datasets used in the analysis by reviewer is therefore likely based on automatic measurements by the ECG device, where the latter dataset is likely the centrally over-read measurements. Combining the two datasets and preferring measurements present in the analysis dataset results in 7 patients with QTcF > 60 msec.*

4.4.2 HR

Table 5 lists the categorical analysis results for maximum HR (≤ 100 bpm and >100 bpm). One subject from healthy volunteers and 114 subjects from patients had post-baseline HR >100 bpm. These findings are indicative of a potential drug-induced increase in HR consistent with the increase in HR that was observed in the by-time analysis (Figure 2).

Table 5: Categorical Analysis for HR

Population	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Healthy volunteers	134	2160	133 (99.3%)	2159 (100.0%)	1 (0.7%)	1 (0.0%)
Patients	509	2674	395 (77.6%)	2419 (90.5%)	114 (22.4%)	255 (9.5%)

4.4.3 PR

Table 6 lists the categorical analysis results for PR (≤ 200 msec; between 200 and 220 msec and > 220 msec with and without 25% increase over baseline). One subject from healthy volunteers and 6 subjects from patients had PR >220 msec with >25% increase over baseline. The increase in PR observed for these patients do not appear to be consistent across time-points within each subject and is therefore unlikely drug related. Moreover, no apparent increase in PR was observed in the by-time analysis (Figure 3).

Table 6: Categorical Analysis for PR

Population	Total (N)		Value <= 220 msec		Value > 220 msec & < 25%		Value > 220 msec & >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Healthy volunteers	134	2160	130 (97.0%)	2143 (99.2%)	3 (2.2%)	10 (0.5%)	1 (0.7%)	7 (0.3%)
Patients	509	2659	493 (96.9%)	2623 (98.6%)	10 (2.0%)	27 (1.0%)	6 (1.2%)	9 (0.3%)

4.4.4 QRS

Table 7 lists the categorical analysis results for QRS (≤ 120 msec and > 120 msec with and without 25% increase over baseline). Two subjects from patients had QRS > 120 msec with >25% increase over baseline. For one of the patients, the increase in QRS was only observed at day 10 and it is therefore not clear that this observation was drug related. Moreover, no apparent increase in QRS was observed in the by-time analysis (Figure 4).

Table 7: Categorical Analysis for QRS

Population	Total (N)		Value <= 120 msec		Value > 120 msec & < 25%		Value > 120 msec & >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Healthy volunteers	134	2160	131 (97.8%)	2157 (99.9%)	3 (2.2%)	3 (0.1%)	0 (0%)	0 (0%)
Patients	509	2674	504 (99.0%)	2659 (99.4%)	3 (0.6%)	13 (0.5%)	2 (0.4%)	2 (0.1%)

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between ΔQTcF and fexinidazole (or metabolite) concentrations. Exposure-response analysis was

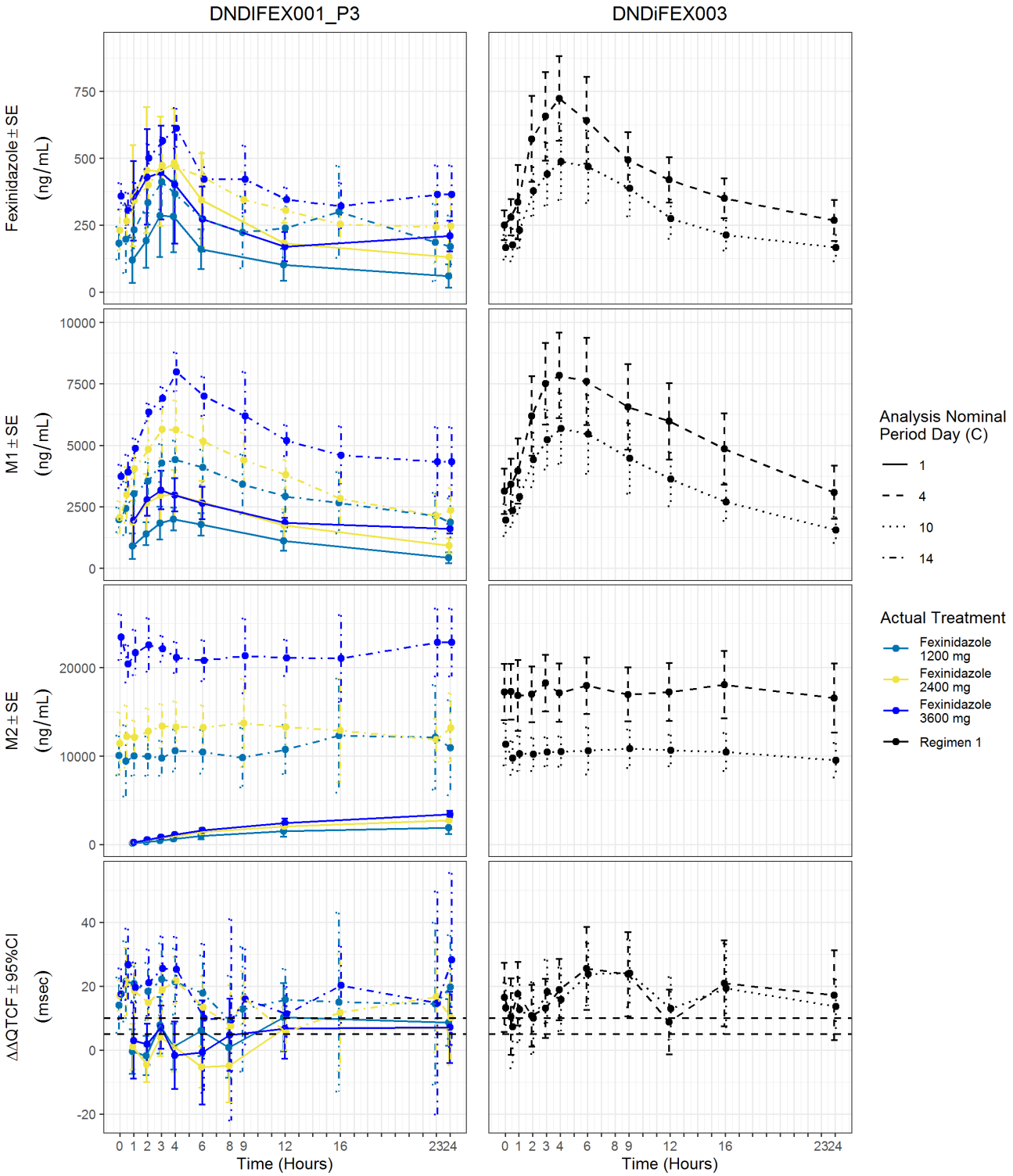
conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK (Studies # DNDiFEX001, Part-1 & 3; and DNDiFEX003; see Section 3.1).

4.5.1 QTc

Prior to evaluating the relationship between fexinidazole concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between fexinidazole concentration and ΔΔQTc and 3) presence of non-linear relationship.

An evaluation of the time-course of fexinidazole and its metabolites concentration and changes in ΔΔQTcF is shown in Figure 5. This analysis suggests that the changes in ΔΔQTcF are associated with M2 concentrations. This finding is consistent with the sponsor's non-clinical assessment, which indicated that M2 has higher potential for blocking the hERG channel compared to the parent and its M1 metabolite (Study # 0507-2007). Figure 2 shows the time-course of ΔΔHR, which indicates the effect of drug on the heart rate which appears to be drug related (see Section 4.3.2 and 0). The exposure response analysis confirmed the concentration dependent increase in heart rate and indicted the magnitude of mean effect on heart rate at the proposed therapeutic doses is below 10 bpm (ΔΔHR: 8.7 bpm; 90% CI: 7.0 to 10.4 bpm; data not shown).

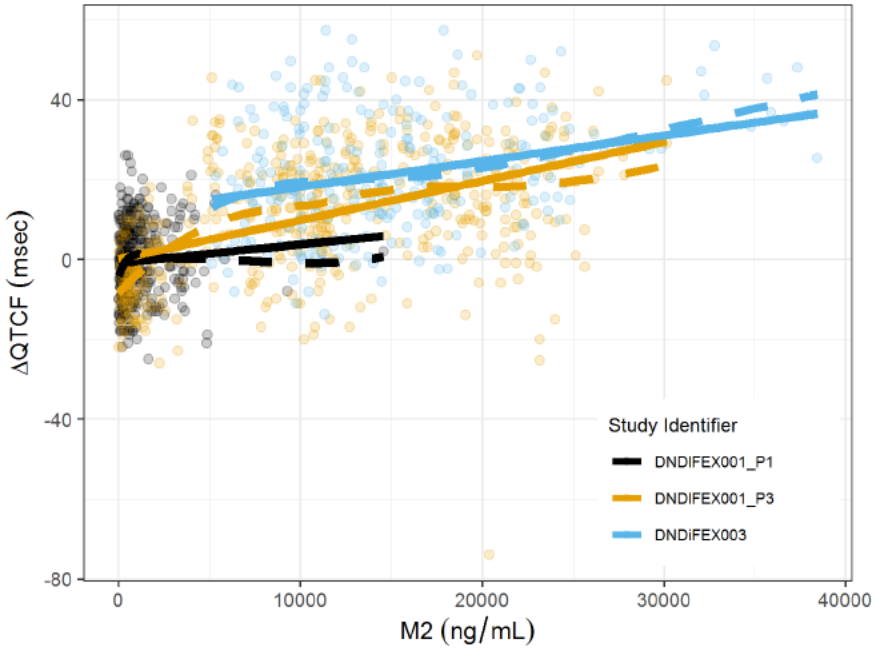
Figure 5: Time course of fexinidazole concentration (top), metabolites (M1 and M2, middle) and QTc (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between M2 metabolite concentration and ΔQTcF was evaluated to determine

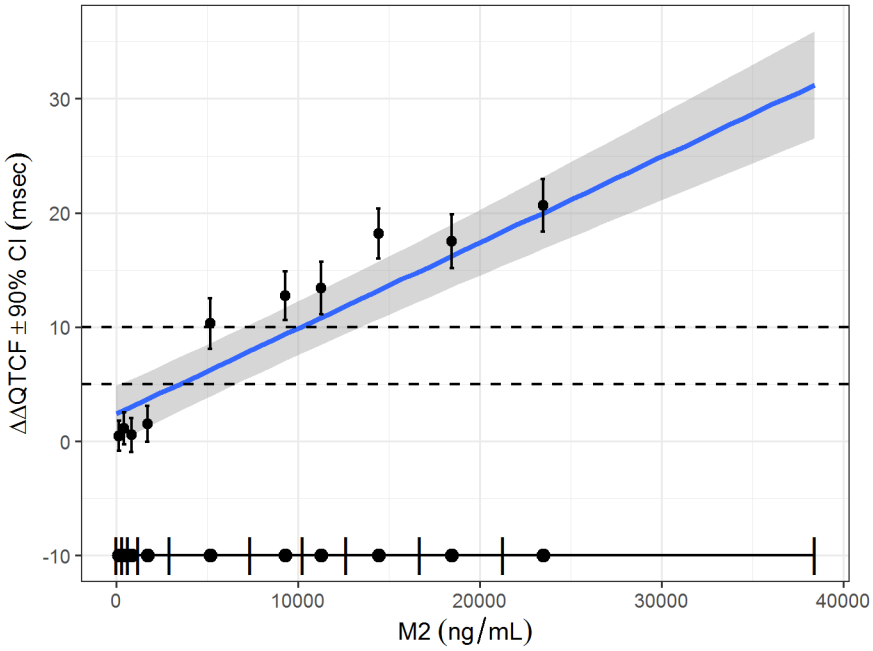
if a linear model would be appropriate. Analysis indicated a concentration dependent increase in ΔQTc for M2 metabolite. Since the sponsor used paper ECGs (digitalized; machine read) in Part I of the Study # DNDiFEX001, the heterogenicity assessment did indicate a marginal difference in the slopes (Figure 6). However, the inclusion of the data from Part I of the Study # DNDiFEX001 did not impact the overall interpretability of the study and the conclusion of this QT assessment. Figure 6 shows the relationship between fexinidazole metabolite (M2) concentration and ΔQTc and supports the use of a linear model.

Figure 6: Assessment of linearity of M2 concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration (M2)-QTc model are provided in Table 1.

Figure 7: Goodness-of-fit plot for QTc



5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

1. Product Information			
Generic Name	Fexinidazole	Brand Name	(b) (4)
Drug class	Antiprotozoal		
Combination product	No		
Indication	Treatment of human African trypanosomiasis		
Therapeutic Dose	The proposed dosing regimen includes body-weight based loading and maintenance doses with once daily dosing for 10 days under fed condition (see Section 3.1)		
Maximum Tolerated Dose	Not established		
Dosage Form	Tablets	Route of Administration	Oral

2. Clinical Cardiac Safety
Refer to the sponsor's highlights of clinical pharmacology and clinical safety.

3. QT Studies								
3.1 Primary Studies								
Protocol number / Population	**ECG Quality**		**Arms**		**Sample size**		**ECG & PK assessments**	
	Assessment	**Ok?**	**Arms**	**High dose covers?**	**No subjects**	**Ok?**	**Timing**	**Ok?**
Protocol number: DNDiFEX001	Central read? Yes Blinded? Yes	Yes	Highest dose: 3600 mg (once daily; under fasting	Above therapeutic (M2 exposures)	See Section 3.1.1	Yes	See Section 3.1.1	Yes

Population: Healthy subjects Design: Parallel	Replicates? Yes		condition; in Part-III of the Study) Placebo: Yes Positive control: No					
Protocol number: DNDiFEX003 Population: Healthy subjects Design: Parallel	Central read? Yes Blinded? Yes Replicates? Yes	Yes	Highest dose: 2400 mg (once daily; Day 1 to 4 - under fed condition) Placebo: Yes Positive control:	Above therapeutic (M2 exposures)	See Section 3.1.1	Yes	See Section 3.1.1	Yes

3.1 Secondary Studies	
Not applicable.	
3.3 Data pooling	
Data pooling?	Yes
Did sponsor propose an assessment for heterogeneity?	Unknown
Is the data pooling appropriate?	Yes (See Section 4.5)
4. Analysis plan	

4.1 Study Objective related to QT	
What QTc effect size is the analysis trying to exclude?	10 ms (E14)
4.2 Dose Justification	
Not provided.	
4.3 QT correction method	
Is an HR increase or decrease greater than 10 bpm?	No
Primary method for QT correction	QTcF
4.4 Assay Sensitivity	
Assay sensitivity methods proposed by sponsor	☐ Moxifloxacin ☐ Exposure-margin ☐ QT bias assessment ☒ Not applicable (Positive Studies) ☐ Other
Concentration dependent increase in QT prolongation was observed in these studies.	
4.5 By Time Analysis	
4.5.1 Investigational drug	
Primary analysis	Yes
Did the sponsor use IUT or descriptive statistics?	Descriptive statistics
For IUT: Does the sponsor use MMRM to analyze longitudinal values that considers the correlation across time-points or use ANCOVA by time-point without considering correlation?	N/A
For IUT: Is the MMRM model specified correctly with regards to covariance structure, covariates, etc?	N/A

Describe the model proposed by the sponsor. If not applicable, state N/A.	
4.5.2 Positive control	
Primary analysis	N/A
Did the sponsor adjust for multiplicity?	Unknown
Describe the model proposed by the sponsor. If not applicable, state N/A.	
4.6 Concentration-QTc analysis	
4.6.1 Investigational drug	
5.Primary analysis	Yes
What is the dependent variable in the sponsor's model?	Single delta
White paper model?	Unknown
Which concentration covariate(s) are included in the model?	Multiple - Univariate
Did the sponsor propose an assessment of delayed effects?	Yes
Did the sponsor propose an assessment of linearity?	Yes
Did the sponsor propose model selection criteria?	Yes
What methods did the sponsor use for predicting the QT effect?	☒ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals
The linear drug component effect consisted of the product of slope parameters and plasma concentrations. The influence of fexinidazole, M1 and M2 concentrations was investigated separately. A random subject level effect on slope was included in the model and kept if the between subject variance was significantly not null. The covariance between the random intercept and the random slope effects was assessed and kept in the model if significantly not null. Departure from linearity was investigated using diagnostic plots and supported	

by including quadratic concentration effects in the model. These effects were tested at the 5% level. In case of significance, alternative non-linear Emax models were to be investigated. For patient studies, the concentration-response relationship was investigated for ΔQTcSS as response variable with fexinidazole, M1 and M2 concentrations as dependent variables in 3 distinct models. A sequential approach was used since concentrations data for fexinidazole, M1 and M2 were not available at all time points of ECG measurement and concentrations were predicted from the pop-PK model developed on the same patient population. Scatter plots of individual values (ΔQTcSS) versus time-matched predicted concentrations were performed for each compound. A trend curve was added on the figures. If the scatter plots suggested potential trends between ΔQTc and plasma concentrations, the relationship was modeled using mixed model approaches.	
4.6.2 Positive control	
Primary analysis	No
Same model as investigational drug	N/A
4.7 Categorical analysis	
QTc?	Yes
ΔQTc?	Yes
PR?	Yes
QRS?	Yes
HR?	Yes
T-wave morphology?	Yes

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/

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MICHAEL Y LI
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LARS JOHANNESEN
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CHRISTINE E GARNETT
07/22/2020 10:00:37 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 21, 2020
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214429
Product Name and Strength:	Fexinidazole Tablets, 600 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sanofi-aventis U.S. LLC (Sanofi)
FDA Received Date:	March 12, 2020, May 27, 2020, and July 7, 2020
OSE RCM #:	2020-483
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Fexinidazole Tablets, the Division of Anti-Infectives (DAI) requested that we review the proposed Fexinidazole prescribing information (PI), container labels (blistercards), and carton labeling (wallet), for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

On March 12, 2020, an original New Drug Application for Fexinidazole (b) (4) Tablets, 600 mg was submitted, pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) and in accordance with Title 21, Part 314 of the Code of Federal Regulations.

On April 17, 2020, the Agency held a teleconference with Sanofi to share its current thinking about the proposed proprietary name, Fexinidazole (b) (4) ***.

On April 23, 2020, Sanofi submitted an Amendment requesting withdrawal of the proposed proprietary name, Fexinidazole (b) (4) ***, and requesting that the established name, Fexinidazole, be used in its place.

On May 27, 2020, Sanofi submitted revised labeling (blister wallets and package insert), changing the product name "Fexinidazole (b) (4) "*** to "Fexinidazole."

On July 7, 2020, Sanofi submitted their response[a], to our June 23, 2020, information request[b], in which they provided details regarding the proposed packaging, along with the requested short video demonstrating how the proposed package is opened by pressing and holding down the button, while pulling out the medication card.[c]

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A

[a] Response to FDA Request dated June 23, 2020 (Fexinidazole NDA 214429) Bridgewater (NJ): sanofi-aventis U.S. LLC; 2020 JUL 07. Available from: \\cdsesub1\evsprod\nda214429\0015\m1\us\quality-response-23jun2020.pdf.

[b] Rodger, A. FDA Communication: NDA 214429 Fexinidazole Packaging - Request for Information. Silver Spring (MD): FDA, CDER, OND, OND DIVISION (US); 2020 JUN 23. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80577fb2.

[c] Instructional Video (Fexinidazole NDA 214429) Bridgewater (NJ): sanofi-aventis U.S. LLC; 2020 JUL 07. Available from: \\cdsesub1\evsprod\nda214429\0015\m1\us\instructional-video.mp4.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

We were not able to determine if the proposed packaging would be child-resistant. Therefore, as stated above, an information request was sent.[b] In their response, Sanofi stated, "*The blister pack and outer enclosure are joined together. The package is comprised of an inner sleeve, blister pack card* (b) (4) ". Furthermore, Sanofi states that their "*supplier,* (b) (4) *has demonstrated the* (b) (4) *closure system complies with the CFR requirements for child-resistant (CR) packaging. The study was completed with a general format pack utilizing the same design mechanism we will employ for the fexinidazole packages.*"[a] Thus, Sanofi's response addresses our concerns regarding if the packaging is child-resistant and we therefore have no further recommendations related to the packaging at this time.

Tables 2 and 3 below include the identified medication error issues with the submitted PI, container labels (blistercards), and carton labeling (wallet), our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issue			
1.	As currently presented, the proposed fexinidazole packaging is intended to provide a 10-	If the Applicant were to change the redosing instructions to instead recommend redosing if	If the Applicant changes the current proposed information, such as to instead recommend redosing if

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	day regimen. Also, Section (b) (4) informs that if "…vomiting occurs after receiving fexinidazole, do not re-dose."	vomiting occurs after receiving a dose, we want to point out that the current proposed wallet packaging is not conducive to redosing because it does not include extra tablets.	vomiting occurs after receiving fexinidazole, the review team will need to consider the current proposed wallet packaging and how such redosing would best occur.
Highlights of Prescribing Information – *Dosage and Administration*			
1.	(b) (4)		
Full Prescribing Information – Section 1, *Indications and Usage*			
2.	(b) (4)		

[d] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2020 JUN 24]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(b) (4)	
Full Prescribing Information – Section 2, *Dosage and Administration*			
1.	As currently presented, the first sentence in this section includes the important information (b) (4)	As presented this important information may be missed and result in medication errors such as; missed dose, wrong technique (not taking a dose in a fed condition which could result in the incomplete absorption of the drug), or wrong time.	Create a header such as, "Important Administration Instructions" and then relocate the important information (b) (4) under this newly created header.
2.	As currently presented, "Table 1" includes the word, (b) (4), both within the title of the table, as well as within the header of the second column of the table.	The word (b) (4) is not consistent with the Section title "DOSAGE AND ADMINISTRATION"…	To provided consistency with the sentence preceding "Table 1" (i.e., (b) (4) within the title of the "Table 1", as well as within the header of the second column of the table, replace the word (b) (4) with the words "Recommended Dosage." For example, "Table 1: Recommended Dosage of Fexinidazole (b) (4) and the header of the second column

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			(b) (4) [redacted]
3.	As currently presented, the title of Table 1 (i.e., (b) (4) [redacted] is inconsistent with the *Indications and Usage* information (i.e., (b) (4) [redacted]	Inconsistent labeling statements may contribute to confusion that can result in medication error.	To provide consistency and clarity, add the information (b) (4) [redacted] to the end of the current Table 1, title. For example, "Table 1: (b) (4) [redacted]
4.	(b) (4) [redacted]		
5.	As currently presented, the first column, "Body weight", includes the extraneous terms (b) (4) [redacted] ."	(b) (4) [redacted]	
6.	As currently presented, Table 1, includes the numeric dosages represented as, "1800" and "1200."	Numerals (i.e., doses) larger than 1,000 without properly placed commas (e.g., 1000), have been misinterpreted	To decrease the potential for wrong strength/dose medication errors and improve the legibility of this large number we recommend

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		as hundreds "100" or ten-thousands "10000."	insertion of a comma in the numbers "1800" and "1200." For example, "1,800 mg" and "1,200 mg."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the National Drug Codes (NDCs) are denoted by placeholders (NDC xxxx-xxxx-xx).	To facilitate identification of the dosage form, the NDC is required per 21 CFR 201.57(c)(17)(iii).	We have provided a recommendation to the Applicant to revise their current NDC placeholders (i.e., XXXXX-XXXX-XX) on their carton labeling. Additionally, in accordance with 21 CFR 201.57(c)(17)(iii), they will need to be add the NDC to the *How Supplied* section.
2.	(b) (4)		
3.			

Table 3. Identified Issues and Recommendations for Sanofi-aventis U.S. LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels (blistercards)			
1.	As currently presented, the word "Day" associated with the numbers lacks prominence.	The word "Day" associated with the numbers, may be missed or misinterpreted resulting in wrong dose schedule medication errors.	To provide clarity and increase prominence, increase the font on the word "Day" associated with the numbers.
2.	As currently presented, the number of tablets associated with the dose (i.e., 1, 2, or 3) lacks prominence.	The number of tablets associated with the dose (i.e., 1, 2, or 3), may be missed or misinterpreted resulting in wrong dose medication errors.	To provide clarity, increase the prominence of the number of tablets associated with the dose (i.e., 1, 2, or 3) by increasing the font size, changing color of the font, and/or highlighting the number, as well as the word "TABLETS", within the statement. For example, "TAKE X TABLETS ONCE DAILY WITH FOOD AT THE SAME TIME EACH DAY."
Carton Labeling (wallet)			
1.	As currently presented, your intended expiration date format is "YYYY-MM."	It is unclear if the "MM" portion of the expiration date format (i.e., YYYY-MM) on your proposed carton labeling is intended to be numerical or alphabetical. The use of non-standard expiration dates can result in confusion regarding the actual expiration date leading to deteriorated drug medication errors (i.e., the alphabetical	Please provide clarification that the "MM" portion of the expiration date format (i.e., YYYY-MM) on your proposed carton labeling is intended to be numerical or alphabetical. If the proposed "MM" portion of the expiration date format is intended to be alphabetical, we recommend use of the expiration date format of "YYYY-MMM" using a hyphen or a space to separate the

Table 3. Identified Issues and Recommendations for Sanofi-aventis U.S. LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		abbreviation "JU" can represent both "June" and "July" and the alphabetical abbreviation "MA" can represent both "March" and "May").	portions of the expiration date.
2.	As currently presented, the National Drug Code (NDC) is denoted by a placeholder (NDC XXXXX-XXXX-XX).	We are unable to review the intended NDC for appropriateness from a medication error perspective.	Add the intended NDC numbers on the container labels and carton labeling and submit for our review.
3.	As currently presented, the PDP, of the 14 tablet carton, includes the statement "for children 6 years and older weighing 20 to less than 35 kg."	The lower weight (20) may be overlooked because it does not include the appropriate unit of measure (kg).	To provide clarity and minimize the risk of misinterpretation, add the unit of measure, "kg" after the first Arabic numeral in the weight range (i.e., "20"). For example, revise the current statement "for children 6 years and older weighing 20 to less than 35 kg." to instead "for children 6 years of age and older weighing at least 20 kg to less than 35 kg."

5 CONCLUSION

Our evaluation of the proposed Fexinidazole PI, container labels (blistercards), and carton labeling (wallet), identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Sanofi-aventis U.S. LLC so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Fexinidazole that Sanofi-aventis U.S. LLC submitted on May 27, 2020 and July 7, 2020.

Table 4. Relevant Product Information for Fexinidazole	
Initial Approval Date	N/A
Active Ingredient	fexinidazole
Indication	for the treatment of both first-stage (hemolymphatic) and second-stage (meningoencephalitic) of human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense in adults and children ≥6 years old and weighing ≥20 kg.
Route of Administration	oral
Dosage Form	tablets
Strength	600 mg
Dose and Frequency	(b) (4)
How Supplied	
Storage	(b) (4) Store in the original package in order to protect from light and moisture.

Container Closure	Packaged in push-through blister foil trapped in child-resistant dosepak for commercial distribution. This aluminum/aluminum blister packaging was chosen (b) (4)

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Fexinidazole labels and labeling submitted by Sanofi-aventis U.S. LLC.

- Container labels (blistercards) received on March 12, 2020
- Carton labeling (wallet) received on May 27, 2020
- Prescribing Information received on May 27, 2020 available at: \\cdsesub1\evsprod\nda214429\0010\m1\us\proposedpi.doc

F.2 Label and Labeling Images

(b) (4)

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

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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/

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