CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219491Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	December 8, 2025
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 219491
Product Name, Dosage Form, and Strength:	Nuzolvence (zoliflodacin) granules for oral suspension, 3 grams
Applicant Name:	Entasis Therapeutics, Inc. (ETI)
FDA Received Date:	December 5, 2025
TTT ID #:	2025-14183-2
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Entasis Therapeutics, Inc. submitted revised container label and carton labeling received on December 5, 2025 for Nuzolvence. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Nuzolvence (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to the Agency's additional container label and carton labeling recommendations.

2 REGULATORY HISTORY

On November 14, 2025, the Agency included additional container label and carton labeling recommendations in their IR labeling communication to ETI.[a]

On December 2, 2025, ETI provided their written responses to the Agency's IR dated November 14, 2025, along with noting that the updated container label and carton labeling would be provided with the next round of labeling discussions.[b]

On December 5, 2025, ETI submitted their revised container label and carton labeling, which is the subject of this review.[c]

3 CONCLUSION

We find the revised container label and carton labeling acceptable from a medication error perspective and have no additional recommendations at this time. Additionally, we defer to the Office of Pharmaceutical Quality to determine if retention of the currently proposed storage statement on the submitted revised container label and carton labeling is acceptable.

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[a] Nguyen, J. Labeling Discussion Comments for NDA 219491. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2025 NOV 14. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807ec4a9.

[b] Clinical Information Amendment (1.11.3) for Nuzolvence (zoliflodacin) NDA 219491. Waltham (MA): Entasis Therapeutics, Inc.; 2025 DEC 02. Available at: \\CDSESUB1\EVSPROD\nda219491\0043\m1\us\111-info-amend\clin-info-request.pdf.

[c] Cover Letter: Response to FDA Information Request dated 01-DEC-2025 (Label) for Nuzolvence (zoliflodacin) NDA 219491. Waltham (MA): Entasis Therapeutics, Inc.; 2025 DEC 05. Available at: \\CDSESUB1\EVSPROD\nda219491\0045\m1\us\12-cover-letter\cover.pdf.

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VALERIE S VAUGHAN
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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
ARIA Sufficiency Memorandum for Pregnancy Safety Concerns
Version: 2024-09-13

Date:	11/19/2025
Product Name(s):	NUZOLVENCE (zoliflodacin)
Application Type/Number(s):	NDA 219491
Sponsor/Applicant:	Entasis Therapeutics
NEXUS Task Tracking Tool ID #:	2025-16605
Reviewer(s):	Ikponmwosa Osaghae, MD, PhD, Epidemiologist, Division of Epidemiologist II Yan Li, PhD, Team Lead (Acting) Division of Epidemiology II
Division Leadership:	Adebola Ajao, PhD, Deputy Director Division of Epidemiology II
Sub-Office Director:	David Moeny, RPh, MPH, Deputy Director Office of Pharmacovigilance and Epidemiology
Sentinel Program Lead:	Patricia Bright, PhD, MSPH Office of Surveillance and Epidemiology

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 219491 is being reviewed for NUZOLVENCE (zoliflodacin), a first in class spiropyrimidinetrione antibacterial that inhibits bacterial type II topoisomerase enzymes (i.e., DNA gyrase [topoisomerase II] and topoisomerase IV). Zoliflodacin is indicated for the treatment of uncomplicated gonorrhea due to *Neisseria gonorrhoeae* in adult and pediatric patients 12 years and older, weighing at least 35 kg. The proposed dose is 3 g administered as a single oral dose with a half-life of 6.4 hours (fasted) and 5.5 hours (fed).

1.2. Describe the Safety Concern

In animal reproduction studies, oral administration of zoliflodacin to pregnant mice during organogenesis resulted in increased risk of fetal malformation (exencephaly) (≥ 1.5 times the maximum recommended human dose [MRHD]), increased implantation losses (≥ 1.5 times the MRHD), and decreased fetal weight (≥ 3 times the MRHD). No adverse effects on maternal or embryo-fetal development were observed in pregnant mice at 0.6 times the MRHD. In embryo-fetal development studies in rats, there were no fetal malformations at approximately 10 times the MRHD, but there was decreased pregnancy rate (10 times the MRHD) and decreased embryo-fetal survival (10 times the MRHD). However, there was no effect on embryo-fetal survival at 5 times the MRHD. At all zoliflodacin doses, decreased fetal weights and delays in ossification of the skeleton were observed in pregnant rats. In rats administered zoliflodacin throughout pregnancy, parturition, and lactation, there were no fetal malformations or adverse effects on pup birth weight at maternal AUC exposures up to 2-fold higher than the MRHD. There were no reports of pregnancies exposed to zoliflodacin during the clinical development program.

Given findings of exencephaly, a rare neural tube defect, in mice and early embryonic death and reduced litter weights in both rats and mice, warnings and precautions regarding the potential risk for pregnant women were recommended by the review team for addition to Section 5 of the labeling for zoliflodacin. In addition, pregnancy testing requirements prior to initiating treatment with zoliflodacin were recommended for addition to Section 2 (DOSAGE AND ADMINISTRATION) and Section 8.3 (Females and Males of Reproductive Potential) of the zoliflodacin labeling. Although this product is not expected to be used as a first line treatment for gonorrhea, given that gonorrhea is a common infection among females of reproductive age, there is potential for unintended use of zoliflodacin during pregnancy.

Based on the inconsistent findings of fetal malformations seen in animal studies, the strength of concern for the primary outcome, exencephaly, is assessed to be at the moderate level. In addition, the strength of concern for miscarriage and small-for-gestational-age at birth is at the moderate level, while the strength of concern for the signal of delayed ossification is at the weak level (Table 1).

Table 1: Available Data on Safety Concern and Strength of Concern

Outcome (safety concern)	Source(s) of safety concern	Strength of concern* (Weak, moderate, strong)
Malformations (exencephaly)	Data from mice indicate exencephaly at ≥ 1.5 times MRHD. No fetal malformations observed in rats at approximately 10 times the MRHD.	Moderate

Miscarriage	Data from studies in mice indicate increased implant losses at ≥ 1.5 times MRHD, and in rats indicate decreased embryofetal survival at 10 times MRHD.	Moderate
Small-for-gestational-age at birth	Data from studies in mice indicate decreased fetal weights at ≥ 3 times MRHD, and in rats indicate decreased fetal weights at all doses.	Moderate
Delayed ossification	Data from studies in rats indicate delayed ossification at all dose levels.	Weak

*Takes into account the signal strength (an assessment of the "strength" of the signal, based on the magnitude of the association, the quality of the source of information about the safety concern(s) as well as the validity and reliability of data to support the signal) and the level of clinical concern (an assessment of the "level of clinical concern" [e.g., seriousness of safety concern, magnitude of risk, prevalence of exposure] based on clinical and scientific knowledge and following discussions with the relevant team members).

A post-marketing requirement for a descriptive pregnancy safety study (DPSS) will be issued due to the cases of exencephaly observed in animal reproduction studies (mice only) and the expectation that a limited number of pregnant women would be exposed to zoliflodacin and be available in the post-marketing setting (due to the warning and pregnancy testing requirements) to allow for a registry or claims-based study. Long-term data collection and analyses from the DPSS will help monitor and characterize the risk of embryofetal toxicity of zoliflodacin in real-world settings and will help inform regulatory actions to ensure the safe use of zoliflodacin.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))
Ensure that the selected purpose(s) is consistent with the other PMR documents in DARRTS. More than one purpose may be chosen.

- ☐ Assess a known serious risk
- ☐ Assess signals of serious risk
- ☒ Identify unexpected serious risk when available data indicate potential for serious risk

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant individuals exists and exposure is expected
- ☐ No approved indication in pregnant individuals, but practitioners may use product off-label in pregnant individuals
- ☒ No approved indication in pregnant individuals, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication in pregnant individuals, but use in individuals of childbearing age is a general concern

2.2. Regulatory Goal[1]

- ☐ Signal evaluation of specific outcome(s) – *implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical product and the health outcome of interest*.
- ☐ Signal refinement of specific outcome(s) – *further investigation of an identified potential safety signal to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome*.
- ☒ Signal identification – *detection of new and unexpected potential medical product safety concerns and may be for a targeted or multiple safety concern(s)/health outcome(s)*.
  - ☐ Targeted evaluation of specific safety concern
  - ☒ Simultaneous identification of multiple unspecified adverse outcomes

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☐ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☐ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☒ Other, please specify: Single arm descriptive pregnancy safety study

2.4. Identify the epidemiologic domain(s) where ARIA is not sufficient and provide a rationale on ARIA insufficiency for those epidemiologic domain(s). Then, provide an assessment of the overall ARIA sufficiency.

Epidemiologic Domain	Explanation on ARIA insufficiency
☒ Study Population	The population of interest includes pregnant women and their infants (for live birth outcomes), with algorithms available to identify both populations. It is expected that a limited number of zoliflodacin-exposed pregnant women would be available in the post-marketing setting due to the associated labeling warnings and pregnancy testing requirements. However, the ARIA system lacks access to exposed pregnancies from countries outside the U.S. where zoliflodacin is approved, which limits its use for a worldwide descriptive study.
☐ Exposures (and Comparators)	ARIA is sufficient for the exposure.
☒ Outcomes	The broad-based surveillance may include pregnancy and maternal complications, adverse effects on the developing

[1] Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.

	fetus and neonate, and adverse effects on infants in exposed pregnancies. The ARIA system lacks access to detailed case narratives. Given that the study for broad-based pregnancy outcomes being considered is descriptive, without sample size requirements, and without a comparison group, having detailed case narratives is necessary to identify and validate outcomes and to assess exposure and outcome temporality. Only a subset of pregnancy and birth outcomes have validated algorithms in the ARIA system.
☒ Covariates	ARIA does not have detailed information on potential confounders. The descriptive pregnancy safety study being considered would need to collect detailed information on potential covariates, such as lifestyle factors, prenatal supplement use, and over the counter medication use.
☐ Analytic Tools	ARIA is sufficient for the analytic tools.

Overall ARIA sufficiency determination

☒ Insufficient
☐ Sufficient

2.5. If ARIA is deemed insufficient, include the PMR language to be included in the approval letter.

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Nuzolvence (zoliflodacin) during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life.

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

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

Memorandum

Date: November 6, 2025

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

Abimbola Adebowale, Associate Director for Labeling, Division of Anti-Infectives (DAI)

From: Qumerunnisa Syed, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for NUZOLVENCE™ (zoliflodacin) for oral suspension

NDA: 219491

Background:
In response to DAI's consult request dated April 25, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for NUZOLVENCE™ (zoliflodacin) for oral suspension.

PI/IFU:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on October 30, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed IFU, and comments were sent under separate cover on November 4, 2025.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on September 30, 2025, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Qumerunnisa Syed at 301-796-8897 or Qumerunnisa.syed@fda.hhs.gov.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	November 5, 2025
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 219491
Product Name, Dosage Form, and Strength:	Nuzolvence (zoliflodacin) granules for oral suspension, 3 grams
Applicant Name:	Entasis Therapeutics, Inc. (ETI)
FDA Received Date:	November 4, 2025
TTT ID #:	2025-14183-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Entasis Therapeutics, Inc. submitted revised container label and carton labeling received on November 4, 2025 for Nuzolvence. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Nuzolvence (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] Additionally, per ETI's Response to FDA Identified Issues & Recommendations,[b] "*The carton labeling has been updated to reflect the inclusion of a medication guide per the discussion of item 8(c) during the Late Cycle Meeting (16 October 2025).*"[c]

2 REGULATORY HISTORY/DISCUSSION

On September 30, 2025, ETI submitted "*…revised artwork for Carton and Container/Sachet (packet), for color change only. No other changes besides the change of color are being made*."[d,e,f]

We note that Office of Pharmaceutical Quality (OPQ) added the recommendation "*Please revise the storage condition statement in the container label and carton labeling to read as:* (b) (4) However, included in ETI's Response to FDA Identified Issues & Recommendations, they "*…respectfully requests to retain the original proposed storage conditions,* (b) (4) Thus, we defer to OPQ to determine if this is acceptable.

3 CONCLUSION

Entasis Therapeutics, Inc. implemented all of our recommendations and we have no additional recommendations at this time. Additionally, we defer to OPQ to determine if retention of the

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[a] Myers, D. Label and Labeling Review for Nuzolvence (NDA 219491). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 JUL 31. TTT ID: 2025-14183.

[b] Quality Information Amendment – Entasis Response to FDA Identified Issues & Recommendations dated 10/21/2025 for NDA 219491. Waltham (MA): Entasis Therapeutics, Inc.; 2025 NOV 04. Available at: \\CDSESUB1\EVSPROD\nda219491\0035\m1\us\111-info-amend\quality-info-amend-21oct2025.pdf.

[c] Nguyen, J. FDA Communication: Late Cycle Meeting Background Package for NDA 219491. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2025 OCT 06. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807dfcf0.

[d] Cover Letter: Revised Artwork for Carton and Container/Sachet for Nuzolvence (zoliflodacin) NDA 219491. Waltham (MA): Entasis Therapeutics, Inc.; 2025 SEP 30. Available at: \\CDSESUB1\EVSPROD\nda219491\0029\m1\us\12-cover-letter\cover.pdf.

[e] Labeling: Revised Draft Labeling – Carton Design NP R Colors for Nuzolvence (zoliflodacin) NDA 219491. Waltham (MA): Entasis Therapeutics, Inc.; 2025 SEP 30. Available at: \\CDSESUB1\EVSPROD\nda219491\0029\m1\us\114-labeling\114a-draft-label\revised-nuzolvence-carton.pdf.

[f] Labeling: Revised Draft Labeling – Container Sachet Design NP R Colors for Nuzolvence (zoliflodacin) NDA 219491. Waltham (MA): Entasis Therapeutics, Inc.; 2025 SEP 30. Available at: \\CDSESUB1\EVSPROD\nda219491\0029\m1\us\114-labeling\114a-draft-label\revised-nuzolvence-container.pdf.

currently proposed storage statement on the submitted revised container label and carton labeling is acceptable.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 4, 2025
To:	Joseph Nguyen, PharmD. Regulatory Project Manager **Division of Anti-Infectives (DAI)**
Through:	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Qumerunnisa Syed, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name):	NUZOLVENCE (zoliflodacin)
Dosage Form and Route:	for oral suspension
Application Type/Number:	NDA 219491
Applicant:	Entasis Therapeutics Inc.

1 INTRODUCTION

On April 15, 2025, Entasis Therapeutics Inc. submitted for the Agency's review a New Molecular Entity (NME) New Drug Application (NDA) 219491 for NUZOLVENCE (zoliflodacin) for oral suspension. The Applicant seeks approval of this product for the treatment of uncomplicated gonorrhea due to *Neisseria gonorrhoeae* (*N. gonorrhoeae*) in adult and pediatric patients 12 years and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infectives (DAI) on April 30, 2025 and April 25, 2025, respectively for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for NUZOLVENCE (zoliflodacin), for oral suspension.

2 MATERIAL REVIEWED

- Draft NUZOLVENCE (zoliflodacin) for oral suspension IFU received on April 15, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 23, 2025.
- Draft NUZOLVENCE (zoliflodacin) for oral suspension Prescribing Information (PI) received on April 15, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 23, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the PI
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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MARCIA B WILLIAMS
11/04/2025 11:48:34 AM

MEMORANDUM

USE-RELATED RISK ANALYSIS REVIEW MEMO

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	October 30, 2025
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 219491
Product Name, Dosage Form, and Strength:	Nuzolvence[a] (zoliflodacin) granules for oral suspension, 3 grams
Applicant/Sponsor Name:	Entasis Therapeutics, Inc. (ETI)
TTT ID #:	2025-14176-1
DMEPA 1 Safety Evaluator:	Tianyi Zhang, PhD, MS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, MCHES, CPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted a response to our recommendations for Nuzolvence (zoliflodacin) convenience kit's mixing container. The Division of Anti-Infectives (DAI) requested that we review the response for Nuzolvence (Appendix A) to determine if it is acceptable from a medication error perspective. The response is in response to recommendations that we made during a previous use-related risk analysis (URRA) review.[b]

2 DISCUSSION AND CONCLUSION

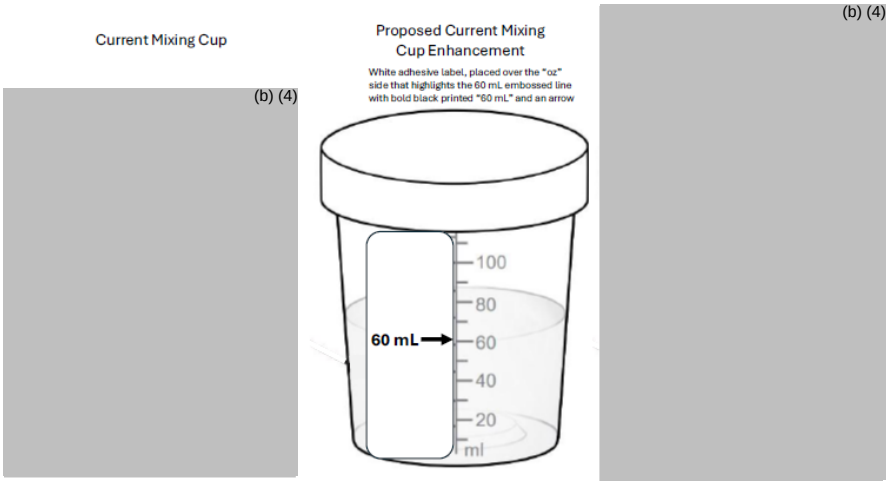
Regarding our recommendations to pursue a mixing container that has a dark "fill line", an embossed, bolded "60 mL" graduation mark that is easily identifiable against the container's clear background, and with no unnecessary graduation marks (i.e., 1-4 oz), the Applicant agreed to "*modify the existing dosing container to more clearly demarcate the 60 mL fill line and to obscure the unnecessary graduation markings*". The Applicant stated, "*An extensive search concluded that there are no off-the-shelf options that satisfy the FDA's recommendations*".

[a] The proposed proprietary name, Nuzolvence, was found conditionally acceptable by DMEPA on March 13, 2025 (PNR# 2024-1044726016). Of note, ETI refers to the product as its proprietary name placeholder, zoliflodacin convenience kit, throughout their submission.

[b] Zhang, T. Use-Related Risk Analysis Review for Nuzolvence (zoliflodacin) (NDA 219491). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 SEP 22. TTT ID No.: 2025-14176.

Therefore, within the current review cycle, the Applicant proposed to "*utilize current mixing container by adding a white adhesive label, with a line and "60 mL" printed in bold black ink, to the outside of the container over the top of the left side markings (1-4 oz markings) to indicate where the 60 mL embossed line is on the container and assist the patient with locating the correct water filling level. The intention of this adhesive label is to cover the extraneous, unnecessary liquid measure markings and to assist the patient with identifying the correct marking; the embossed line will remain the target mark since it is part of the mold and provides a consistent volume indication. The IFU images will be updated accordingly to depict the use of the stickered container.*" Additionally, the Applicant proposed (b) (4) The images of the mock-ups of the proposed mixing container with white adhesive label and (b) (4) are provided below in Figure 1.

Figure 1: Mock-Up of Proposed Adhesive Label (Near Term) and (b) (4)



In response to the aforementioned Applicant's proposed mitigation and future plans, we met with the DAI clinical teams on October 9, 2025. The DAI clinical team found the Applicant's proposed mitigation reasonable because the risk of overdose or underdose is expected to be minimal. The Nuzolvence (zoliflodacin) convenience kit contains a single-dose packet of 3 grams of zoliflodacin granules for suspension, and, as long as the granules are fully dissolved, small variations in water volume around the designated 60 mL level in the provided cup would not affect the actual drug dose administered. Therefore, in this particular instance, we find the Applicant's proposed mitigations and future plans reasonable. Based on the provided information, We have no additional recommendations for Nuzolvence (zoliflodacin) convenience kit.

APPENDIX A. APPLICANT'S RESPONSE TO OUR USE-RELATED RISK ANALYSIS REVIEW RECOMMENDATIONS RECEIVED ON OCTOBER 3, 2025

Response to our use-related risks analysis review recommendations available from:

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Clinical Inspection Summary (CIS)

Date	10/16/2025
From	John Lee, M.D., Primary Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Shayna Dooling, Medical Officer Jae Ho Hong, Medical Officer Ramya Gopinath, Clinical Team Leader Peter Kim, Division Director Joseph Nguyen, Regulatory Project Manager Division of Anti-Infectives (DAI)
Application	NDA 219491
Applicant	Entasis Therapeutics, Inc.
Drug	Zoliflodacin (Nuzolvence™)
NME / Original NDA	NME Original NDA
Proposed Indication	Treatment of uncomplicated gonorrhea due to Neisseria gonorrhoeae in adult and pediatric patients 12 years and older, weighing at least 35 kg
Consult Date	05/08/2025
CIS Goal Date	10/22/2025
Review Clock	Priority Review
Action Goal Date	12/15/2025
PDUFA Due Date	12/15/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For this NDA 219491, four BIMO review-based Good Clinical Practice (**GCP**) inspections (3 clinical investigators and sponsor) were conducted in auditing Study STI_Zoli001:

- Lindley Barbee, M.D. (Seattle, Washington; Site 840-102)
- Sinead Delany-Moretlwe, M.D. (Johannesburg, South Africa; Site 710-003)
- Nittaya Phanuphak Pungpapong, M.D. (Bangkok, Thailand; Site 764-001)
- Entasis Therapeutics, Inc. (Waltham, Massachusetts; sponsor)

Based on the inspection findings, the study appears to have been conducted in observance of GCP principles and in compliance with FDA regulations. The data generated by the clinical investigators (**CIs**) appear to be acceptable in support of this NDA.

II. BACKGROUND

This original NDA from Entasis Therapeutics, Inc. supports the approval of zoliflodacin (provisionally Nuzolvence™) for treating uncomplicated gonorrhea due to infection by *Neisseria gonorrhoeae* (**NG**) in adults and adolescents (age ≥ 12 years, weight ≥ 35 kg).

The Center for Disease Control and Prevention estimates 1.6 million new cases of gonorrhea in the US annually, and the World Health Organization has estimated 82 million new cases globally in 2020. Ceftriaxone is currently the first-line treatment of choice for uncomplicated gonorrhea with Cefixime as an alternate. Neither ceftriaxone nor cefixime is an option for individuals with β-lactam allergy, and antibiotic-resistant NG further complicates therapy.

The pivotal study supporting this NDA was identified for on-site audit at four GCP inspections (3 CIs and sponsor). No review concerns were identified for these otherwise routine pre-approval inspections.

Study STI_Zoli001: *A multi-center, randomized, open-label, non-inferiority trial to evaluate the efficacy and safety of a single, oral dose of zoliflodacin compared to a combination of a single intramuscular dose of ceftriaxone and a single oral dose of azithromycin in the treatment of patients with uncomplicated gonorrhoeae*

This randomized, active-controlled, open-label non-inferiority study was conducted over 4 years (2019 – 2023) in 930 subjects randomized at 16 study centers in 4 countries: Belgium, the Netherlands, South Africa, Thailand, and US. The primary study objective was to assess the efficacy of a single oral 3-gram dose of zoliflodacin in treating uncomplicated urogenital gonorrhea relative to the use of the comparator regimen, single doses of IM 500-mg ceftriaxone plus oral 1-gram azithromycin.

Subject Selection

- Age 12 years or older, body weight ≥ 35 kg, recent signs and symptoms of urogenital gonorrhea or as determined by culture, nucleic acid amplification, Gram stain, or methylene blue/gentian violet stain; OR recent unprotected sex with someone test-confirmed for NG
- For women of child-bearing potential: negative urine pregnancy test at screening and use of a highly effective method of contraception

- For men with a partner of child-bearing age: willingness to delay conception during the trial and for 28 days after treatment

The screen-selected subjects were excluded for:

- Co-infection requiring additional systemic antibiotics with activity against NG; use of any systemic or intravaginal antibiotics with activity against NG within 30 days; chronic renal, hepatic, or other condition interfering with drug elimination
- Immunosuppression as evidenced by medical history, clinical examination or a recent (≤ 1 month) CD4 count (< 200 cells/µL); use of systemic corticoids or other immunosuppressive therapy within 30 days
- Use of moderate/strong CYP3A4 inducers within 30 days or 5 drug half-lives, whichever is greater; cytotoxic or radiation therapy within 30 days; confirmed/suspected complicated or disseminated gonorrhea; pregnant or nursing

Treatment Groups and Regimen

- Single oral 3 g dose of zoliflodacin (granules for oral suspension)
- Single intramuscular 500 mg dose of ceftriaxone + single 1 g dose of oral azithromycin

Study Evaluations

- *Primary endpoint:* Microbiological cure as determined by culture at urethral or cervical sites at Test of Cure (**TOC**, Day 6±2)
- *Key secondary endpoint:* Incidence, severity, causality, and seriousness of treatment-emergent AEs; safety laboratory testing and physical examination

III. INSPECTION RESULTS

1. Lindley Barbee, M.D.
908 Jefferson Street
Seattle, Washington 98104

Inspection Dates: August 18 – 26, 2025

Protocol STI_Zoli001, Site 840-102: 70 subjects were screened, 70 were enrolled, and 57 completed the study. Case records were completely reviewed for a random sampling of 19 enrolled subjects.

- Study conduct at this CI site was audited for: adherence to the study protocol, institutional review board (**IRB**) oversight, site monitoring, staff training, study medication disposition and accountability, and CI financial disclosure.
- Case records review covered: informed consent, subject eligibility, subject enrollment and randomization, efficacy endpoint assessment, and adverse event monitoring.
- Data verification (against source data) covered: treatment assignment, major efficacy endpoints, adverse events, protocol deviations, and concomitant medication use.

The inspectional findings were noteworthy for 4 subjects not excluded for: limited use of non-study antibiotics and CYP3A4 inhibitors (1 subject), self-reported history of current substance abuse (2 subjects), and inadequate contraception (1 subject).

Reviewer's comment: These findings appeared isolated, minor, and unlikely to significantly impact the study outcome (4 of 930 subjects, < 0.5%). For each specific protocol deviation (nature), the frequency decreases further: 0.1% (antibiotic / CYP3A4 inhibitor), 0.2% (substance abuse), and 0.1% (inadequate contraception). For each protocol deviation, an appreciable impact on the relevant efficacy endpoints is not expected. Deviation-related adverse events (including pregnancy) were not observed.

Significant GCP deficiencies or regulatory violations were otherwise not observed. The sponsor's monitoring appeared adequate. The study records showed complete CI financial disclosure, adequate reporting of adverse events and protocol deviations, and acceptable drug accountability. The major efficacy and adverse event data were verifiable.

2. Sinead Delany-Moretlwe, M.D.
Hillbrow Health Precinct 22
Esselen Street Hillbrow
Johannesburg, South Africa

Inspection Dates: September 1 – 5, 2025

Protocol STI_Zoli001, Site 710-003: 194 subjects were screened, 149 subjects were enrolled, and 135 completed the study. Case records were reviewed in detail for a random sampling of 40 enrolled subjects.

- Study conduct at this CI site was audited for: adherence to the study protocol, IRB oversight, site monitoring, staff training, study medication disposition and accountability, and CI financial disclosure.
- Case records review covered: informed consent, subject eligibility, subject enrollment and randomization, efficacy endpoint assessment, and adverse event monitoring.
- Data verification (against source data) covered: treatment assignment, major efficacy endpoints, adverse events, protocol deviations, and concomitant medication use.

Significant GCP deficiencies or regulatory violations were not observed. The sponsor's monitoring appeared adequate. Informed consent forms were obtained for all subjects. The study records showed complete CI financial disclosure, adequate reporting of adverse events and protocol deviations, and acceptable drug accountability. The major efficacy and adverse event data were verifiable.

3. Nittaya Phanuphak Pungpapong, M.D.
104 Ratchadamri Road
Lumpini Pathumwan
Bangkok, Thailand

Inspection Dates: August 25 – 29, 2025

Protocol STI_Zoli001, Site 764-001: 108 subjects were screened, 105 subjects were enrolled, and 103 completed the study. All subject case records were reviewed, including detailed review for a random sample of 20 enrolled subjects.

- Study conduct at this CI site was audited for: adherence to the study protocol, IRB oversight, site monitoring, staff training, study medication disposition and accountability, and CI financial disclosure.

- Case records review covered: informed consent, subject eligibility, subject enrollment and randomization, efficacy endpoint assessment, and adverse event monitoring.
- Data verification (against source data) covered: treatment assignment, major efficacy endpoints, adverse events, protocol deviations, and concomitant medication use.

The inspectional findings were noteworthy for 7 subjects under 18 years of age without either signed parental consent or documented IRB waiver. The protocol allowed enrollment of minors of age 12 years and older. If unable to obtain signed parental consent, minors could be enrolled with IRB approval. For the 7 minors without signed parental consent, verbal IRB approval (by phone call) was documented in the study records but was not followed by a written IRB approval.

Significant GCP deficiencies or regulatory violations were otherwise not observed. The sponsor's monitoring appeared adequate. The study records showed complete CI financial disclosure, adequate reporting of adverse events and protocol deviations, and acceptable drug accountability. The major efficacy and adverse event data were verifiable.

4. Entasis Therapeutics, Inc.
35 Gatehouse Drive
Waltham, MA 02451

Inspection Dates: July 18 – 24, 2025

Protocol STI_Zoli001: This BIMO review-based sponsor inspection consisted of a general records review, to evaluate compliance with the GCP principles and regulations applicable to the sponsor, including oversight of CI sites.

The records reviewed included: product accountability records, monitoring correspondence, vendor contracts, documentation of data management procedures, safety reporting records, staff qualification and training, and clearance records for electronic data systems. The CI sites selected to evaluate the adequacy of the sponsor's oversight included those inspected separately, Sites 840-102, 710-003, and 764-001.

No significant regulatory violations were observed. The sponsor's oversight of the study including CI site monitoring appears to have been adequate to assure subject safety and study data quality.

{See appended electronic signature page}

John Lee, M.D., Primary Reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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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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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993

Division of Pediatrics and Maternal Health Review

Date: October 2, 2025 **Date consulted:** April 25, 2025

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and
Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH, ORPURM, OND

Lynne P. Yao, MD, Division Director, DPMH, ORPURM, OND

To: The Division of Anti-Infectives (DAI)

Drug: NUZOLVENCE (zoliflodacin) granules for oral suspension

NDA: 219491

Applicant: Entasis Therapeutics

Subject: Pregnancy and Lactation Labeling Formatting and Recommendations

Proposed Indication: Treatment of uncomplicated gonorrhea due to *Neisseria gonorrhoeae* in adult and pediatric patients 12 years and older, weighing at least 35 kg

Materials
Reviewed:

- July 23, 2025. Pharmacology/Toxicology IND assessment and evaluation. IND 139105. Leah Rosenfeld, PhD, Pharmacology/Toxicology Reviewer, DARRTS Reference ID 5629952.
- June 10, 2025. Pharmacology/Toxicology IND assessment and evaluation. IND 118958. Leah Rosenfeld, PhD, Reviewer, DARRTS Reference ID 5605832.
- April 25, 2025, DAI consult for zoliflodacin NDA 219491 to review PLLR aspects of labeling, DARRTS Reference ID 5579413.
- April 15, 2025, Original New Drug Application for NDA 219491 for zoliflodacin for the treatment of uncomplicated gonorrhea.

1 INTRODUCTION

On April 15, 2025, Entasis Therapeutics submitted an original New Drug Application (NDA 219491) for zoliflodacin granules for oral suspension for the treatment of uncomplicated gonorrhea due to Neisseria gonorrhoeae in adult and pediatric patients 12 years and older, weighing at least 35 kg.

The Division of Anti-Infectives (DAI) consulted the Division of Pediatrics and Maternal Health (DPMH) on April 25, 2025, to assist with the Pregnancy and Lactation subsections of labeling.

2 BACKGROUND

2.1 Drug Characteristics[1,2,3]

- *Drug Class:* Zoliflodacin is the first in a new class of antibacterial products called spiropyrimidinetrione antibiotics
- *Dosage Form and Administration:* Zoliflodacin is mixed with 60 mLs of water. For adults and pediatric patients ages 12 and older, weighing at least 35 kg, 3g of zoliflodacin is administered as a single oral dose.
- *Mechanism of Action (MOA):* Zoliflodacin inhibits bacterial topoisomerase type II enzymes [GyrB (subunit of DNA gyrase) and topoisomerase IV]. Topoisomerase are enzymes required for bacterial DNA replication and cell division and DNA gyrase aids in DNA replication and transcription . Zoliflodacin inhibits the activity of both GyrB and topoisomerase IV causing disruption of DNA replication and repair ultimately leading to bacterial cell death. Zoliflodacin has high affinity *in vitro* activity again *N. gonorrhoeae*.

[1] Jacobsson, Susanne, et al. "Pharmacodynamic Evaluation of Zoliflodacin Treatment of Neisseria Gonorrhoeae Strains with Amino Acid Substitutions in the Zoliflodacin Target GyrB Using a Dynamic Hollow Fiber Infection Model." Frontiers in Pharmacology, vol. 13, 14 Apr. 2022, https://doi.org/10.3389/fphar.2022.874176.
[2] Miller, Alita A, et al. Determination of MIC Quality Control Ranges for the Novel Gyrase Inhibitor Zoliflodacin. Vol. 57, no. 9, 26 Aug. 2019, https://doi.org/10.1128/jcm.00567-19.
[3] O'Donnell, John, et al. "Single-Dose Pharmacokinetics, Excretion, and Metabolism of Zoliflodacin, a Novel Spiropyrimidinetrione Antibiotic, in Healthy Volunteers." Antimicrobial Agents and Chemotherapy, vol. 63, no. 1, 1 Jan. 2019, www.ncbi.nlm.nih.gov/pmc/articles/PMC6325203/, https://doi.org/10.1128/AAC.01808-18.

- *Molecular Weight:* 487.4 g/mol
- *Terminal Half-life:* 6.47 hours (fasted); 5.5 hours (fed)
- *Absorption:* Single ascending dose rapidly absorbed, time to max concentration (T_{max}) 1.5 and 2.3 hours (delayed in fed state T_{max} = 4 hours)
- *Metabolism:* Predominately CYP3A4/5, with lesser contributions from CYP1A2, CYP2C9, CYP2C8, and CYP2C19
- *Excretion:* urine (urinary unchanged <5% of total dose) and fecal elimination 18.2% and 79.6% of dose, respectively

2.2 Warnings and Precautions

- *Clostridioides difficile* infection and development of drug-resistant bacteria are listed as Warnings and Precautions.

2.3 Common Adverse Reactions

- Most common treatment adverse reactions were of the nervous system to include headache and dizziness.

3 REVIEW

3.1 Gonorrhea Infection during Pregnancy

Gonorrhea is a bacterial sexually transmitted disease caused by *Neisseria gonorrhoeae*.[4] Gonorrhea is most commonly spread through sexual contact but can also be spread from a pregnant mother's genital tract to the newborn during birth through infected fluids which can result in serious adverse events for the newborn.[5] The most serious infections spread to a newborn include ophthalmia neonatorum, sepsis and meningitis.[6] Gonorrhea can be asymptomatic and may not be recognized until complications occur. The most effective prevention of newborn transmission includes screening of pregnant women and treatment of infected individuals.[6] According to the Centers for Disease Control and Prevention (CDC), all pregnant women who are under 25 years of age and those over 25 years of age, if at increased risk, should be screened for gonorrhea during the 1st and 3rd trimesters of pregnancy. However, any pregnant woman who tests positive for gonorrhea should be treated and retested within 3 months.[7]

[4] Oriol Mitjà, et al. "Treatment of Bacterial Sexually Transmitted Infections in Europe: Gonorrhoea, Mycoplasma Genitalium, and Syphilis." The Lancet Regional Health - Europe, vol. 34, 1 Nov. 2023, pp. 100737–100737, https://doi.org/10.1016/j.lanepe.2023.100737.

[5] Comunián-Carrasco, Gabriella, et al. "Antibiotics for Treating Gonorrhoea in Pregnancy." Cochrane Database of Systematic Reviews, 21 Feb. 2018, www.cochrane.org/CD011167/PREG_antibiotics-treating-gonorrhoea-pregnancy, https://doi.org/10.1002/14651858.cd011167.

[6] CDC. "Gonococcal Infections among Neonates - STI Treatment Guidelines." Www.cdc.gov, 14 July 2021, www.cdc.gov/std/treatment-guidelines/gonorrhea-neonates.htm.

[7] Centers for Disease Control and Prevention. "STI Screening Recommendations." Www.cdc.gov, 2021, www.cdc.gov/std/treatment-guidelines/screening-recommendations.htm.

According to the CDC, cases of gonorrhea in the overall population increased by 63% from 2014 to 2020 in the United States.[8] According to published literature, global prevalence of gonorrhea among pregnant women from 2010 – 2022 was estimated at 2.6 million which is equivalent to 1.85% of the estimated 19 million pregnant women during that time period.[9] In addition, prevalence greatly varies across regions, estimated to be 3.53% in the African regions, 1.95% in the Western Pacific regions, 1.35% in the America's and 1.32% in Mediterranean regions with the lowest prevalence estimates in the European region at 0.52% and Southeast Asian region at 0.81%.[9] According to the literature, prevalence variations are most likely due to differences in socioeconomic circumstances, coinfection rates and guidelines for prevention and treatment.[9]

The CDC and the World Health Organization recommend treatment of gonorrhea in all infected patients, including pregnant patients, with a one-time dose of ceftriaxone injection (500 mg intramuscular).[10] Treatment for gonorrhea should also include treatment for chlamydia, if a chlamydia infection has not been ruled out, with azithromycin 2 grams as a single oral dose.[10]

3.2 Pregnancy

Nonclinical Experience[11,12]

In embryo-fetal development (EFD) studies, female rats were administered oral zoliflodacin 200, 500, or 1000 mg/kg/day two weeks prior to mating through gestational day 16. At 1000 mg/kg/day, (AUC_{0-24} exposures 9.9-fold higher than the MRHD), the pregnancy rate and embryofetal survival were decreased but no zoliflodacin related malformations. There was no effect on embryofetal survival at 500 mg/kg/day (AUC exposures 5-times higher than the MRHD). At all dose levels, there were decreased fetal weights and delays in ossification of the fetal skeleton.

EFD studies in mice administered oral zoliflodacin 250, 500, and 1000 mg/kg/day during organogenesis showed fetal malformations (exencephaly) at ≥500 mg/kg/day (AUC exposure ≥1.5-times higher than the MRHD). There were increased implant losses at 500 mg/kg/day (at an AUC exposure >1.5-times higher than the MRHD) and decreased fetal weight at 1000mg/kg/day (AUC exposure 3-times higher than the MRHD). The NOAEL for embryofetal development was 250 mg/kg/day, at an AUC exposure of 0.6-times the MRHD.

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[8] Cyr, Sancta St. "Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020." MMWR. Morbidity and Mortality Weekly Report, vol. 69, no. 50, 2020, https://doi.org/10.15585/mmwr.mm6950a6.

[9] Vaezzadeh, Kosar, et al. "Global Prevalence of Neisseria Gonorrhoeae Infection in Pregnant Women: A Systematic Review and Meta-Analysis." Clinical Microbiology and Infection, Aug. 2022, https://doi.org/10.1016/j.cmi.2022.08.008.

[10] Updated Recommendations for the Treatment of Neisseria Gonorrhoeae, Chlamydia Trachomatis, and Treponema Pallidum (Syphilis) and New Recommendations on Syphilis Testing and Partner Services. 17 July 2024, iris.who.int/bitstream/handle/10665/378228/B09099-eng.pdf, https://doi.org/10.2471/b09099.

[11] June 10, 2025. Pharmacology/Toxicology IND assessment and evaluation. IND 118958. Leah Rosenfeld, PhD, Reviewer, DARRTS Reference ID 5605832.

[12] July 23, 2025. Pharmacology/Toxicology IND assessment and evaluation. IND 139105. Leah Rosenfeld, PhD, Pharmacology/Toxicology Reviewer, DARRTS Reference ID 5629952.

In pre- and post-natal development (PPND) studies in rats administered oral zoliflodacin 0, 50, 100 or 200 mg/kg/day from gestation day 6 to lactation day 20, there was no evidence of maternal toxicity or adverse effects on prenatal or postnatal growth of the offspring at (maternal AUC maternal exposures up to 2.3-fold higher than the MRHD at the end of gestation).

Refer to the Office of Pharmacology/Toxicology reviews for further details.

Review of Clinical Data

Applicant's review of literature

The Applicant conducted a review of literature regarding zoliflodacin use and pregnancy, and no data were found.

Clinical Development Program

There were no pregnancies in the zoliflodacin clinical development program.

DPMH's review of literature

DPMH conducted a review of published literature in PubMed and Embase using the search terms "zoliflodacin," "zoliflodacin and pregnant women," "zoliflodacin and pregnancy and birth defects," "zoliflodacin and pregnancy and congenital malformations," "zoliflodacin and pregnancy and stillbirth," "zoliflodacin and spontaneous abortion" and zoliflodacin and pregnancy and miscarriage." No clinical data were found for review.

Reviewer comment: There are no clinical data for review regarding zoliflodacin use during pregnancy. Animal reproduction studies were conducted in rats and mice revealing early embryonic death in rats and reduced litter weights in both species along with increased skeletal variations and delayed ossification. Additionally, exencephaly, a rare neural tube defects, was observed in three separate litters in mice at doses 1.5 times the maximum human recommended dose. In addition, there are approximately 15 FDA approved products with exencephaly observed in the reproductive toxicology studies. The labeling for these products regarding the exencephaly finding vary as only one product has a Boxed Warning and a Warnings and Precautions section on embryofetal toxicity along with language in subsection 8.1, only one product has a contraindication along with the Boxed Warning and a Warning and Precautions section on embryofetal toxicity along with language on the exencephaly finding in subsection 8.1, five products have a Warnings and Precautions on embryofetal toxicity along with language regarding the exencephaly finding in subsection 8.1, and the remaining eight products have the exencephaly finding listed in subsection 8.1 only. Upon discussions with the DAI non-clinical and clinical teams, DPMH recommends adding Warnings and Precautions language for embryofetal toxicity to the zoliflodacin labeling.

3.3 Lactation

Nonclinical Experience[11,12]

There are no animal reproduction data with regard to lactation.

Review of Literature

DPMH's review of literature

DPMH conducted a review of published literature regarding zoliflodacin use during breastfeeding, and no data were found. Likewise, no lactation data information were located using HalesMeds[13] or LactMed.[14]

Reviewer comment: There are no human or animal data regarding zoliflodacin use during breastfeeding. Refer to the Discussion/Conclusions section of the review for DPMH's conclusion.

3.4 Females and Males of Reproductive Potential

Nonclinical Experience[11,12]

In the fertility and early embryonic development (FEED) studies in rats male rats for 4 weeks prior to mating at 1000 mg/kg/day (7.4-times the MRHD) caused a complete loss of fertility, and at 500 mg/kg/day (AUC exposures of 3.9-times the MRHD) a reduction in male rat fertility with decreased pregnancy rate and increased pre- and post-implantation loss. Pairing the same male rates with new untreated female partners after a 29-day recovery period showed full recovery of male fertility; however, there were still minimal to mild testicular tubular degeneration on histopathology after 57 days recovery. There was no effect on male fertility at 200 mg/kg/day (at 2-fold the MRHD based on AUC exposure comparison).

Following 4-weeks of daily oral dosing in general toxicity studies, adverse microscopic changes in the testes were present in rat at 1000 mg/kg/day and dog at 200 mg/kg/day (at AUC exposures of about 10-times and 7-times higher than the MRHD, respectively). These testicular changes were partially to completely reversed after three months.

Oral administration of zoliflodacin at 1000 mg/kg/day (AUC exposures of 12-fold the MRHD extrapolated from exposures in nonpregnant rats) to female rats for 2 weeks prior to mating reduced pregnancy rates. There was no effect on pregnancy rates or embryofetal survival at 500 mg/kg/day (at AUC exposures of >5fold the MRHD).

Refer to the Office of Pharmacology/Toxicology reviews for further details.

[13] Hale, Thomas. Medications and Mothers Milk. https://www.halesmeds.com/. Accessed 31 March 2025.
[14] LactMed. National Library of Medicine. National Center for Biotechnology Information. https://www.ncbi.nlm.nih.gov/books/NBK501922/. Accessed 31 March 2025.

Review of Literature

Applicant's review of literature

The Applicant conducted a review of literature regarding zoliflodacin use and fertility, and no data were found.

DPMH's review of literature

DPMH conducted a review of literature regarding fertility and zoliflodacin, and no data were found. In addition, no data were located in ReproTox.

Reviewer comment: There are no human data on the effects of fertility from zoliflodacin use. The male rat FEED studies showed reduced fertility and increased early pregnancy loss at 4 times the clinical dose. DAI has consulted the Division of Urology, Obstetrics and Gynecology (DUOG) with regard to observed testicular toxicity seen in some of the non-clinical data FEED studies. Due to the concerning animal findings of exencephaly, DPMH recommends adding pregnancy testing requirements to section 2 and subsection 8.3 of the labeling. Since there are concerns regarding decreased male fertility, DPMH also recommends adding language regarding male infertility to subsection 8.3. DPMH does not recommend adding a contraception requirement to the zoliflodacin labeling as this drug will only be administered as a single oral dose and has a relatively short half-life. Refer to the Discussion/Conclusions section of the review for DPMH's conclusion.

4 DISCUSSION AND CONCLUSIONS

4.1 Pregnancy

There are no clinical data for review regarding zoliflodacin exposure during pregnancy. Animal reproduction studies were conducted in rats and mice revealing early embryonic death in rats and reduced litter weights in both species along with increased skeletal variations and delayed ossification. Additionally, a few cases of exencephaly, a rare neural tube defect, were also observed in mice in three separate litters. DPMH recommends adding a Warnings and Precautions statement for embryofetal toxicity to labeling because there is the potential for a clinically significant risk to the fetus demonstrated in animal studies and the risk has implications for prescribing decisions and patient management. Since the causal relationship between exposure to zoliflodacin during pregnancy and exencephaly is not well established and the risk to humans is theoretical, DPMH does not recommend a Contraindication for Pregnancy at this time.

Since gonorrhea is a common infection in females of reproductive potential, it is possible that there may be unintended use of zoliflodacin in pregnant women. DPMH recommends the issuance of a postmarketing requirement (PMR) for a descriptive pregnancy safety study (DPSS) for the following reasons: 1.) There are findings of early embryonic death in rats and reduced litter weights in both rats and mice. In addition, cases of exencephaly were observed in the reproduction studies conducted in mice, 2.) There is potential risk of a safety signal because a fetus will be exposed to a drug that they would not have otherwise been exposed to, 3.) a pregnancy registry and claims database study would not be feasible as it is unlikely there will be a sufficient number of pregnant patients because of the Warning and Precautions statement on embryofetal toxicity, and the product is not expected to be used as first-line treatment for gonorrhea.

4.2 Lactation

There are no human or animal data regarding zoliflodacin use during breastfeeding. There are Warnings and Precautions for *Clostridioides difficile* infection and development of drug-resistant bacteria in currently proposed labeling that suggest the potential for adverse effects in the breastfed infant. Based on the drug's characteristics, zoliflodacin is likely to be transferred to breastmilk. Therefore, DPMH recommends including language in labeling noting that NUZOLVENCE may cause intestinal flora alteration of the breastfeeding infant. . Additionally, labeling will include the standard benefit/risk statement:

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DRUG-X and any potential adverse effects on the breastfed infant from DRUG-X or from the underlying maternal condition.

Lactating women and their healthcare providers often must make decisions about drug treatment and continuation of breastfeeding during therapy without any human data in labeling. Because gonorrhea affects females of reproductive potential, and there is the potential for zoliflodacin use during lactation, DPMH recommends DAI issue a PMR for a clinical lactation study (milk only or mother-infant pair study) to determine the amount of drug transferred into breastmilk for the following reason: 1.) Based on the drug's characteristics, it is likely that zoliflodacin will be present in human milk.

4.3 Females and Males of Reproductive Potential

Based on data from animal toxicity and fertility studies, NUZOLVENCE may impair human male fertility and cause testicular toxicity. These studies demonstrate that testicular toxicity was partially reversible after two to three months.

DAI has consulted DUOG with regard to the observed testicular toxicity observed in the non-clinical FEED studies. DPMH recommends adding pregnancy testing requirements to section 2 and subsection 8.3 of the zoliflodacin labeling along with language regarding male infertility to subsection 8.3. DPMH agrees with the DAI Clinical Team and DUOG with including a Warnings and Precautions section on

"Embryo-Fetal Toxicity: Potential Risk for Men with Female Partners of Reproductive Potential" and "Male Infertility and Testicular Toxicity." Although contraception in females exposed to zoliflodacin is not recommended, there will be recommendation in subsection 8.3 for contraception use in males with female partners of reproductive potential for at least 3 months (time it takes for sperm to regenerate) after single-dose administration.

5 LABELING RECOMMENDATIONS

DPMH met with DAI and DUOG on multiple occasions during the review cycle to discuss labeling for subsections *2.1 Pregnancy Testing in Females of Reproductive Potential, 5.1 Embryo-Fetal Toxicity: Potential Risk for Pregnant* (b) (4)*, 5.2 Embryo-fetal Toxicity: Potential Risk for Men with Female Partners of Reproductive Potential, 5.3* (b) (4) *Testicular Toxicity, 8.1 Pregnancy, 8.2 Lactation, 8.3 Females and Males of Reproductive Potential* and section *17 Patient Counseling Information* of the zoliflodacin labeling in compliance with the PLLR as outlined below. The following recommended language is the result of discussions between DAI, DUOG and DPMH; however, DPMH refers to the final NDA action for final labeling language.

DPMH Proposed PLLR Labeling

(b) (4)

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

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/s/

CARRIE M CERESA
10/02/2025 01:51:31 PM

MIRIAM C DINATALE
10/02/2025 02:45:35 PM

LEYLA SAHIN on behalf of LYNNE P YAO
10/06/2025 10:26:10 AM

Division of Urology, Obstetrics and Gynecology (DUOG) Consult

From: Marjorie Dannis MD, Medical Officer
Division of Urology, Obstetrics and Gynecology (DUOG)

Mark S. Hirsch MD, Medical Team Leader, DUOG
Audrey Gassman MD, Deputy Division Director, DUOG

To: Joseph Nguyen, Regulatory Project Manager,
Division of Anti-Infectives (DAI)

Shayna Dooling, M.D., Medical Officer, DAI
Ramya Gopinath, Medical Team Leader, DAI

Date of Consult Request: July 23, 2025
Date of Consult Completion: September 26, 2025

Sponsor: Entasis Therapeutics
Drug: Nuzolvence (zoliflodacin)
Proposed Doses: 3 grams as single oral dose
Proposed Indication: Treatment of uncomplicated urogenital gonorrhea due to *Neisseria gonorrhoeae* in adult and pediatric patients 12 years and older
.
Consult Request: Provide an assessment of testicular toxicity and input on:

- Recommended language pertaining to male fertility issues in the Package Insert.
- The need for additional nonclinical or clinical fertility postmarketing requirement (PMR) studies

1. Background

Zoliflodacin is a spiropyrimidinetrione antibacterial drug that inhibits bacterial DNA synthesis by inhibition of bacterial type II topoisomerase enzymes (e.g., DNA gyrase (topoisomerase II) and topoisomerase IV). The proposed indication is the treatment of uncomplicated urogenital gonorrhea caused by Neisseria gonorrhoeae in adults and in pediatric patients 12 years and older weighing at least 35 kg.

On April 15, 2025, NDA 219491 was submitted and was granted a priority review. The PDUFA goal date is December 15, 2025.

On July 23, 2025, DUOG was consulted regarding testicular toxicity/male fertility issues that had been identified in animal studies, including:

- "In a male rat fertility study with dosing of zoliflodacin for 4-weeks prior to mating, fertility was reduced to 0% and 69% at exposures about 7-fold and 4-fold the clinical dose, respectively. Fertility was not affected at the low dose (about 2-fold the clinical exposure by AUC) or when mating was repeated after a 4-week washout period in the same animals".

- "Histopathology in the male reproductive organs was reported in the 28-day toxicology studies in rats - mild to moderate depletion of the seminal vessels (3- to-10-fold the clinical exposure), minimal to mild epidydimal cellular debris (7-to-10-fold the clinical exposure), and minimal to mild testicular degeneration (10-fold the clinical exposure) - and in dogs - mild to moderate testicular degeneration and moderate cellular debris (7-fold the clinical exposure) at the end of dosing. In both the rat and dog, at least partial recovery was reported by the end of a 3-month recovery period with findings that were uncertain if they were test article-related or background."

DAI requests DUOG's input on:

a) Recommended language pertaining to fertility issues in Section 8.3 of the PI.
b) The need for additional nonclinical or clinical fertility PMR studies

2. Overview of the Testicular Toxicity Findings

Here we provide an overview of the key male reproductive toxicity findings from the nonclinical studies with focus on 1) testicular toxicity and male factor infertility, and 2) embryonal loss in the male rat fertility study.

In addition to the overview, we also provide brief summaries of the key nonclinical studies relevant to male reproductive toxicity.

2.1 Overview of the Key Male Reproductive Toxicity Findings in Nonclinical Studies

Zoliflodacin is a testicular toxin in rats and dogs. The drug caused testicular toxicity after drug administration of 2 to 28 days. Minimal to moderate degeneration of the seminiferous tubules (germinal epithelium) was observed in rats and dogs at exposures roughly 3- to 10-fold the exposure after human dosing. Although the nonclinical studies demonstrated NOAELs (no observed adverse event levels) for testicular effects, the margins of safety from the NOAELs to the human exposure were small (<5 times). The testicular toxicity due to zoliflodacin in animals appeared to be largely, though not completely, reversed in the 28-day rat and 28-day dog toxicology studies.

Also, in the male rat fertility study, reduced number of live embryos and increased number of embryonic losses were observed in untreated female rats mated with male rats administered zoliflodacin at exposures approximately 4-times the clinical exposure for 4 weeks. The reduction in fertility was fully reversible after 4 weeks. However, the underlying testicular and epididymal histopathology was only partially reversed.

The nonclinical data indicate that zoliflodacin disrupted spermatogenesis and damaged the testes in animals. Zoliflodacin also caused embryonal loss related to an effect on rat sperm. Testing of male reproductive function in humans has not been done. The impact of zoliflodacin on human male reproduction is currently unknown.

2.2 Brief Summaries of the Key Nonclinical Studies Relevant to Male Reproductive Toxicity

1-Month Oral Toxicology Study (with 3-Month Recovery) in Rats

Minimal/mild testicular degeneration was noted at 1000 mg/kg, minimal/mild epididymal cellular debris was noted at 500-1000 mg/kg, and mild/moderate seminal vesicle secretory depletion was observed at all doses The NOAEL was 200 mg/kg with a safety margin of 3-fold based on AUC.

The 3-Month recovery group results included one male with mild testicular tubular degeneration and minimal epididymal debris and another male with severe testicular atrophy and marked epididymal hypocellularity. The recovery male with severe findings may represent a background testicular abnormality.

> *Consultant's Comment: In the recovery results, it was unclear to the pathologist whether these abnormalities were due to persistence of drug-related changes or were secondary to background/spontaneous findings. However, persistence of the testicular findings in one of four males could suggest incomplete reversibility.*

1-Month Oral Toxicology Study (with 3-Month Recovery) in Dogs

Mild/moderate testicular degeneration was noted at 200 mg/kg and 500 mg/kg with moderate cellular debris noted in the epididymis at 500 mg/kg. The NOAEL was 100 mg/kg with a safety margin of 2-fold based on AUC. The 3-Month recovery results included two males with hypo-spermatogenesis at 500 mg/kg.

> *Consultant's Comment: In the recovery group, again it was unclear to the pathologist whether these findings were due to persistence of drug-related changes (indicating a delay of recovery of spermatogenesis) or represented a background finding.*

Ferti1ity Early Embryonic Development Study (+Recovery) in Male Rats

A reduced male fertility index was noted at 500 mg/kg and 1000 mg/kg; however, both these findings showed reversibility after 4 weeks. Histopathological findings at the End of the 9-week recovery period included testicular degeneration in one male in the 200 mg/kg group, two males in the 500 mg/kg group and eight males in the 1000 mg/kg group (no testicular abnormalities were seen in the control group). In addition, the findings for the recovery male in the 200 mg/kg group showed marked tubular cellular debris and marked decreased cellularity and spermatids in the epididymis. The NOAEL was 200 mg/kg with a safety margin of 2-fold based on AUC.

> *Consultant's Comment: It remains unclear whether the testicular degeneration observed in the 200 mg/kg recovery male were drug-related or background.*

14-Day IV Tox Study in Dogs (with 28-Day Recovery)

The NOAEL was 100 mg/kg with a safety margin of 3-fold based on AUC. The recovery results showed minimal bilateral hypo-spermatogenesis in one high-dose male and mild unilateral hypo-spermatogenesis in one control male.

14-Day Oral Tox Study in Rats with 2-Day MTD Phase (Not Good Laboratory Practice [GLP])

Minimal/moderate exfoliation of germinal epithelial cells was noted at 500 mg/kg, 1000 mg/kg and 2000mg/kg. In addition, minimal/moderate immature sperm were observed in the epididymis at 500 mg/kg and 1000 mg/kg The NOAEL was 250 mg/kg with a safety margin of 4-fold based on AUC.

> *Consultant's Comment: Although the 14-Day oral toxicity study in rats was not a GLP study, the results were consistent with the results from the other GLP studies and showed adverse effects on the testicle after just 2 days of drug administration.*

3. Consultant's Conclusions

1. Zoliflodacin is a testicular toxin in rats and dogs. The drug caused testicular toxicity after drug administration of 2 to 28 days. Minimal to moderate degeneration of the seminiferous tubules (germinal epithelium) was observed in rats and dogs at exposures roughly 3- to 10-fold the exposure after human dosing. In these studies, the margins of safety from the NOAELs to the human dose were small (all less than 5-fold). The testicular toxicity appeared to be largely, though not completely, reversed in the 28-day rat and 28-day dog toxicology studies.

2. In the male rat fertility study, reduced number of live embryos and increased number of embryonic losses were observed in untreated female rats mated with male rats administered zoliflodacin at exposures approximately 4-times the clinical exposure for 4 weeks. The NOAEL in that study provided a very small (2-fold) margin of safety to the human dose. The reduction in rat fertility was fully reversible after 4 weeks. However, the underlying testicular and epididymal histopathology was only partially reversed.

3. Testing of male reproductive function in humans has not been done. The impact of zoliflodacin on human male reproduction is currently unknown.

4. Warnings in product labeling are needed to convey the potential risks to male reproduction (see Section 4).

5. Human investigations are needed to confirm or refute an adverse effect of zoliflodacin on human spermatogenesis (see Section 5).

4. DUOG Consult Recommendations for Product Labeling

Based on the available nonclinical evidence, we recommend two Warnings be incorporated into the product labeling, as follows:

> ***5.2 Embryo-Fetal Toxicity: Potential Risk for Men with Female Partners of Reproductive Potential***
> *Based on data from an animal toxicity study, the risk of early pregnancy loss may be increased in partners of males treated with NUZOLVENCE. Reduced number of live embryos and increased number of embryonic losses were observed in untreated female rats mated with male rats administered zoliflodacin at exposures approximately* (b)(4) *times the clinical exposure at the MRHD for 4 weeks.*

Risk mitigation for men: Advise males with female partners of reproductive potential to use effective contraception for at least 3 months after (b) (4) *administration of NUZOLVENCE [see Use in Specific Populations (* (b) (4) *8.3) and Nonclinical Toxicology (13.1)].*

5.3 (b) (4) ***Testicular Toxicity***

Based on (b) (4) *animal* (b) (4) *studies, NUZOLVENCE may impair* (b) (4) *male fertility and cause testicular toxicity.* (b) (4)

Advise males that (b) (4) *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)].*

5. DUOG Consult Recommendations for a Postmarketing Requirement (PMR) Study

Based on the available nonclinical evidence, we recommend that DAI request an active-controlled human sperm study as a postmarketing requirement.

The study should be designed as a randomized, active-controlled, parallel-arm trial of approximately 200 men. The investigational drug should be administered at a dose and frequency that is representative of its intended clinical use. The Sponsor should obtain semen analyses at baseline and at the end of 13 weeks.

For details on conducting a human sperm study, refer to Section V in the FDA Guidance for Industry, Testicular Toxicity: Evaluation During Drug Development (October 2018) https://www.fda.gov/media/117948/download.

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/s/

MARJORIE F DANNIS
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MARK S HIRSCH
09/26/2025 11:51:10 AM
I concur.

AUDREY L GASSMAN
09/26/2025 11:52:18 AM

USE-RELATED RISK ANALYSIS REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	September 18, 2025
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 219491
Product Name, Dosage Form and Strength:	Nuzolvence[a] (zoliflodacin) granules for oral suspension, 3 grams
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Rx
Device Constituent:	Oral Suspension Cup
Applicant/Sponsor Name:	Entasis Therapeutics, Inc. (ETI)
Submission Date:	April 15, 2025; July 14, 2025; September 9, 2025
OSE TTT #:	2025-14176
DMEPA 1 Safety Evaluator:	Tianyi Zhang, PhD, MS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Deputy Director	Jason Flint, MBA, PMP

[a] The proposed proprietary name, Nuzolvence, was found conditionally acceptable by DMEPA on March 13, 2025 (PNR# 2024-1044726016). Of note, ETI refers to the product as its proprietary name placeholder, zoliflodacin convenience kit, throughout their submission.

1 REASON FOR REVIEW

The review evaluates the use-related risk analysis (URRA) submitted under new drug application (NDA) 219491 for Nuzolvence (zoliflodacin) oral suspension cup to determine whether Entasis Therapeutics, Inc. (ETI) needs to submit human factors (HF) validation study results to support their marketing application.

1.1 MATERIALS CONSIDERED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Materials Considered	Section/Appendix
Relevant Product Information	Section 1.2
Relevant Regulatory History Related To Nuzolvence's Human Factors Development Program	Section 1.3
Use-Related Risk Analysis and HF-Related Supporting Documents	Appendix A
Information Request Issued During the Review	Appendix B
Product Samples, Labels, and Labeling	Appendix C

1.2 RELEVANT PRODUCT INFORMATION

Table 2. Relevant Product Information for Nuzolvence	
Product Name	Nuzolvence
Application Number	NDA 219491
Initial Approval Date	N/A
Active Ingredient	zoliflodacin
Indication	uncomplicated Neisseria gonorrhoeae infection in adult and pediatric patients 12 years and older, weighing at least 35 kg.
Route of Administration	Oral Suspension
Dosage Form	granules for oral suspension
Strength	3 grams
Dose and Frequency	The recommended dosage of Nuzolvence in adult and pediatric patients 12 years and older weighing at least 35 kg is 3 g administered as a single dose orally.

Dose of Nuzolvence	Body weight (kg)	Prandial state

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Nuzolvence</th></tr>
<tr><td></td><td>
<table>
<tr><td rowspan="2">3 g administered as a single, oral dose</td><td>≥ 35 kg to < 50 kg</td><td>Take on an empty stomach, 1 hour before or 2 hours after food</td></tr>
<tr><td>≥ 50 kg</td><td>Take with food</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>Nuzolvence (zoliflodacin) (b) (4) for oral suspension is supplied as a kit.
<table>
<tr><th>Package Configuration</th><th>Strength</th><th>NDC Code</th></tr>
<tr><td>Carton containing 1 (b) (4) packet of zoliflodacin and one 120 mL mixing container with lid</td><td>3 g</td><td>68547-915-10</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>Nuzolvence should be stored at room temperature (b) (4) in the original packaging. Do not freeze. (b) (4)</td></tr>
<tr><td>Container Closure/Device Constituent</td><td>(b) (4)</td></tr>
<tr><td>Intended Users</td><td>Adult patients, Caregivers, and Healthcare providers (HCPs)</td></tr>
<tr><td>Intended Use Environment(s)</td><td>Clinical and home</td></tr>
</table>

1.3 RELEVANT REGULATORY HISTORY RELATED TO NUZOLVENCE'S HUMAN FACTORS DEVELOPMENT PROGRAM

On July 2, 2025, we searched for previous DMEPA reviews and FDA/ETI interactions relevant to this current review using the terms, "*IND 118958*", "*NDA 219491*", and "*zoliflodacin*". See details below.

- On September 4, 2024, ETI submitted a type B meeting request under IND 118958 to discuss the Chemistry, Manufacturing, and Controls strategy for zoliflodacin convenience kit.
    - On September 10, 2024, we granted the meeting and had a teleconference meeting with ETI on November 18, 2024. In the meeting minutes dated December 17, 2024, we recommended ETI conduct and submit a URRA.[b]
- On April 4, 2025, ETI submitted the URRA for zoliflodacin convenience kit under IND 118958. ETI's cover letter stated "*Please note that this same information related to the zoliflodacin convenience kit will be submitted with the zoliflodacin NDA later this month. Therefore, the Sponsor is not requesting formal feedback on this submission to the IND*." Based on the aforementioned information, on June 3, 2025, we notified ETI the submission of URRA for zoliflodacin convenience kit under IND 118958 is considered withdrawn.[c]
- On April 15, 2025, ETI submitted an NDA for zoliflodacin convenience kit for the treatment of uncomplicated Neisseria gonorrhoeae infection under NDA 219491. The submission included the same URRA, which is the subject of this review.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide our evaluation of the URRA.

[b] Walters, D. Meeting Minutes for zoliflodacin. Silver Spring (MD): FDA, CDER, OND (US); 2024 December 17. IND 118958.

[c] Bui Nguyen, T. Human Factors Use Risk Related Analysis Withdrawal Letter. Silver Spring (MD): FDA, CDER, OND (US); 2025 June 3. IND 118958.

2.1 USE-RELATED RISK ANALYSIS

ETI submitted a URRA for their proposed product, Nuzolvence oral suspension cup.

We reviewed the URRA for the proposed product and, based on the information we have at this time, the tasks evaluated appear to be comprehensive and appropriate based on what ETI proposes for the design and intended use of this product.

We did not identify any additional use-related issues that were not analyzed; however, we identified additional issues related to the product samples that we discuss in section 3 below.

3 ADDITIONAL LABELING COMMENTS

Based on the five product samples we received, we evaluated the physical mixing container and identified discrepancies between the IFU image and the physical mixing container (see Figures 1 and 2 below). Specifically, we note the following issues:

- The mixing container in the IFU image (b) (4) (see Figure 1) (b) (4) However, the physical mixing container (b) (4) (see Figure 2).
- The mixing container in the IFU image (b) (4) (see Figure 1). However, the physical mixing container (b) (4) (see Figure 2).

Figure 1: IFU Image of the mixing container

(b) (4)

Figure 2: Physical mixing container

(b) (4)

As such, based on the aforementioned information we issued in the information request (IR) on July 11, 2025, requesting ETI ensure that the intend-to-market mixing container aligns with the mixing container IFU images:

In the IR response dated July 14, 2025, ETI stated the following:

> "*When identifying and selecting a proposed commercial mixing container, the Sponsor ensured that any container under consideration for commercial use would have embossed gradations and a marking for the "60 mL" dose on the outside of the mixing container to avoid the challenges identified in the human factors engineering work. The proposed commercial mixing container satisfies these criteria.*
>
> *The Sponsor acknowledges that in addition to having gradations and markings on the outside of the container, it was recommended in the human factors [formative] testing that*

the mixing container should include a dark "fill line" that is easily identifiable against the container's clear background. However, by proposing a commercial mixing container with clearly embossed external gradations and markings, the Sponsor believes that the proposed commercial mixing container sufficiently addresses the visibility concerns raised during testing and that markings on the intended commercial mixing container are clearly visible.

The Sponsor acknowledges the discrepancies between Figure 1 in the IFU and the sample mixing container provided to the Agency. While Figure 1 in the IFU was intended as a conceptual representation rather than an exact depiction, the Sponsor acknowledges the opportunity to provide greater clarity to the end user and will revise the IFU accordingly to more accurately reflect the proposed container's features."

In an additional IR response dated September 9, 2025, ETI submitted the updated IFU and stated that the updated IFU "*incorporates the following modifications to ensure alignment with the proposed container:*

- (b) (4) *are presented to reflect the actual markings on the proposed commercial mixing container.*
- *The 60 mL fill line is now emphasized using directional arrows,* (b) (4) *for improved visual clarity*."

We acknowledge the Applicant's aforementioned justification; however, we do not agree, and we continue to provide the following recommendations:

- The physical mixing container (b) (4) as recommended by the human factors formative testing results. We do not agree that "*the currently proposed commercial mixing container sufficiently addresses the visibility concerns raised during human factors formative testing or that markings on the intended commercial mixing container are clearly visible*". Our guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (April 2016) recommends avoiding container closures that provide poor visual contrast between the container closure material and label information (e.g., materials that have debossed or embossed information directly on the container closure), which has led to incorrect doses errors. As such, we strongly recommend ETI pursue a mixing container that has a dark "fill line" and an embossed, bolded "60 mL" graduation mark that is easily identifiable against the container's clear background.
- The physical mixing container (b) (4) that may cause confusion. The physical mixing container (b) (4), while the mixing container in the IFU image (b) (4) (b) (4). The guidance for industry Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products (May, 2011), as referenced in our guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (April 2016), recommends "*Dosage delivery devices should*

not bear extraneous or unnecessary liquid measure markings that may be confusing." The [redacted] on the currently proposed commercial mixing container are [redacted] because the IFU [redacted] As such, we strongly recommend ETI pursue a mixing container that has no unnecessary graduation marks (i.e., 1-4 oz).

Based on the changes made to the mixing container, we recommend ETI revise the labels and labeling images accordingly.

We provide the aforementioned recommendations to ETI in Section 4.1. We determine that this change can be implemented without submitting HF validation study results.

We note the DMEPA 1 Nomenclature and Labeling review team evaluated product specific labels and labeling under a separate cover.[d]

4 CONCLUSION

Our review of the use-related risk analysis did not identify any new, differing, or unique risks for the proposed product. As such, we agree with Entasis Therapeutics, Inc.'s justification for not submitting human factors (HF) validation study results as part of their marketing application. However, we identified issues with the product samples.

We provide our response and recommendations to Entasis Therapeutics, Inc. in section 4.1.

4.1 RECOMMENDATIONS TO ENTASIS THERAPEUTICS, INC.

Based on our review of the use-related risk analysis (URRA), we have determined that human factors (HF) validation study results do not need to be submitted with your marketing application. However, our evaluation of your product samples identified issues. We recommend that you implement these recommendations, and we determine that in this instance, you may implement these revisions without submitting HF validation study results for Agency review:

- The physical mixing container [redacted] as recommended by the human factors formative testing results. We do not agree that "*the currently proposed commercial mixing container sufficiently addresses the visibility concerns raised during human factors formative testing or that markings on the intended commercial mixing container are clearly visible*". Our guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (April 2016) recommends avoiding container closures that provide poor visual contrast between the container closure material and label information (e.g., materials that have debossed or embossed information directly on the container closure), which has led to incorrect doses errors. As such, we strongly recommend you pursue a mixing container that has a dark "fill line" and an embossed, bolded "60 mL" graduation mark that is easily identifiable against the container's clear background.

[d] Myers, D. Nuzolvence (zoliflodacin) Label and Labeling Review NDA 219491. Silver Spring (MD): FDA, CDER, OND (US); 2025 July 31. TTT No.: 2025-14183.

- The physical mixing container [redacted] that may cause confusion. The physical mixing container [redacted], while the mixing container in the IFU image [redacted] The guidance for industry Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products (May, 2011), as referenced in our guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (April 2016), recommends "*Dosage delivery devices should not bear extraneous or unnecessary liquid measure markings that may be confusing*." The [redacted] on the currently proposed commercial mixing container are [redacted] because the IFU [redacted] As such, we strongly recommend you pursue a mixing container that has no unnecessary graduation marks (i.e., 1-4 oz).

Based on the changes made to the mixing container, we recommend you revise the labels and labeling images accordingly.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. USE-RELATED RISK ANALYSIS AND HF-RELATED SUPPORTING DOCUMENTS

The use-related risk analysis (URRA) for Nuzolvence submitted on April 15, 2025 can be accessible in EDR via: \\CDSESUB1\EVSPROD\nda219491\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\uncomplicatedgonorrhea\5354-other-stud-rep\urrareport\human-factors-testing.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On 7/11/2025, we issued an Information Request (IR) to request the intend-to-market IFU artwork and clarification on whether the mixing container will match the IFU image.

- On 7/14/2025, Entasis Therapeutics, Inc. provided a response that can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda219491\0015\m5\53-clin-stud-rep\535-rep-effic-safety-stud\uncomplicatedgonorrhea\5354-other-stud-rep\hfresponse\response-to-ir-dated-10-jul-2025.pdf
- On 9/9/2025, Entasis Therapeutics, Inc. provided additional response with the updated IFU that can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda219491\0025\m5\53-clin-stud-rep\535-rep-effic-safety-stud\uncomplicatedgonorrhea\5354-other-stud-rep\hfresponse\response-to-hf-ir.pdf and \\CDSESUB1\EVSPROD\nda219491\0025\m1\us\114-labeling\114a-draft-label\ifu.pdf

APPENDIX C. PRODUCT SAMPLES, LABELS, AND LABELING

C.1 Product Samples

The product samples were submitted for our review and we provide recommendations for improvement in the Section 4.1 above.

C.2 List of Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error experiences with similar products, we reviewed the following Nuzolvence labeling submitted by Entasis Therapeutics, Inc. on July 7, 2025.

Container Labels	\\CDSESUB1\EVSPROD\nda219491\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-nuzolvence-container.pdf
Carton Labeling	\\CDSESUB1\EVSPROD\nda219491\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-nuzolvence-carton.pdf
Instructions for Use	\\CDSESUB1\EVSPROD\nda219491\0015\m1\us\114-labeling\114a-draft-label\ifu.pdf

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

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JASON A FLINT
09/22/2025 12:12:37 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 31, 2025
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 219491
Product Name, Dosage Form, and Strength:	Nuzolvence (zoliflodacin), granules for oral suspension, 3 grams
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Entasis Therapeutics, Inc. (ETI)
FDA Received Date:	April 15, 2025
TTT ID #:	2025-14183
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 INTRODUCTION

As part of the approval process for Nuzolvence (zoliflodacin) granules for oral suspension, the Division of Anti-Infectives (DAI) requested that we review the proposed Nuzolvence Prescribing Information (PI), Instructions for Use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND/REGULATROY HISTROY

On March 11, 2025, we found the proposed proprietary name, Nuzolvence, conditionally acceptable under IND 118958.[a]

On April 15, 2025, Entasis Therapeutics, Inc. (ETI) submitted their 505(b)(1) Original New Drug Application (NDA) 219491 for Nuzolvence (zoliflodacin).[b]

On June 4, 2025, we found the proposed proprietary name, Nuzolvence, conditionally acceptable under NDA 219491.[c]

On June 10, 2025, the Agency sent an Information Request (IR) to ETI requesting confirmation if the Instructions for Use (IFU) and Prescribing Information (PI) will be included inside the carton, as opposed to attached to the outside of the carton, of the marketed product.[d]

On June 11, 2025, in response to the Agency's IR dated June 10, 2025, ETI provided confirmation that both the IFU and PI will be included inside the carton of the marketed product, and appropriately folded.[e]

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Label and Labeling	B

[a] Myers, D. Proprietary Name Review for Nuzolvence (IND 118958). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 MAR 11. PNR ID No. 2024-1044726016.

[b] Cover Letter: Submission: Original New Drug Application and Request for Proprietary Name Review for Nuzolvence (zoliflodacin) NDA 219491. Waltham (MA): Entasis Therapeutics, Inc. (ETI); 2025 APR 15. Available from: \\CDSESUB1\EVSPROD\nda219491\0001\m1\us\12-cover-letter\cover-letter-sn0001-initial-application.pdf.

[c] Myers, D. Proprietary Name Memorandum for Nuzolvence (NDA 219491). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 JUN 04. PNR ID No. 2025-1044726400.

[d] Nguyen, J. FDA Communication Dated 06/10/2025: Information Request (Labeling) – NDA 219491 (zoliflodacin) – Due June 12, 2025. Silver Spring (MD): FDA, CDER, OND, OAP, DAI (US); 2025 JUN 10. NDA 219491. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807c1103.

[e] Multiple Module Information Amendment: Response to IR dated 10-Jun-2025 for Nuzolvence (zoliflodacin) NDA 219491. Waltham (MA): Entasis Therapeutics, Inc. (ETI); 2025 JUN 11. Available from: \\CDSESUB1\EVSPROD\nda219491\0007\m1\us\111-info-amend\response-to-ir-dated-10-jun-2025.pdf.

3 CONCLUSION

The proposed Nuzolvence Prescribing Information (PI), Instructions for Use (IFU), container label, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Anti-Infectives (DAI) in Section 4 and for Entasis Therapeutics, Inc. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for the Division of Anti-Infectives (DAI)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 *Dosage and Administration*			
1.	As currently presented in subsection 2.1 (b) (4) the text associated with the first bullet point (b) (4) includes the word "not" which may be overlooked. Additionally, the first sentence is presented in passive voice and appears before the intended action (i.e., mix with water).	Post-marketing reports indicate that negative statements (e.g., do not) may have the opposite of the intended meaning because the word "not" can be overlooked, and the warning may be misinterpreted as an affirmative action.[f] If a negative statement is unavoidable, it should follow an affirmative statement to ensure end users understand the intended action. Additionally, instructions should be written in active and command voice to increase clarity of the intended action.	We recommend beginning this text with the intended action and then bolding the font of the word "not", to help provide clarity and minimize this word "not" being missed or overlooked. For example, revise to "…NUZOLVENCE must be mixed with water before administering. Do not mix with other liquids or sprinkle on food."
2.	As currently presented, Table 1 "Administration of NUZOLVENCE with or without food based on weight" under subsection 2.2	Error prone symbols may lead to misinterpretation and medication error.	We recommend replacing the symbols (i.e., "≥" and "<") with their intended meanings. For example, revise to "35 kg to less than 50 kg" and "greater than or equal to 50 kg". See

[f] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

Table 2. Identified Issues and Recommendations for the Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) contains the error-prone symbols "≥" and "<."		*Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.[g]
Full Prescribing Information – Section 16 *How Supplied/Storage and Handling*			
1.	A description of the dosage form is not provided (e.g., white to off-white granules).	A description of identifying characteristics of the dosage form is required per 21 CFR 201.57(c)(17)(iii).	Provide a description of identifying characteristics of the granules for oral suspension in accordance with 21 CFR 201.57(c)(17)(iii).
Instructions for Use (IFU)			
1.	Under (b) (4) the first sentence of the second bullet point, (b) (4) is presented in passive voice, which lacks clarity. Additionally, the intended action, "Always mix NUZOLVENCE with water before taking (see instructions below)"is presented after a negative statement (i.e., not).	Writing instructions in active and command voice increases clarity of the intended action. Additionally, generally, if a negative statement is unavoidable, it should follow an affirmative statement. Using affirmative statements helps to ensure that end users understand the intended action.	We recommend revising to: "Always mix NUXOLVENCE with water before taking (see instructions below)." Additionally, we recommend removing (b) (4) as this language may not be readily understood by lay-users.
2.	As currently presented under "Taking NUZOLVENCE, Step 7 does not direct end-	For added clarity.	Incorporate additional instruction in Step 7 to instruct end-users to remove the lid

[g] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

Table 2. Identified Issues and Recommendations for the Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	users to remove the lid prior to drinking the mixture in the mixing container.		prior to drinking the mixture. For example, add the direction: "a. Remove the lid from the mixing container by twisting it counter-clockwise. b. Drink all the mixture from the mixing containing." Additionally, we recommend adding an appropriate associated graphic to depict the intended action in the new 7a instruction (i.e., twisting the lid counterclockwise).

The following editorial revisions are recommended to improve readability and/or clarity:

1. In the Highlights of Prescribing Information, under the header *Dosage and Administration*, to align with subsection 2.2 of the Full Prescribing Information, include the missing clarification that the recommended dosage is for "adult and pediatric patients 12 years and older weighing at least 35 kg." Additionally, we recommend adding the clarifying information "one packet" following "3 g", for example:

(b) (4)

2. Under subsection 2.1 (b) (4), revise the text associated with the third bullet point, such that it is consistent with Steps 5 and 6 in the IFU, for example:

(b) (4)

3. Under subsection 2.2 (b) (4), define, by writing out, the unit of measure (grams) followed by the abbreviation (g) enclosed by parentheses, with their first appearance in the document (e.g., Full Prescribing Information). Subsequent references to the abbreviation can be made just by the abbreviation alone. Additionally, we recommend adding the clarifying information "one packet" following

Table 2. Identified Issues and Recommendations for the Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the dose strength, for example: (b) (4)		
	4. Under subsection 16.1 *How Supplied*, add "Instructions for Use" as a component of the carton. For example, revise to: "Carton containing 1 unit-dose packet (b) (4) one 120 mL mixing container with lid, and Instructions for Use." For example, (b) (4)		

5 RECOMMENDATIONS FOR ENTASIS THERAPEUTICS, INC.

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the strength statement on the container label and carton labeling lacks prominence and adequate spacing between the number and the unit of measure (i.e., "3g").	Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding	Increase the prominence (e.g., increase the font size (height)) of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. Additionally, we recommend placing adequate space between the numeric portion of the strength and unit of measure to improve readability (i.e., "3 g" instead of "3g").

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		with other written, printed, or graphic matter.	
2.	The placeholder for the lot number is missing.	Lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	Add the placeholder for the lot number in accordance 21 CFR 201.10(i)(1).
3.	The placeholder for the expiration date is missing.	The label of an official drug product shall bear an expiration date per USP General Chapter <7>.	Add the placeholder for the expiration date in accordance with USP General Chapter <7>. The USP Chapter <7>Labeling requires the expiration date to appear on the immediate container and all other packaging. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. We recommend you ensure that there are no other numbers located in close proximity to the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date format you intend to use.

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	As currently presented, the package type term, unit-dose packet, is not stated on the principal display panel (PDP) of the container label.	Consistent use of the correct package type term will promote proper use of the drug product. The lack of this information may lead to wrong technique medication errors during preparation of the product.	Add "unit-dose" prior to "packet" in the current statement "This packet contains 3 g of zoliflodacin." on the PDP. For example, "This unit-dose packet contains 3 g of zoliflodacin."
2.	The statement of dosage, (b) (4) which may cause confusion.	(b) (4)	For clarity, revise the statement of dosage on the container label to: DOSAGE AND USE: See Prescribing Information Or RECOMMENDED DOSAGE: See Prescribing Information
3.	The DIRECTIONS statement (b) (4) Furthermore, we note the word "not" is included in the statement "Do not mix with other liquids or sprinkle on food," which may be overlooked.	(b) (4) Furthermore, postmarketing reports indicate that negative statements (e.g., not) may have the opposite of the intended meaning because the word "not" can be overlooked, and the warning may be misinterpreted as an affirmative action.[h]	For clarity, revise the statement, (b) (4) under DIRECTIONS to "see *Instructions for Use*". Furthermore, we recommend bolding the word "not" in the last sentence. For example, revise to "Do not mix with other liquids or sprinkle on food."
4.	As currently presented, the route of	We (b) (4) when there is a	To help mitigate the risk of wrong administration

[h] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	administration statement (b) (4) (b) (4)	safety concern or data that supports the product must be given by a specific route. Additional context may help (b) (4)	medication errors, we recommend revising the route of administration statement to, for example: "FOR ORAL USE – MUST BE MIXED WITH WATER."
Carton Labeling			
1.	The statement "Do not mix with other liquids or sprinkle on food" is missing under the DIRECTIONS section, which is inconsistent with other labeling components.	When included, important preparation information should be presented consistently across all labels and labeling to help minimize medication error. The statement is included on the container label.	Revise the DIRECTIONS section to add the statement "Do not mix with other liquids or sprinkle on food." Note, we recommend bolding the word "not" to minimize the risk of it being overlooked and the statement interpreted as the opposite of its intent.
2.	As currently presented, included in the contents on the PDP of the carton, the "mixing container" (b) (4)	(b) (4) may lead to confusion.	We recommend removing (b) (4) from the contents on the PDP of the carton, (b) (4) For example, revise to "1 mixing container, 120 mL, with lid".

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) [redacted]		
3.	Under the contents section on the PDP of the carton, the statement (b) (4) [redacted] could be misinterpreted.	"3 g" is referring to the amount of active ingredient, zoliflodacin, (b) (4) [redacted]	We recommend deleting (b) (4) [redacted] from the statement to increase clarity. For example, revise to "1 packet containing 3 g of zoliflodacin".
4.	As currently presented, the package type term (b) (4) [redacted] appears on the PDP, side panels, and top panel.	Per USP <659> (b) (4) [redacted] Since Nuzolvence is for oral administration, "unit-dose" is the appropriate term.	In accordance with USP <659> revise all occurrences of (b) (4) [redacted] on the carton labeling (i.e., PDP, side panels, and top panel) to reflect the appropriate package type terminology. For example, "UNIT-DOSE KIT."
5.	The product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product	Add the product identifier to the carton labeling. For additional information, see *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.[i] Ensure there is sufficient space between the linear barcode and 2-D matrix barcode to facilitate proper scanning.

[i] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 3. Identified Issues and Recommendations for Entasis Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		identifier includes the national drug code (NDC), serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Nuzolvence received on April 15, 2025 from Entasis Therapeutics, Inc.

<table>
<tr><th colspan="2">Table 4. Relevant Product Information for Nuzolvence</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>zoliflodacin</td></tr>
<tr><td>Indication</td><td>For the treatment of uncomplicated gonorrhea due to Neisseria gonorrhoeae in adult and pediatric patients 12 years and older, weighing at least 35 kg.</td></tr>
<tr><td>Dosage Form</td><td>granules for oral suspension</td></tr>
<tr><td>Strength</td><td>3 grams</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dose and Frequency</td><td>3 grams administered as a single dose.
Administration of NUZOLVENCE with or without food based on weight
<table>
<tr><th>Dose of NUZOLVENCE</th><th>Body weight (kg)</th><th>(b) (4)</th></tr>
<tr><td rowspan="2">3 g administered as a single, oral dose</td><td>≥ 35 kg to < 50 kg</td><td>Take on an empty stomach, 1 hour before or 2 hours after food</td></tr>
<tr><td>≥ 50 kg</td><td>Take with food</td></tr>
</table></td></tr>
<tr><td>General Dosing Instructions</td><td>• See Instructions for Use for details on preparation and administration of NUZOLVENCE granules for oral suspension. NUZOLVENCE should not be taken in its dry form. Always mix with water before administering. Do not mix with other liquids or sprinkle on food.
• Accurately measure 60 mL of water into the provided mixing container.
• Add the entire contents of one packet of NUZOLVENCE to the mixing container and immediately place the provided lid on the mixing container securely and shake for at least 60 seconds. Continue to shake until all granules are suspended and there is a uniform suspension.
• Once NUZOLVENCE is mixed, the entire contents of the mixing container should be consumed immediately.
• Then add an additional 60 mL of water to the same mixing container, shake, and administer the entire additional 60 mL of water to ensure the full dose of medication is consumed.
• The entire dose should be administered within 15 minutes of mixing. If the dose is not administered within 15 minutes of mixing, a new dose of medicine must be prepared.</td></tr>
</table>

Table 4. Relevant Product Information for Nuzolvence	
How Supplied	Supplied as a kit. Package Configuration: Carton containing 1 (b) (4) packet (b) (4) and one 120 mL mixing container with lid.
Storage	Store at room temperature (b) (4) in the original packaging. Do not freeze. (b) (4)
Container Closure	sealed (b) (4)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error data, we reviewed the following Nuzolvence labels and labeling submitted by Entasis Therapeutics, Inc.

- Prescribing Information (PI) (images not available) received on April 15, 2025
  - Clean proposed (Draft) PI available at the following link: \\CDSESUB1\EVSPROD\nda219491\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-pi.pdf.
  - Annotated Draft PI available at the following link: \\CDSESUB1\EVSPROD\nda219491\0001\m1\us\114-labeling\114a-draft-label\annotated-draft-labeling-text.pdf.
- Instructions for Use (IFU) (images not included) received on April 15, 2025, and available at the following link: \\CDSESUB1\EVSPROD\nda219491\0001\m1\us\114-labeling\114a-draft-label\draft-labeling-text-ifu.pdf.
- Container label(s) received on April 15, 2025
- Carton labeling received on April 15, 2025

[j] 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/

DEBORAH E MYERS
07/31/2025 02:11:38 PM

VALERIE S VAUGHAN
07/31/2025 02:23:48 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY PRODUCTS

Date: June 26, 2025

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Associate Director, Cardiac Safety IRT, DCN

To: Joseph Nguyen, RPM
DAI

Subject: QT Consult to NDA 219491 (SDN 1)

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

This memo responds to your consult to us dated 4/15/2025 regarding the Division's QT related question. We reviewed the following materials:

- Clinical Pharmacology summary (NDA219491 / SDN 1);
- Previous IRT reviews for IND # 118958 dated 09/11/2024; 05/23/2018 and 01/13/2016 in DARRTS;
- Proposed label (link);
- CSR for the food effect study (NDA219491 / SDN 1);
- Cardiabase ECG safety report for food effect study (NDA219491 / SDN 1);
- Population Pharmacokinetics Report (NDA219491 / SDN 1);
- TQT study report (NDA219491 / SDN 1); and
- Exposure response report (NDA 219491/0001; link).

1 Responses for the Review division

Question: Division has submitted a consult and requested IRT feedback on following:

1. The validity of the TQT threshold of 42.1 µg/mL, against the highest exposure assessed, BA Study STI_Zoli002, which evaluated PK and ECG data collected in healthy volunteers administered 3 g and 4 g in both fed and fasted state.

- Individual subjects in the 3 g fed, 4 g fasted, and 4 g fed cohorts had observed Cmax concentrations exceeding the TQT threshold of 42.1 µg/mL.
- Maximum observed Cmax was 53.1 µg/mL.
- The Applicant reported "There were no notable mean changes from baseline following dosing with zoliflodacin for any 12-lead safety ECG parameter measured."

2. The appropriateness of the Applicant's proposed labeling language with respect to QT prolongation.

IRT's response: Findings from the TQT study indicated that zoliflodacin causes a linear concentration-dependent increase in QTc interval. The linear C-QTc relationship is supported by findings from the hERG assay, which demonstrated concentration-dependent inhibition of hERG current.

We disagree with the Applicant's proposal to use the TQT study data to derive a threshold concentration for QTc prolongation. This is because there is considerable uncertainty in the proposed threshold concentration of 42 µg/mL due to limited data above 30 µg/mL. While there were two individual ECG/PK pairs with reported concentrations exceeding 40 µg/mL, these were both likely spurious, as neighboring time-points within each of the two subjects were significantly lower.

Although we do not consider the data to support a specific threshold concentration for exclusion of QTc prolongation, we consider the totality of data adequate to exclude clinically significant QTc prolongation for a single dose of 3 g of zoliflodacin administered with or without food to patients weighing 35 kg or more because:

- Predicted mean ΔΔQTc for the worst-case concentration (female patients weighting ≥ 35 kg to < 50 kg inadvertently taking zoliflodacin 3 g in fed conditions) is 7.8 (upper limit of 90% CI: 10.6) msec and 11.2 (15.1) msec at the geometric mean Cmax and the 95th percentile Cmax, respectively. While these predictions are based on extrapolation, we consider the extrapolation to be reasonable in this case as the mechanism of QTc prolongation is likely to be hERG mediated and thus the C-QTc is expected to be linear. In addition, no clinically significant QTc prolongation was observed in the food effect study, which included 24-h Holter recordings and evaluated doses up to 4 g under fed condition, covering the Cmax of the worst-case scenario.
- There were no clinically concerning cardiovascular adverse events in the completed Phase 3 study for zoliflodacin.

Proposed label: Below are proposed edits to the label submitted to NDA 219491/0001(link).Our changes are highlighted (addition, ~~deletion).~~ Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology

(b) (4)

Concentration-dependent increase in QTc interval was observed in the TQT study. Based on the observed relationship, clinically significant QTc interval prolongation is not expected at the maximum recommended single dose of zoliflodacin.

Reviewer's comment: *The Applicant's description is misleading. This is because there is a significant positive food effect and zoliflodacin was administered under fasting condition in the TQT study in contrast to the proposed clinical dosing with food. As a result, the Cmax in the TQT study does not cover the clinical Cmax.*

We recommend describing that a concentration-QTc relationship was observed, but note that clinically significant QTc prolongation is not expected for a single dose of zoliflodacin.

2 BACKGROUND

2.1 Product Information

Entasis Therapeutics is developing zoliflodacin for the treatment of uncomplicated gonorrhea due to *Neisseria gonorrhoeae* (N. gonorrhoeae) in adult and pediatric patients 12 years and older. Zoliflodacin (also known as ETX0914; MW: 487.4 g/mol) is single-dose, oral antibiotic.

The Applicant has proposed the following dosage for treatment of uncomplicated gonorrhea due to *N. gonorrhoeae* in adult and pediatric patients 12 years and older, weighing at least 35 kg:

- For patients with body weight > 35 kg to < 50 kg, **a single 3 g dose** of zoliflodacin granules for oral suspension in the **fasted state** (i.e., 1 hour before eating or 2 hours after eating).
- For patients with body weight > 50 kg, **a single 3 g dose** of zoliflodacin granules for oral suspension in the **fed state**.

2.2 Applicant's position related to the question

In the TQT study, single 2 g and 4 g doses of zoliflodacin administered after overnight fasting produced geometric mean Cmax values of 11.8 μg/mL and 19.4 μg/mL. The mean ΔΔQTcF for the 2 g dose was 1.5 msec (upper 95% confidence limit: 2.5 msec), while the 4 g dose resulted in a mean ΔΔQTcF of 3.0 msec (upper 95% confidence limit: 4.4 msec).

In the Phase 3 study zoliflodacin was administered with food. Since food increase zoliflodacin Cmax by 1.5-folds, the geometric mean Cmax of the 4 g single dose (fasted) in the TQT study was lower than the clinically relevant exposure of the proposed therapeutic dose i.e., 3 g (fed state).

Concentration-QTc analysis of data from the TQT study indicated concentration-dependent QTc prolongation. The upper bound of the 95% one-sided CI of the mean ΔΔQTcF was predicted to exclude 10 msec at a total-drug plasma concentration of approximately 42.1 μg/mL and lower. Thus, the total-drug plasma concentration of 42.1 μg/mL was considered as a **theoretical safety threshold** in support of the zoliflodacin dose justification.

The Applicant states that over the course of the clinical development program of zoliflodacin, some subjects had a total-drug Cmax value greater than 42.1 μg/mL without an overt clinical safety signal.

Co-administration of 3 g zoliflodacin with high-fat meal increases zoliflodacin Cmax by 1.5-fold. Therefore, due to QTc prolongation safety concern at drug plasma concentration ≥ 42.1 μg/mL, the Applicant has proposed a single 3 g dose under fasted conditions in patients with body weight > 35 kg to < 50 kg.

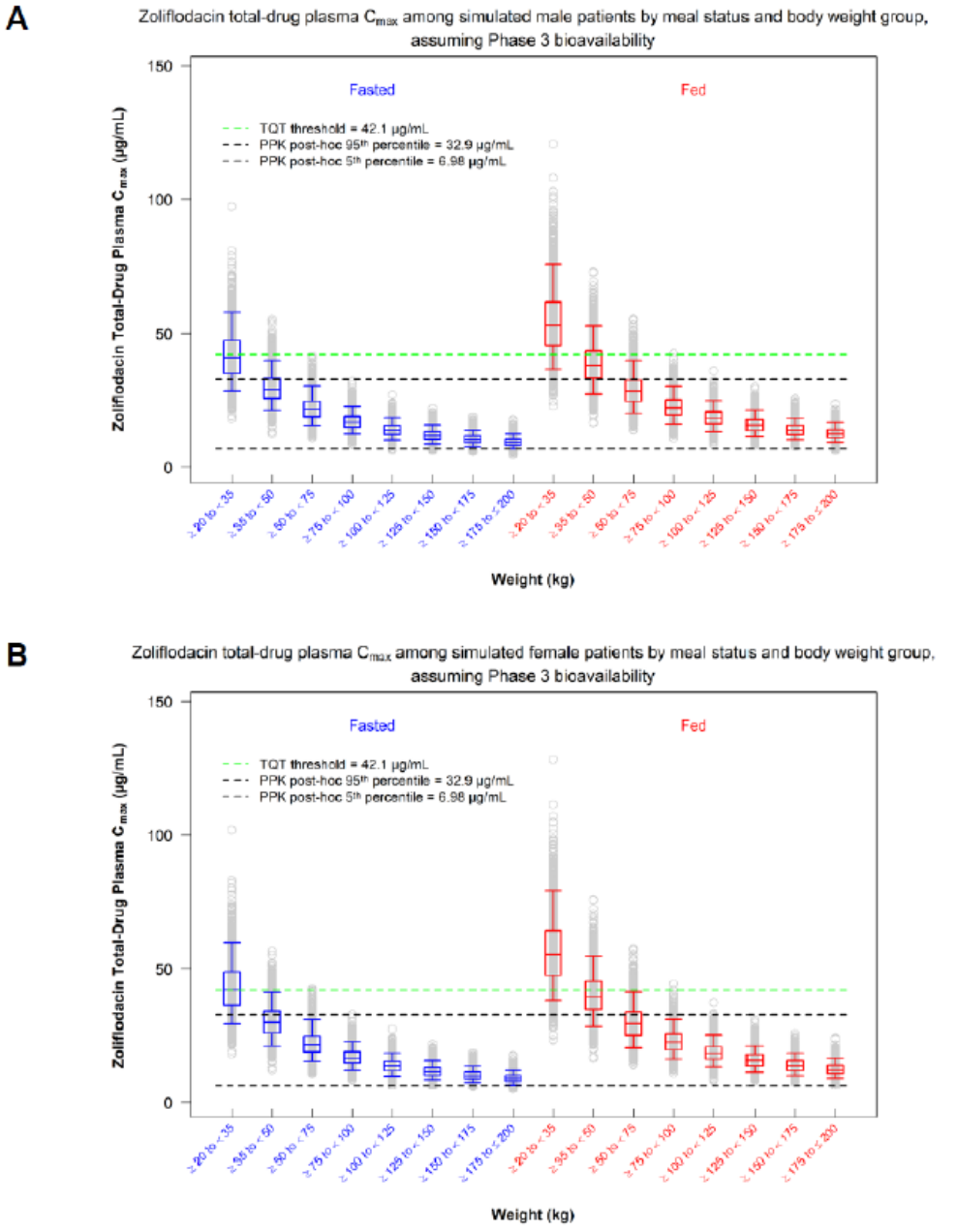
As shown in Figure 1, the 95th percentile for total-drug plasma Cmax values (represented by the upper whisker of the box-and-whisker plots) was lower than the TQT threshold of 42.1 μg/mL (represented by the green dashed lines) among both simulated male and female patients in the middle and higher body weight groups in both fasted and fed conditions.

However, the 95th percentile exceeded the TQT threshold of 42.1 μg/mL among both simulated male and female patients in the lowest body weight group (≥20 to <35 kg) for fasted patients, and in the two lowest body weight groups (≥20 to <35 kg and ≥ 35 to < 50 kg) for simulated fed patients.

Taken together, these simulation results indicate that for the lowest body weight group assessed (≥20 to <35 kg), a single oral 3 g dose of zoliflodacin resulted in total-drug plasma Cmax values that were higher than the safety threshold among either male or female simulated patients in either a fed or fasted state.

Therefore, given these simulation results, as well as the absence of clinical data in patients weighing <35 kg, a single oral 3 g dose of zoliflodacin may not be appropriate for this weight group, irrespective of age.

Figure 1. Box and Whisker Plot of Zoliflodacin Total-Drug Plasma Cmax in Comparison to the TQT Threshold Among Simulated Fasted or Fed Male (A) and Female (B) Patients with Uncomplicated Gonorrhea by Body Weight Group, Assuming Phase 3 Bioavailability, After Administration of a Single, Oral 3 g Dose of Zoliflodacin.



Abbreviations: C_{max} = maximum drug concentration; PPK = population pharmacokinetic; TQT = thorough QT/QTc.
Source: Study Report ICPD 00734-2, Figure 8.

Source: Figure 28, Summary of Clinical Pharmacology

Reviewer's Comment: *We have predicted the mean placebo corrected QTc prolongation at the worst-case exposure scenario indicated in Figure 1. The predictions were conducted using a linear C-QTc model developed from the previous TQT study dataset (IND* (b) (4).

As shown in Table 1, worst case QTc prolongation would occur in female patients weighting ≥ 35 to < 50 kg inadvertently taking zoliflodacin under fed conditions. In these patients, mean (upper limit of 95%CI) ΔΔQTcF is predicted to be about 7.8 (10.6) msec, 11.2 (15.1) msec, and 12.9 (17.4) msec at the geometric mean Cmax, the 95th percentile Cmax, and the 99th percentile Cmax respectively. Although clinical QTc prolongation cannot be excluded, we do not consider the extent of QTc prolongation to be clinically significant because of the following reasons: 1) zoliflodacin will be administered as a single dose, therefore no risk from accumulated exposure;2) The predicted mean increase in QTc at the 99th percentile Cmax only marginally exceeds 10 msec; and the upper 95% CI is less than 20 msec.

The lack of clinically concerning QTc prolongation is supported by absence of concerning cardiovascular adverse events in the completed phase 3 clinical trial and lack of significant QTc prolongation in the food effect study. Zoliflodacin exposures in the phase 3 study reflects the anticipated real-world exposures in patients.

Table 1. Predictions of ΔΔQTcF From Concentration-QTcF Model

Actual Treatment	Zoliflodacin (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
TQT study Zoliflodacin 2 g, fasted	11,765.6	1.6	(0.9 to 2.4)
TQT study Zoliflodacin 4 g, fasted	19,252.9	3.3	(2.1 to 4.5)
Fed, Male, ≥ 35 to < 50 kg, geometric mean Cmax	38,000.0	7.5	(4.8 to 10.1)
Fed, Female, ≥ 35 to < 50 kg, geometric mean Cmax	39,700.0	7.8	(5.1 to 10.6)
Fasted, Male, ≥ 35 to < 50 kg, 95th percentile Cmax	40,000.0	7.9	(5.1 to 10.7)
Fed, Male, ≥ 50 to < 75 kg, 95th percentile Cmax	40,000.0	7.9	(5.1 to 10.7)
Fasted, Female, ≥ 35 to < 50 kg, 95th percentile Cmax	41,300.0	8.2	(5.3 to 11.1)
Fed, Female, ≥ 50 to < 75 kg, 95th percentile Cmax	41,500.0	8.2	(5.4 to 11.1)
Fed, Male, ≥ 50 to < 75 kg, 99th percentile Cmax	45,700.0	9.2	(6.0 to 12.4)
Fed, Female, ≥ 50 to < 75 kg, 99th percentile Cmax	47,400.0	9.6	(6.2 to 12.9)
Fed, Male, ≥ 35 to < 50 kg, 95th percentile Cmax	52,800.0	10.8	(7.0 to 14.5)
Fed, Female, ≥ 35 to < 50 kg, 95th percentile Cmax	54,800.0	11.2	(7.3 to 15.1)
Fed, Male, ≥ 35 to < 50 kg, 99th percentile Cmax	59,900.0	12.3	(8.0 to 16.6)
Fed, Female, ≥ 35 to < 50 kg, 99th percentile Cmax	62,500.0	12.9	(8.4 to 17.4)

2.3 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety (link) and summary of clinical pharmacology.

Table 2 shows the anticipated therapeutic Cmax after single dose 3 g zoliflodacin administered under fed state as in the Phase 3 study. The predicted geometric mean Cmax (%CV) of in all patients is 28.5 (21.6) µg/mL while in female patients 15 -17 yrs is 32.9 µg/mL. The mean Cmax of the highest dose in the QTc assessment covers only 0.58 high clinical exposure scenario.

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	3 g oral suspension (fed state)	*32.9 µg/mL (C_{max})
Applicant's High clinical exposure scenario	No high clinical scenario.	32.9 µg/mL (C_{max})
Highest dose in QT assessment	4 g oral suspension formulation (fasting state)	#19.2 µg/mL (C_{max})
C_{max} Ratio	0.58	

*The predicted zoliflodacin Cmax in patients taking 3 g single dose with meal was 28. 5 µg/mL (Cmax) (Table 20 clin pharm summary). The predicted Cmax in female patients 15 -17 yrs is 32.9 µg/mL.
#TQT study, Table 8, IRT Review IND # (b) (4) dated 07/09/2020.

Reviewer's comment: *Since zoliflodacin causes QTc prolongation in a concentration-dependent manner and high clinical exposure (32.9 µg/mL) is within the highest decile of concentrations in the QTc assessment, the linear C-QTc model developed in that assessment can be used to interpolate QTc effects at the high clinical exposure scenario. It should be noted however that the predicted QTc effect at high clinical scenario is highly uncertainty due to few observed data points in this concentration range.*

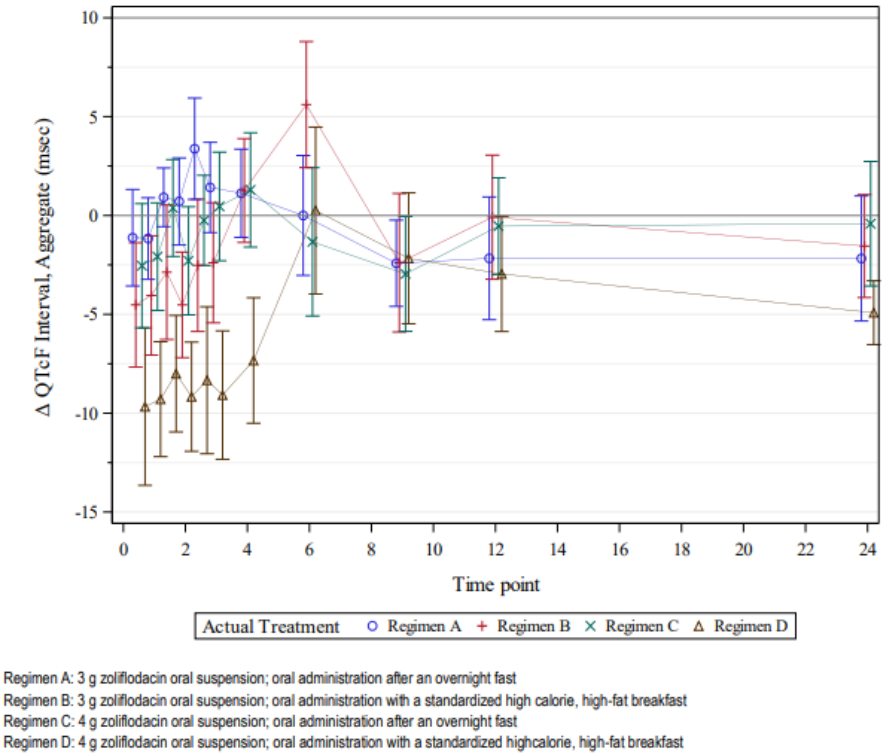
2.4 Food effect study

The Applicant conducted an open-label, randomized, cross-over food effect study with 2 cohorts of 24 subjects each with 3 and 4 g of zoliflodacin. 12-lead 24-h Holter ECGs were collected at each dosing visit. ECGs were extracted for analysis at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 24 h post-dose.

An increase in HR was observed in all treatment groups, which appears to be related to the intake of food. In the two fasted treatment regimens, the increase in HR occurred after intake of lunch whereas in the two fed treatment regimens, the increase was already present after intake of breakfast. In all 4 treatment regimens, the increase in HR was maintained until 12 h after drug intake and then decreased.

The maximum mean increase is less than 10 msec for all treatments groups (Figure 2). However, it should be noted that the results in this study should be interpreted with caution because of the absence of a positive or a placebo control.

Figure 2: Mean (90% CI) for ΔQTcF in the food effect study



Regimen A: 3 g zoliflodacin oral suspension; oral administration after an overnight fast
Regimen B: 3 g zoliflodacin oral suspension; oral administration with a standardized high calorie, high-fat breakfast
Regimen C: 4 g zoliflodacin oral suspension; oral administration after an overnight fast
Regimen D: 4 g zoliflodacin oral suspension; oral administration with a standardized highcalorie, high-fat breakfast

Source: Cardiabase ECG Report, Figure 2

Reviewer's comment: *The Cmax for 4 g zoliflodacin in the food effect study (37.5 µg/mL) is similar to the predicted Cmax for 3 g zoliflodacin for males and females ≥ 35 to < 50 kg (*Table 2*).*

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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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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DEVI KOZELI on behalf of LARS JOHANNESEN
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Lars is OOO

CHRISTINE E GARNETT
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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: 6/12/2025

TO: Division of Anti-Infectives (DAI)
Office of Infectious Diseases (OID)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: NDA 219491

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the sites listed below. The rationale for this decision is noted below.

Rationale

PAREXEL International GmbH: The Office of Inspections and Investigations (OII) conducted an inspection for the clinical site in May 2024. The inspection was conducted under the following submission: NON-RESPONSIVE

OSIS concluded that data from the reviewed study were reliable.

(b) (4)**:** OSIS conducted an inspection for the analytical site in (b) (4). The inspection was conducted under the following submissions: NON-RESPONSIVE

The following objectionable conditions were observed:

- (b) (4)
-

After review of the objectionable conditions and the written response from the site, OSIS determined (b) (4) but that the remaining data from the reviewed studies were reliable. (Final OSIS Review – (b) (4)).

Sites

Facility Type	Facility Name	Facility Address
Clinical	PAREXEL International GmbH	Early Phase Clinical Unit – Berlin, Campus DRK Klinikum Berlin Westend, House 31, Spandauer Damm 130, Berlin, Brandenburg, Germany

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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/s/

FELECIA P HAGOOD
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