NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	New Drug Application (NDA) 505(b)(2)
Application Number(s)	NDA 216755
Priority or Standard	Standard
Submit Date(s)	11/23/2022
Received Date(s)	11/23/2022
PDUFA Goal Date	9/23/2023
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	See electronic signature date
Established/Proper Name	Metronidazole oral suspension
(Proposed) Trade Name	LIKMEZ
Pharmacologic Class	Nitroimidazole antimicrobial
Applicant	Saptalis Pharmaceuticals, LLC
Dosage form	Oral suspension
Applicant proposed Dosing Regimen	*Trichomoniasis:* Adults with symptomatic or asymptomatic trichomoniasis and their sexual partners: • One-day treatment – 2 g given either as a single oral dose or in 2 divided oral doses of 1 g each, given on the same day. • Seven-day course of treatment – 250 mg three times daily for 7 consecutive days. *Amebiasis:* Adults: • For acute intestinal amebiasis (acute amebic dysentery): 750 mg orally three times daily for 5 days to 10 days. • For amebic liver abscess: 500 mg or 750 mg orally three times daily for 5 days to 10 days. Pediatric patients: 35 mg/kg/24 hours to 50 mg/kg/24 hours, divided into three doses, orally for 10 days *Anaerobic Bacterial Infections:* • Adults: 7.5 mg/kg every six hours (approx. 500 mg for a 70-kg adult) to a maximum dose of 4 g during a 24-hour period, orally for 7 to 10 days.
Applicant Proposed Indication(s)/Population(s)	Indicated for • Trichomoniasis in adults • Amebiasis in adults and pediatric patients • Anaerobic Bacterial Infections in adults
Recommendation on Regulatory Action	Approval

Recommended Indication(s)/Population(s) (if applicable)	Indicated for • Trichomoniasis in adults • Amebiasis in adults and pediatric patients • Anaerobic Bacterial Infections in adults
Recommended Dosing Regimen	*Trichomoniasis:* Same as above *Anaerobic Bacterial Infections:* same as above *Amebiasis:* Same as above for adult dosing Pediatric patients: 35 mg/kg/24 hours to 50 mg/kg/24 hours, divided into three doses, to a maximum dose of 2250 mg/24 hours (maximum dose 750 mg/dose or 7.5 mL/dose), orally for 10 days (maximum dose added)

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMPP= Division of Medical Policy Programs
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

DPV=Division of Pharmacovigilance
DPMH=Division of Pediatrics and Maternal Health

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Glossary

AE	adverse event
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
ECG	electrocardiogram
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IND	Investigational New Drug
LD	Listed Drug
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PI	prescribing information
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1.Product Introduction

Metronidazole is a nitroimidazole drug with antibacterial and antiparasitic activity. The proposed product is LIKMEZ, an oral suspension formulation of metronidazole, also referred to as ATI-1501 during clinical development. The chemical name is 2-methyl-5-nitroimidazole-1-ethanol. The drug product is available as 500 mg/5 mL oral suspension with strawberry peppermint flavor in a 200 mL container. This will be the first metronidazole oral suspension to be approved in the US.

1.2.Conclusions on the Substantial Evidence of Effectiveness

In accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, this NDA for LIKMEZ (Metronidazole) oral suspension was submitted relying on the FDA's findings of safety and effectiveness of the listed drug (LD), FLAGYL (Pfizer, NDA 012623, metronidazole 500 mg tablet). The proposed indications are the same as in the LD's approved labeling, (i.e., for the treatment of symptomatic and asymptomatic trichomoniasis in adults and their sexual partners, amebiasis in adults and pediatric patients, and anaerobic bacterial Infections in adults).

The Applicant did not conduct any clinical efficacy trials with LIKMEZ for the indications noted above. The bridge for safety and efficacy from the LD to LIKMEZ is based on a comparison of metronidazole bioavailability (BA) between the LD and LIKMEZ. The Applicant conducted two single dose cross-over BA studies under fasting and fed conditions using metronidazole 500 mg tablets (approved under ANDA 070033) from Teva Pharmaceuticals, which are therapeutically equivalent to the LD, as the reference drug and LIKMEZ 500 mg/5mL as the test drug. The pharmacokinetic (PK) parameters of LIKMEZ were comparable to the reference drug. Thus, the Clinical Pharmacology review team concluded that an acceptable PK bridge has been demonstrated between LIKMEZ and the LD. In conclusion, LIKMEZ may be approved under Section 505(b)(2) based on the results of the comparative BA studies and the Agency's previous findings of safety and effectiveness of the LD, FLAGYL tablets.

1.3.Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant submitted this 505(b)(2) NDA 216755 for LIKMEZ 500 mg/5mL, a new oral suspension formulation of metronidazole. Metronidazole oral suspension (LIKMEZ) is a nitroimidazole antimicrobial drug. NDA 216755 relies on FDA's previous findings of safety and effectiveness of the LD, FLAGYL, metronidazole 500 mg oral tablets. The proposed indications are the same as the indications approved for the LD, i.e., symptomatic and asymptomatic trichomoniasis in adults, trichomoniasis in asymptomatic sexual partners, anaerobic bacterial infections in adults, and amebiasis in adult and pediatric patients. LIKMEZ is a taste-masked suspension that may provide a more palatable, easier to swallow alternative to tablets, particularly for patients with dysphagia and pediatric patients.

The Applicant conducted two single dose relative bioavailability (BA) studies, 21-VIN-0347 and 21-VIN-0348 under fasting and fed conditions, respectively, comparing metronidazole BA of LIKMEZ and therapeutically equivalent to the LD metronidazole 500 mg tablets as the reference drug. The studies demonstrated that LIKMEZ has comparable metronidazole BA to the LD.

The safety data provided in the submission include 96 healthy subjects enrolled in the BA studies. There were no deaths or serious adverse events (SAEs). Of the 6 discontinuations, one was related to the study drug (vomiting). Based on similar exposures and the experience with oral administration of metronidazole, the safety profile of the metronidazole suspension is expected to be similar to the LD.

Metronidazole has been used in clinical practice for over 50 years, with a well characterized safety profile. Notable warnings and serious adverse reactions associated with metronidazole include carcinogenicity in mice and rats for which unnecessary use of the drug in patients should be avoided and use should be reserved for the conditions described in the indications and usage section (Boxed warning), central and peripheral nervous system effects (Warnings), use with care in patients with blood dyscrasias (Warnings), and irreversible hepatotoxicity/acute liver failure in patients with Cockayne syndrome (Contraindications). Common adverse reactions include nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, and an unpleasant metallic taste.

Upon review of the published medical literature and the FDA Adverse Event Reporting System (FAERS) database, there were a few cases of tinnitus reported with use of metronidazole most of which predated the last revision of the FLAGYL prescribing information (PI) dated December 2021. At this time, tinnitus will be monitored in routine post-marketing surveillance.

In conclusion, LIKMEZ can be approved based on the results of the comparative BA studies, previous findings of safety and effectiveness of the LD (FLAGYL), and the safety data from published literature and FAERS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Trichomoniasis is a parasitic disease caused by *Trichomonas vaginalis* through sexual contact. It can present both in males and females as symptomatic or asymptomatic (in about 70% of patients) infection). Symptoms in females include diffuse, malodorous, or yellow green vaginal discharge with or without vulvar irritation. In males, symptoms may include frequent urination, thin whitish urethral discharge, and penile irritation. *T. vaginalis* infection in females can contribute to adverse pregnancy outcomes such as low birth weight, premature rupture of membranes and increased risk of preterm delivery. Acquisition of HIV has been reported to be associated with trichomoniasis. The reported cure rates are over 90% with either metronidazole or tinidazole. • Amebiasis is an infection caused by the parasite, *Entamoeba histolytica*. It can present commonly as diarrhea and less commonly as dysentery, also called amebic colitis, in which diarrheal stools may be mixed with mucus and visible or microscopic blood. Amebiasis can present with extraintestinal symptoms which can be more severe. This includes amebic liver abscess which can occurs ten times as often in males than females and infrequently in children. In adults, it can present as a rapid onset acute illness with fever and right upper abdominal tenderness/pain or as a sub-acute illness with prominent weight loss, less frequently fever, and abdominal pain. Children can present with non-specific symptoms such as high fever, abdominal distention, irritability, and increased respirations. Death usually results from rupture of the liver abscess into the	• Trichomoniasis can contribute to increased adverse outcomes in pregnancy and increased risk for HIV infection. Prompt diagnosis and treatment may help to prevent these outcomes. • Amebiasis and amebic liver abscess, if left untreated, can cause significant morbidity and mortality. Amebiasis, mainly amebic dysentery can cause severe abdominal pain mimicking the presentation of an acute abdomen. It can cause intussusception, perforation, peritonitis, and necrotizing colitis in young children. Amebic liver abscess can cause acute, sub-acute and chronic diseases contributing to significant morbidity. Death can occur from rupture of liver abscess to extraintestinal sites. Early diagnosis and treatment will help prevent these outcomes. • Anerobic infections can cause various clinical manifestations involving multiple organs that can lead to increased morbidity

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	peritoneum, thorax, or pericardium or, from extensive liver damage and liver failure. In children, delay in diagnosis due to an atypical presentation may lead to worsening and death. • Anerobic infections are caused by a variety of bacterial species and may involve various body sites. *Bacteroides species, Clostridium species, Eubacterium species, Peptococcus species, Peptostreptococcus species, Fusobacterium species* can cause intra-abdominal infections (e.g., peritonitis, abscesses, liver abscess), skin and skin structure infections as well as gynecological infections. *Bacteroides* and *Clostridium species* are known to cause septicemia. *Bacteroides species* can also cause bone and joint infections, central nervous system infections, lower respiratory tract infection, and infective endocarditis. The presenting symptoms and signs vary according to the organ involved. These infections, if left untreated can be life threatening.	and mortality. Early diagnosis and appropriate treatment can prevent potential complications and death.
Current Treatment Options	• For trichomoniasis, currently approved treatments include metronidazole tablets or capsules, tinidazole tablets and secnidazole oral granules. • For amebiasis and amebic liver abscess, currently approved treatments include metronidazole tablets or capsules and tinidazole tablets. Paromomycin, an intraluminal agent, is FDA approved and effective against intestinal amebiasis and is used for treatment of asymptomatic carriers and for follow up treatment with tinidazole for amebic liver abscess. For amebic liver abscess, surgical treatment may be required in addition to medical treatment. • For anerobic bacterial infection, there are various classes of antibacterial drugs that are currently approved. These include metronidazole (IV or oral forms), beta-lactam/beta-lactamase inhibitor combinations, carbapenems second generation cephalosporins namely cefoxitin (IV) and cefotetan (IV), clindamycin (IV and oral), quinolones (moxifloxacin IV or oral),	• There are several treatment options for the infections for which LIKMEZ is indicated. LIKMEZ may improve compliance and may be used as an alternative to metronidazole tablets in certain situations such as in patients with difficulty swallowing tablets or in the event of a drug shortage.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	eravacycline (IV), and tigecycline (IV). Second generation cephalosporins are more active against *Bacteroides fragilis* but due to increasing resistance, they are not recommended as empiric treatment. Additionally, clindamycin resistance to *Bacteroides fragilis* is increasing, and it is a less reliable option as compared to other antibacterial drugs. • The safety and effectiveness of metronidazole in pediatric patients have not been established, except for the treatment of amebiasis.	
Benefit	• LIKMEZ is an oral suspension formulation which provides an alternative for patients who have difficulty with swallowing pills (e.g., patients with dysphagia and pediatric patients).	• LIKMEZ provides an alternative for patients who have difficulty with swallowing pills (e.g., patients with dysphagia and pediatric patients). This will be the first metronidazole oral suspension to be approved in the US.
Risk and Risk Management	• The safety profile of metronidazole is described in the PI of the LD (FLAGYL tablets). Based on similar exposures and the experience with oral administration of metronidazole, the safety profile of the metronidazole suspension is expected to be similar to the LD. • Serious adverse reactions associated with the use of metronidazole are described in the PI along with recommendations for monitoring and mitigation strategies. The LD has a Boxed Warning stating that metronidazole has been shown to be carcinogenic in mice and rats and unnecessary use of the drug should be avoided. Other warnings include but are not limited to risk of central and peripheral nervous system effects, and to use with care in patients with blood dyscrasias.	• Safety information noted in the LD is adequately communicated in the PI for LIKMEZ. • A contraindication for use in patients with trichomoniasis during the first trimester of pregnancy, currently included in the FLAGYL PI, (b) (4) . • The FLAGYL PI does not provide a maximum dose limit for the pediatric indication for treatment of amebiasis, and thus, a maximum dose has been added to decrease the risk of an overdose. • Similar revisions will be suggested for the PI of other relevant metronidazole products.

1.4.Patient Experience Data

Patient experience data was not submitted as part of this application.

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2 Therapeutic Context

2.1.Analysis of Condition

Trichomoniasis

Trichomoniasis is a sexually transmitted disease caused by a flagellate parasite, *Trichomonas vaginalis.* About 70% of patients with trichomoniasis are asymptomatic.[1] Symptoms in females include diffuse, malodorous, or yellow green vaginal discharge with or without vulvar irritation. In males, the disease may present with symptoms of urethritis, epididymitis, or prostatitis. The estimated annual incidence of trichomoniasis in the United States was 2.6 million in 2018.[2] *T. vaginalis* can contribute to significant adverse pregnancy outcomes. *T. vaginalis* has been reported to be associated with a 1.4-times greater likelihood of preterm birth, premature rupture of membranes, and infants who are small for gestational age. Acquisition of HIV has also been associated with trichomoniasis. In women without HIV viral suppression, *T. vaginalis* infection is associated with a 1.5-fold increased risk for HIV acquisition and is associated with an increase in vaginal shedding of HIV, which is reduced with treatment. Additionally, in women with HIV infection, *T. vaginalis* has been reported to be associated with increased risk for pelvic inflammatory disease (PID). Nucleic acid amplification testing (NAAT) is the most sensitive and specific method available for the diagnosis of trichomoniasis. In females, the specimen can be collected from vaginal specimens, endocervical swabs, or urine. In men, a specimen can be collected from anterior urethral or prostatic secretions, or urine. Antigen testing is also available for diagnosis in women and can aid in more rapid diagnosis. Wet mount and culture are older methods and are less sensitive and specific than NAAT. Additionally, culture results can have a longer turnaround time. The reported cure rates for trichomoniasis are reported as 94% to 98% with metronidazole treatment and 92 to 100% with tinidazole treatment.[1]

Amebiasis

Amebiasis is an infection caused by a parasite, *Entamoeba histolytica* which can present most commonly as diarrhea or less commonly as dysentery. Amebic dysentery/colitis is defined as diarrhea with mucus or visible or microscopic blood in stool. Approximately 15% to 33% of cases of amebiasis are accompanied by dysentery [3]. Extraintestinal involvement includes amebic liver abscess which is a more severe presentation that occurs ten times as often in males than females and infrequently in pediatric patients. It can present as an acute illness with fever and right upper abdominal tenderness/pain or as a sub-acute illness with prominent weight loss, abdominal pain, and less often, with fever. Approximately 80% of patients develop

[1] STD Facts - Trichomoniasis (cdc.gov)
[2] https://www.cdc.gov/std/trichomonas/stats.htm
[3] Entamoeba Species, Including Amebic Colitis and Liver Abscess William A. Petri Jr., Rashidul Haque, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition), 2015

symptoms rapidly (typically within 2 to 4 weeks). Hepatomegaly is a typical finding. In pediatric patients, the disease presentation is more non-specific with high fever, abdominal distention, irritability, and tachypnea while abdominal pain is reported infrequently. Some initially present with only with fever. Extraintestinal presentations include direct extension of the liver abscess to the pleura or pericardium and brain abscess. Death usually results from rupture of the liver abscess into the peritoneum, thorax, or pericardium or, from extensive liver damage and liver failure. Delay in diagnosis in children due to an atypical presentation may lead to worsening and death. Diagnostic methods include detection of *E. histolytica* antigen in the stool, serological testing in serum by ELISA which can detect intestinal as well as extraintestinal infection, PCR in stool sample and aspirate from abscess sites.

Anerobic infections

Anerobic bacteria, which are bacteria that can grow in the presence of low oxygen tension, can affect various organs. The disease manifestations may vary depending on the pathogenic bacteria and organ system involvement. *Bacteroides, Clostridium, Eubacterium, Peptococcus*, *Peptostreptococcus,* and *Fusobacterium* can cause a variety of infections including intra-abdominal infections such as peritonitis, abscesses, including in the liver, skin and skin structure infections, gynecological infections such as endometritis, endomyometritis, tubo-ovarian abscesses, and postsurgical vaginal cuff infection. *Bacteroides* and *Clostridium species* are known to cause septicemia. *Bacteroides species* can cause bone and joint infections, central nervous system infections such as meningitis and brain abscess, lower respiratory tract infection such as pneumonia, empyema, and lung abscess, and infective endocarditis. The presenting symptoms and signs depend on the organ involved. These infections, if left untreated can be life threatening. The diagnosis is based on clinical presentation and laboratory testing. Anerobic bacteria are very fastidious and require nutrient rich media for culture which may need to be selective for a particular bacterium. The methods that are currently available include identification using phenotypic characteristics, biochemical testing, gas-liquid chromatography, MALDI-TOF MS and whole genome sequencing (WGS). Antimicrobial susceptibility testing is done by agar dilution, broth microdilution, disk diffusion, gradient tests, automated systems, phenotypic and molecular resistance detection techniques.[4]

2.2.Analysis of Current Treatment Options

Currently available treatment options for trichomoniasis include metronidazole tablets and capsules, tinidazole tablets and secnidazole granules. For treatment of amebiasis, treatment options include metronidazole tablets or capsules, tinidazole tablets, and luminal agents, paromomycin and diloxanide furoate. Diloxanide furoate is available only through the Centers

[4] Gajdács M, Spengler G, Urbán E. Identification and Antimicrobial Susceptibility Testing of Anaerobic Bacteria: Rubik's Cube of Clinical Microbiology? Antibiotics (Basel). 2017 Nov 7;6(4)

for Disease Control (CDC). Paromomycin, an intraluminal agent, is FDA-approved and effective against intestinal amebiasis and is used for the treatment of asymptomatic carriers and for follow-up treatment with tinidazole for amebic liver abscess. For amebic liver abscess, surgical treatment may be required in addition to medical treatment.

Currently, for patients who have difficulty swallowing or in pediatric patients (for the treatment of amebiasis), there are no approved oral liquid formulations. In these patients, metronidazole tablets are compounded by hospital pharmacies. Alternatively, the drug is mixed with food such as apple sauce or yogurt for ease of swallowing and increased palatability. Tinidazole can be compounded into a suspension by the pharmacist as per the prescribing information (PI). Metronidazole and tinidazole tablets are described as having an unpleasant and sharp metallic taste and may become more unpalatable on compounding into a suspension. Also, there remains a risk of alteration of the dose to some extent when the medication is crushed or reformulated by a pharmacist.

Currently, the majority of available treatment options for anerobic infections are in intravenous or intramuscular forms. Oral treatment options include metronidazole tablets or capsules, clindamycin and moxifloxacin tablets. Metronidazole remains an excellent oral option due to high bioavailability (almost 100%) on oral administration, however, as noted above, it may be difficult to administer to pediatric patients and those with dysphagia. Clindamycin is available as an oral option but increasing resistance to *Bacteroides fragilis* makes it a less reliable option. Moxifloxacin is available in tablet form but should not be crushed.

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indications

Indication	Generic Name	Trade Name	Year of Approval	Dosing/ Administration	Comments
Trichomoniasis					
Asymptomatic trichomoniasis, Symptomatic trichomoniasis and sexual partners	Metronidazole	FLAGYL	1963	250 mg PO TID X 7 days 2 grams PO X one time dose	500 mg PO BID X 7 days is as per CDC treatment guidelines (not currently in FLAGYL PI).
	Tinidazole	Tindamax	2004	2 grams PO one time dose	
	Secnidazole	Solosec	2021 (Trichomoniasis)	2-gram packet of granules PO X 1 time dose	Initial approval for bacterial vaginosis in 2017

Indication	Generic Name	Trade Name	Year of Approval	Dosing/ Administration	Comments
Amebiasis					
Amebic diarrhea/ Dysentery	Metronidazole		1963	500 mg – 750 mg PO TID X 7-10 days	
Amebic Liver Abscess				750 mg TID X 10 days	
Amebic diarrhea/ Dysentery	Tinidazole		2004	2 grams PO once daily X 3 days	
Amebic liver abscess				2 grams PO once daily X 5 days, followed by luminal agent (paromomycin)	
Amebic diarrhea/ dysentery/ asymptomatic carrier or, as an adjunct to tinidazole for treatment of amebic liver abscess	Paromomycin			30 mg/kg/day PO in three divided doses per day for 5-10	These are intraluminal agents
	Diloxanide furoate			500 mg PO TID for 10 days	Diloxanide furoate is available in US only through the CDC
Anerobic bacterial infections					
	Metronidazole	FLAGYL	1963	7.5 mg/kg IV or oral every six hours X 7 to 10 days. (Max - 4 grams in 24 hours)	Infections of bone and joint, lower respiratory tract and endocardium may require longer treatment
	Beta lactams/Beta-lactamase Inhibitor Combination				
	Ampicillin/ Sulbactam	Unasyn	1986	1.5 gram (1 gram ampicillin + 0.5 gram sulbactam) to 3 g (2 gram ampicillin + 1 gram sulbactam) IV or IM every 6 hours.	

Indication	Generic Name	Trade Name	Year of Approval	Dosing/ Administration	Comments
	Piperacillin/ tazobactam	Zosyn	2005	3.375 grams IV administered over 30 minutes every 6 hours X 7-10 days.	
	Carbapenems				
	Imipenem/ Cilastatin	Primaxin	1985	15-25 mg/kg/dose IV every 6 hours.	
	Meropenem	Merrem	1996	Skin and skin structure infections – 500 mg IV every 8 hours Intra-abdominal infections- 1 gram IV every 8 hours	
	Ertapenem	Invanz	2001	1 gram IV or, IM once daily Intraabdominal infection 5 – 14 days Skin and skin structure infection 7 – 14 days	
	Imipenem/ cilastatin/ relebactam	Recarbrio	2019	Complicated intra-abdominal infection 1.25 grams (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) administered by IV infusion over 30 minutes every 6 hours	In patients who have limited or no alternative treatment options
	Tetracyclines				
	Tigecycline	Tygacil	2003	Initial dose -100 mg IV, followed by 50 mg IV every 12 hours (each infusion over 30 – 60 minutes)	The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and

Indication	Generic Name	Trade Name	Year of Approval	Dosing/ Administration	Comments
				Recommended duration for complicated skin and skin structure infections and complicated intra-abdominal infections is 5 – 14 days.	bacteriological progress
	Eravacycline	Xerava	2018	Complicated intra-abdominal infection 1 mg/kg by IV infusion over approximately 60 minutes every 12 hours for a total duration of 4 - 14 days.	
	Lincosamides				
	Clindamycin	Cleocin	1999	Intravenous- **C. perfringens* 600–1200 mg/day in 2, 3 or 4 equal doses. **Bacteroides fragilis*, *Peptococcus spp.,* or *Clostridium spp. (*other than *C. perfringens)*: 1200–2700 mg/day in 2, 3 or 4 equal doses. Oral – 150 – 300 mg every 6 hours. 300 - 450 mg every 6 hours (severe infections)	*Can also be given as initial rapid infusion followed by continuous infusion Resistance of clindamycin to *Bacteroides fragilis* is increasing and this may be a less reliable option as compared to other antibiotics.
	Fluoroquinolones				
	Moxifloxacin	Avelox	1999	400mg PO or, IV once daily X 5-14 days	
	Cephalosporins				
	Cefoxitin (2^{nd} generation)	Mexofin	1997	Cefoxitin IV 1- 2 grams every 6 - 8 hours	More active against

Indication	Generic Name	Trade Name	Year of Approval	Dosing/ Administration	Comments
					Bacteroides fragilis but due to increasing resistance, not recommended as empiric treatment
	Cefotetan (2^{nd} generation)	Cefotan	1993	Cefotetan 1 - 2 grams IV or IM	
	Off Label Treatment				
	Amoxicillin/ clavulanate	Augmentin	1996	500 mg tablet every 12 hours or, 250 mg tablet every 8 hours. Severe infections 875 mg tablet every 12 hours or, 500 mg tablet every 8 hours.	Used widely for treatment of anaerobic bacterial infections (e.g., in bite wounds, diabetic foot, intra-abdominal and odontogenic infection)

3 Regulatory Background

3.1.U.S. Regulatory Actions and Marketing History

Saptalis Pharmaceuticals, LLC submitted this original 505(b)(2) NDA for LIKMEZ suspension, 500 mg/5 mL for oral administration. The listed drug (LD), FLAGYL (metronidazole oral tablets), NDA 012623, was approved by the Food and Drug Administration (FDA) on July 18, 1963. FLAGYL is marketed and broadly used worldwide. LIKMEZ is not currently marketed in the US or elsewhere.

3.2.Summary of Pre-submission/Submission Regulatory Activity

On November 28, 2016, Appili Therapeutics, Inc. (former Sponsor), submitted pre-investigational new drug application (PIND) 132217. This submission included a meeting request to discuss its drug development with the Division of Anti-Infectives (Division). On February 13, 2017, a type B meeting occurred between the former Sponsor and the Division.

On September 29, 2017, the former Sponsor submitted an investigational new drug (IND) application, which included a phase 1, randomized, open-label, single dose, two sequence, crossover, relative bioavailability, and taste test study of ATI-1501 and the reference drug, 500 mg metronidazole tablets, in healthy adult volunteers. On October 25, 2017, the Division informed the former Sponsor that the IND was safe to proceed.

On June 18, 2018, the former Sponsor submitted an initial pediatric study plan (iPSP) to IND 132217. The Division reviewed the submission and then issued an “Initial Pediatric Study Plan, Written Response” letter on September 14, 2018.

On July 6, 2018, the former Sponsor submitted a Chemistry, Manufacturing and Controls (CMC) meeting request to discuss the CMC development of ATI-1501 in order to support a planned NDA submission. On September 25, 2018, a type C CMC teleconference meeting occurred.

On December 14, 2018, the former Sponsor submitted its revised iPSP in response to the September 12, 2018, Written Response correspondence from the Division. On March 11, 2019, following the review of the proposed iPSP, the Division issued an “Initial Pediatric Study Plan-No Agreement” letter.

On May 29, 2020, the Division issued a “Change of Sponsor” letter to IND 132217. The letter noted a change of Sponsor from Appili Therapeutics, Inc to Saptalis Pharmaceuticals, LLC, (Applicant) effective January 24, 2020.

On November 16, 2020, and June 2, 2021, two type C CMC meetings were held with the Applicant to discuss the CMC topics related to the metronidazole oral suspension formulation.

On November 4, 2021, and January 7, 2022, the Applicant submitted revisions to the iPSP for Division review. On February 11, 2022, and April 07, 2022, the Applicant included additional responses to Division comments and updated its version of the iPSP.

On April 14, 2022, the Applicant submitted a "Request for Proprietary Name" review.

On April 29, 2022, the Division issued an "Agreed Initial Pediatric Study Plan, Agreement" letter to the Applicant.

On November 23, 2022**,** NDA 216755 was submitted as a 505(b)(2) NDA for LIKMEZ suspension, 500 mg/5 mL for oral administration for treatment of trichomoniasis in adults, amebiasis in adults and pediatric patients, and anaerobic bacterial infections in adults. On February 03, 2023, the application was noted to be fileable and would have a Prescription Drug User Fee Act (PDUFA) goal date of September 23, 2023.

On February 21, 2023, the Division of Medication Error Prevention and Analysis (DMEPA) issued a "Proprietary Name Conditionally Acceptable" letter for the proprietary name LIKMEZ.

On February 2, 2023, and February 17, 2023, the Applicant submitted revisions to the "Agreed Initial Pediatric Study Plan" at the Division's request, to address needed revisions in the previously Agreed iPSP dated April 29, 2022. This information was shared with the FDA Pediatric Review Committee (PeRC), and the PeRC agreed with the Division's recommendation and the Applicant's revisions and no formal communication was issued. Please see section 12 Pediatrics of this review for additional details.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portions of Study 21-VIN-0347 and inspection findings are discussed in Section 6.2. In brief, the inspection did not identify any concerns from the study site (Veeda Clinical Research Pvt. Ltd.) regarding reliability of the data or human subject protection for study 21-VIN-0347.

4.2. Product Quality

From the Product Quality perspective, sufficient chemistry, manufacturing and controls (CMC) information for the proposed drug substance (metronidazole) and the drug product (metronidazole oral suspension) was provided in the NDA. The overall CMC information was found acceptable by the Office of Pharmaceutical Quality (OPQ) review team, and no specific product quality related deficiencies were identified. Based on the stability

data provided in the NDA, the expiration dating of 24 months for the drug product to be stored under room temperature conditions (20°C to 25°C) is granted. All manufacturing and testing facilities listed in the NDA were also found acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on July 7, 2023. Therefore, this NDA is recommended for approval by the OPQ review team (for additional details refer to the OPQ Review in DARRTS dated September 8, 2023)

4.3.Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1.Executive Summary

No new nonclinical pharmacology or toxicology data were submitted with this NDA. The Applicant referred to FDA's prior findings of safety in NDA 012623 (FLAGYL) as described in the FDA approved product labeling. There are no nonclinical data that would preclude approval of LIKMEZ metronidazole oral suspension, 500 mg/5 mL.

There were no concerns regarding the excipients used in this new formulation and impurity specifications were consistent with ICH guidelines and found acceptable by the product quality review team. There are no pharmacology/toxicology concerns for any impurities detected in this product. For additional details refer to the OPQ Review, in DARRTS.

Metronidazole is a nitroimidazole antimicrobial. The precise mechanism of action of metronidazole is unclear but after the drug enters the organism by passive diffusion and is activated in the cytoplasm of susceptible anaerobic bacteria, it is reduced. The reduced form of metronidazole and free radicals can interact with DNA leading to inhibition of DNA synthesis and DNA degradation leading to death of the bacteria.

Toxicology

The most significant toxicity detected in nonclinical studies of metronidazole was carcinogenicity, including tumors affecting the liver, lungs, mammary, and lymphatic tissues in several studies of metronidazole in rats and mice, but not hamsters.

Pulmonary tumors were observed in multiple studies in the mouse, including one study in which the animals were dosed on an intermittent schedule (every four weeks). Malignant liver tumors were increased in male mice treated at approximately 1500 mg/m^2 (similar to the maximum recommended daily dose, based on body surface area comparisons). Malignant lymphomas and pulmonary neoplasms were also increased with lifetime feeding of the drug to mice. Mammary and hepatic tumors were increased among female rats administered oral metronidazole. Two lifetime tumorigenicity studies in hamsters were negative.

Metronidazole was mutagenic in the Ames assay but studies in mammals in vivo failed to demonstrate a potential for genetic damage.

Metronidazole did not affect fertility or testicular function in male rats at doses up at 400 mg/kg/day (similar to the maximum recommended clinical dose, based on body surface area comparisons) for 28 days, but rats treated at the same dose for 6 weeks or longer were infertile and showed severe degeneration of the seminiferous epithelium in the testes as well as marked decreases in testicular spermatid counts and epididymal sperm counts. Fertility was restored in

most rats after an eight-week, drug-free recovery period. Reproduction studies performed in rats, rabbits, and mice at doses similar to the maximum recommended human dose (based on body surface area comparisons) revealed no evidence of harm to the fetus due to metronidazole.

6 Clinical Pharmacology

6.1.Executive Summary

The Applicant, Saptalis Pharmaceuticals LLC, submitted a 505(b)(2) application for a metronidazole oral suspension, 500 mg/5 mL. The Applicant is relying on the listed drug (LD) product FLAGYL (metronidazole; 500 mg) tablets, which was approved by the FDA in 1963. The proposed indications are the same as the indications approved for FLAGYL tablets, i.e., for the treatment of trichomoniasis in adults, treatment of anaerobic bacterial infections in adults, and treatment of amebiasis in adult and pediatric patients. The Applicant has conducted two relative bioavailability (BA) studies and is seeking an approval for the proposed drug product based on comparable metronidazole BA between the proposed drug product and the approved reference product Metronidazole Tablets USP 500 mg (Approved under ANDA 070033). The Applicant submitted General Correspondence to the Agency on 09/13/2021 requesting concurrence for the use of this therapeutically equivalent AB rated Metronidazole Tablets, 500 mg for performing the comparative BA studies, and the Agency provided its concurrence on 10/08/2021.

The key clinical pharmacology review issues are listed below:
1. Comparison of metronidazole BA between the proposed drug product (500 mg/5 mL oral suspension) and the Metronidazole Tablets USP 500 mg (Approved under ANDA 070033)
2. The Applicant proposed pediatric dosage and administration instructions

The Applicant provided information was reviewed and the Applicant's proposal to rely on the FDA's previous findings of FLAGYL for efficacy and safety of metronidazole is acceptable from a clinical pharmacology perspective. The Applicant proposed prescribing information (PI) was reviewed and the Review team has proposed revisions (See Section 13) related to pediatric dosage and administration.

6.2.Summary of Clinical Pharmacology Assessment

This NDA is being supported by two relative BA studies: Study 21-VIN-0347 and Study 21-VIN-0348 that were conducted under fasting and fed conditions, respectively. The Applicant has submitted final study reports for these two studies.

The findings from the two BA studies show that under fasting and fed conditions, the geometric mean ratios (test/reference) and 90% confidence intervals of all relevant exposure parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) for metronidazole were within the predefined criteria, i.e., the range of 80% and 125% (criteria are defined in the next section), demonstrating similarity in systemic metronidazole exposures. The observed pharmacokinetic parameters for LIKMEZ from the two BA studies were similar to the LD, however the mean half-life was slightly longer at 9 hours versus 8 hours noted in the LD's PI. Therefore, a recommendation to note the half-life estimate as 9 hours for healthy subjects in the proposed PI was sent to the Applicant.

Table 2. Statistical Results for Pharmacokinetic Parameters of LIKMEZ

Geometric Least Square Means (GLSM) and Ratio (Test/Reference) of GLSM			
PK Parameter (Unit)	**C_{max} (µg/mL)**	**AUC_{0-t} (h*µg/mL)**	**$AUC_{0-\infty}$ (h*µg/mL)**
Fasting			
GLSM (CV%)	12.5 13%	138 6%	142 7%
Ratio (T/R) (90% CI)	106% (101% – 111%)	101% (99% - 103%)	101% (98% - 103%)
Fed			
GLSM (CV%)	9.50 7%	137 4%	141 4%
Ratio (T/R) (90% CI)	99% (96% - 101%)	101% (99% - 102%)	101% (99% - 102%)

CI: Confidence Interval; CV: Co-efficient of Variance; GLSM: Geometric Least Square Means; PK: Pharmacokinetic; R: reference product; T: test product
Source: Adapted from 21-VIN-0347 study report p. 14 and 21-VIN-0348 study report p. 14

Relative Bioavailability Assessment Criteria

The following criteria were used for the above mentioned two relative BA studies to compare the BA between the test and reference drug products with respect to metronidazole. For pharmacokinetic metrics (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$), the criterion similar to the one used in evaluating average bioequivalence is used to compare BA, i.e., the test/reference ratio and 90% confidence interval should fall within the range of 80% to 125% to meet bioequivalence.

BA Evaluation Method and Software: The Applicant utilized natural log(ln)-transformed metronidazole pharmacokinetic parameters and analyzed BA based on the analysis of variance (ANOVA) using PROC GLM in SAS® Software, Version 9.4. The Reviewer's independent BA assessment utilized Phoenix® and Phoenix WinNonlin™.

Site Inspection

An inspection of the clinical and bioanalytical sites was requested for Study 21-VIN-0347 and Study 21-VIN-0348.

With respect to analytical sites, the Office of Study Integrity and Surveillance (OSIS) declined to conduct an inspection for the bioanalytical site (see memo dated 01/05/2023). OSIS determined that an inspection was not needed for the site, as OSIS had conducted a Remote Regulatory Assessment (RRA) for the bioanalytical site in (b) (4), which falls within the surveillance interval. OSIS had concluded that data from the reviewed studies were reliable.

Therefore, favorable inspectional results of the bioanalytical site support the clinical pharmacology recommendations outlined in this review.

For the clinical study sites, OSIS inspected the clinical portions of study 21-VIN-0347 conducted at Veeda Clinical Research Pvt. Ltd., Mehsana, Gujarat, India (see memo signed into DARRTS on 08/30/2023). The OSIS inspection summary notes no identified concerns from the inspection for Veeda Clinical Research Pvt. Ltd., regarding reliability of the data or human subject protection for study 21-VIN-0347. In the OSIS memo, there were four discussion items raised with the site at the inspection close-out. The OSIS memo noted that these discussion items do not impact the data reliability or subject safety. Previous Form FDA 483 observations (from a prior inspection conducted August 23-27, 2021) were related to failing to obtain the x-ray source images from the third-party vendors. This issue was found to have been addressed.

Post-Marketing Requirements

The Review Team recommended Post-Market Requirement (PMR) studies for the additional pediatric indications of treatment of anaerobic bacterial infections, and treatment of trichomoniasis are described in Section 15.

From a Clinical Pharmacology perspective, to support pediatric extrapolation for the treatment of anaerobic bacterial infections and trichomoniasis, additional information on metronidazole pharmacokinetics is required on two aspects: (1) To characterize the metronidazole PK in pediatric patients aged 12 months to < 4 years and (2) To assess the potential impact of age (adults and pediatrics) and infection type/disease state (healthy volunteers and patients), as summarized below.

(1) The Applicant concluded that there is lack of metronidazole pharmacokinetic data in pediatric patients aged 12 months to < 4 years in the literature presented, which is discussed in the previously agreed upon iPSP. We agree with this conclusion. This information is required so that a safe and appropriate dosage of metronidazole can be determined in all age groups of pediatric patients for the indication of anerobic bacterial infections. Specifically, PK information obtained in this study is expected to play a key role in the Applicant's plan to extrapolate effectiveness from adults to pediatric patients. Therefore, we agree with the Applicant's plan to address this information gap by conducting a PK study in pediatric patients aged 12 months to < 4 years with anaerobic bacterial infections under a PMR (See PMR 1 Section 15).
(2) During the review of this NDA, we noted that LIKMEZ pharmacokinetics have thus far only been evaluated in healthy volunteers, and that the Applicant did not provide data on the effect of the disease state on metronidazole pharmacokinetics (in either adult or pediatric patients) in support the planned extrapolation for pediatric indications of anaerobic bacterial infections or treatment of trichomoniasis. To bridge this information gap, we proposed two additional PMRs in the form of literature assessments, to support an indication for the treatment of anaerobic bacterial infections in pediatric patients

aged 0 to < 12 months and 4 years to < 18 years (see PMR 2 Section 15) and to support an indication for the treatment of trichomoniasis in pediatric patients aged 12 years to <18 years (see PMR 3 Section 15). The Applicant agreed with the recommended literature assessments.

6.2.1. Pharmacology and Clinical Pharmacokinetics

No new clinical pharmacology information was submitted except for PK data from two relative BA studies conducted in healthy volunteers (Study 21-VIN-0347 and Study 21-VIN-0348) under fasting and fed conditions.

6.2.2. General Dosing and Therapeutic Individualization

The proposed metronidazole dosage is the same as the dosage recommended in the LD's PI. During the review, it was noted that the LD's PI does not include a maximum pediatric dosage. Therefore, we recommended that the Applicant note a maximum pediatric dosage that aligns with the recommended adult dosage, i.e., not to exceed 750 mg (7.5 mL) dose for the pediatric amebiasis indication. The Applicant agreed with the following text in **Section 2.2 Recommended Dosage for Amebiasis** of LIKMEZ PI:

Pediatric patients: 35 mg/kg/24 hours to 50 mg/kg/24 hours divided into three doses, to a maximum dose of 2250 mg/24 hours (maximum dose of 750 mg/dose or 7.5 mL/dose), orally for 10 days.

6.3.Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

No new clinical pharmacology information was submitted except for PK data from two relative BA studies conducted in healthy volunteers (Study 21-VIN-0347 and Study 21-VIN-0348) under fasting and fed conditions. Refer to the LD's PI for the information on general pharmacology and pharmacokinetic characteristics for metronidazole.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide evidence of effectiveness?
Yes, the clinical pharmacology program provides pivotal evidence of effectiveness. Specifically, this is a 505(b)(2) NDA submission for a new metronidazole oral suspension formulation that is supported based on two comparative BA studies that support a bridge between the proposed oral suspension formulation and the reference (FLAGYL) oral tablet formulation.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?
The proposed metronidazole doses are same as the doses approved for the LD.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No new clinical pharmacology information on individualized dosing regimens or a management strategy for subpopulations based on intrinsic or extrinsic patient factors was submitted.

7 Sources of Clinical Data and Review Strategy

For this 505(b)(2) NDA, the Applicant is relying on the Agency's findings of safety and effectiveness of the LD, FLAGYL tablets. No additional clinical trials were conducted to evaluate the efficacy of the proposed product for the proposed indications. Three clinical studies assessing the comparative BA of metronidazole oral suspension have been conducted. The first trial was conducted using the older formulation of the suspension, ATI 1501 at 250 mg/5 mL. Following completion of this study, approximately 20 randomly selected subjects were enrolled in the Taste Test sub-study to evaluate the palatability of ATI-1501 compared with a single 500 mg tablet of FLAGYL crushed in apple sauce.

Two relative BA studies, Study 21-VIN-0347 and Study 21-VIN-0348 were conducted with LIKMEZ 500 mg/5mL. For this safety review, we only analyzed the data obtained from Studies 21-VIN-0347 and 21-VIN-0348 which studied the currently proposed formulation of the drug product. These studies are described in Sections 6 (Clinical Pharmacology), 10 (Review of Safety), and 17 (Appendices).

8 Statistical and Clinical and Evaluation

No statistical review of the safety and efficacy for the proposed product has been conducted since the Applicant has not conducted any new efficacy studies with their product and are relying on the Agency's finding of safety and effectiveness of the LD.

9 Clinical Microbiology Review

No new clinical microbiology data were submitted with this NDA.
However, updates were made to the label in order to reflect taxonomic changes.

10 Review of Safety

10.1. Safety Review Approach

This NDA application relies on the Agency's previous findings of safety of the LD, FLAGYL. Since the approval of FLAGYL (metronidazole) in 1963, it has been used in the US and worldwide with a well characterized safety profile. The adverse event profile of metronidazole is described in the approved PI.

To demonstrate a PK bridge between LIKMEZ and FLAGYL tablets, the Applicant conducted two single-dose cross-over BA studies in healthy adult volunteers, namely 21-VIN-0347 and 21-VIN-0348 under fasting and fed conditions, respectively. In each study, subjects were randomized such that 24 subjects would receive the test drug (1st treatment period) followed by the reference drug (2nd treatment period). The other 24 subjects would receive the reference drug (1st treatment period) followed by the test drug (2nd treatment period). There was 7-day washout period between the two treatment periods. The total duration of the study was 13 days. The safety and tolerability of LIKMEZ was also ascertained in these two studies, albeit in a small number of subjects. The safety results are described below.

To ensure that no new safety findings were available since the last revision of the FLAGYL PI in December 2021, this reviewer conducted an independent search in PubMed for relevant publications using the keywords "metronidazole" and "adverse events" and in the FAERS database. Additionally, the Applicant was asked to review the safety information from the published literature and pharmacovigilance databases and submit this summary of safety to the NDA.

10.2. Review of the Safety Database

Overall Exposure

A total of 96 healthy subjects were exposed to either the metronidazole tablet (reference drug) or LIKMEZ (test drug) in the BA studies noted below in Table 3. These studies are described in greater detail in Section 17. Tables 4 and 5 show the demographic characteristics of the subjects who completed the study.

Table 3. Summary of BA Studies

Study No.	Study Design	N	Dose of metronidazole tablet*	Dose of LIKMEZ	Fed/fasted	Single or Multidose
21-VIN-0347	Open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover oral comparative bioavailability study	Enrolled: 48 Completed: 44	500 mg tablet	500 mg/5 mL	Fasted	Single dose, crossover
21-VIN-0348	Open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover oral comparative bioavailability study	Enrolled: 48 Completed: 46	500 mg tablet	500 mg/5mL	Fed	Single dose, crossover

Source: Adapted from 21-VIN-0347 clinical study reports, tabular listing of clinical studies, page 1 and 21-VIN-0348 clinical study reports, tabular listing of clinical studies, page 1.
*Metronidazole tablet from Teva Pharmaceuticals

Table 4. Demographic Characteristics in Study 21-VIN-0347

Study No. 21-VIN-0347			
		Treatment Groups	
		Test Product (T) N = 44	Reference Product (R) N = 44
Age (years)	Mean ± SD	32.69 ± 6.81	32.69 ± 6.81
	Range	25.00 – 44.00	25.00 – 44.00
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	40 (90.90%)	40 (90.90%)
	41 – 64	04 (09.10%)	04 (09.10%)
	65 – 75	00 (00.00%)	00 (00.00%)
	> 75	00 (00.00%)	00 (00.00%)
Sex	Male	40 (90.90%)	40 (90.90%)
	Female	04 (09.10%)	04 (09.10%)
Race	Asian	44 (100.00%)	44 (100.00%)
	Black	00 (00.00%)	00 (00.00%)
	Caucasian	00 (00.00%)	00 (00.00%)
	Hispanic	00 (00.00%)	00 (00.00%)
	Other	00 (00.00%)	00 (00.00%)
BMI (Kg/m^2)	Mean ± SD	22.99 ± 3.67	22.99 ± 3.67
	Range	18.94 – 29.58	18.94 – 29.58
Height (cm)	Mean ± SD	157.75 ± 6.90	157.75 ± 6.90
	Range	145.00 – 168.00	145.00 – 168.00
Weight (Kg)	Mean ± SD	56.95 ± 7.96	56.95 ± 7.96
	Range	48.80 – 73.30	48.80 – 73.30

Note: Dropped out subjects are not included in this demographic table.

Table 5. Demographic Characteristics in Study 21-VIN-0348

Study No. 21-VIN-0348			
		Treatment Groups	
		Test Product (T) N = 46	Reference Product (R) N = 46
Age (years)	Mean ± SD	32.24 ± 6.00	32.24 ± 6.00
	Range	20.00 – 44.00	20.00 – 44.00
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	42 (91.30%)	42 (91.30%)
	41 – 64	04 (08.70%)	04 (08.70%)
	65 – 75	00 (00.00%)	00 (00.00%)
	> 75	00 (00.00%)	00 (00.00%)
Sex	Male	42 (91.30%)	42 (91.30%)
	Female	04 (08.70%)	04 (08.70%)
Race	Asian	46 (100.00%)	46 (100.00%)
	Black	00 (00.00%)	00 (00.00%)
	Caucasian	00 (00.00%)	00 (00.00%)
	Hispanic	00 (00.00%)	00 (00.00%)
	Other	00 (00.00%)	00 (00.00%)
BMI (Kg/m^2)	Mean ± SD	23.45 ± 3.08	23.45 ± 3.08
	Range	18.73 – 29.41	18.73 – 29.41
Height (cm)	Mean ± SD	164.77 ± 6.98	164.77 ± 6.98
	Range	145.00 – 178.50	145.00 – 178.50
Weight (Kg)	Mean ± SD	63.68 ± 9.44	63.68 ± 9.44
	Range	46.80 – 87.10	46.80 – 87.10

Note: Dropped out subjects are not included in this demographic table.

Adequacy of the Safety Database:

As the main objective of the BA studies was to compare the rate and extent of absorption of LIKMEZ to metronidazole tablets, and the Applicant relied upon the Agency's previous findings for safety of the LD, FLAGYL, the limited safety database in these BA studies is considered adequate.

10.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no issues with data integrity. The Applicant was asked to provide a clinical overview and a summary of safety findings from the published literature and FAERS, pharmacovigilance database.

Categorization of Adverse Events

The Applicant has defined the terms adverse event (AE) and serious adverse event (SAE) as follows:

An AE is any untoward medical occurrence or clinical investigation in a subject after administration of a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not causally related to the medicinal (investigational) product.

The following terms define the severity of an AE:

- Mild: Signs and symptoms are transient and minor irritant type; aware of symptom but easily tolerated; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation.
- Moderate: Discomfort enough to cause interference with usual activities; persistent or requiring treatment.
- Severe: Any symptom which causes a subject's inability to perform usual activity; needs hospitalization and treatment.

A SAE is any untoward medical occurrence during a study which satisfies one or more of the following conditions:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or permanent disability
- Is a congenital anomaly/birth defect.
- Important Medical Event

Routine Clinical Tests

Pre-study screening laboratory tests conducted in the healthy volunteers included complete blood count with a differential, a metabolic panel consisting of a blood glucose level, blood urea, creatinine, total protein, albumin, serum glutamic-oxaloacetic transaminase (SGOT),

serum glutamic pyruvic transaminase (SGPT), total bilirubin, conjugated and unconjugated bilirubin, alkaline phosphatase, uric acid level, cholesterol , lactate dehydrogenase (LDH), ABO and Rh blood typing, C reactive protein (CRP), anti-Hepatitis C virus antibodies (IgG and IgM), Hepatitis B surface Ag, screening and confirmatory tests for HIV I and II and urinalysis. For female subjects, serum beta HCG level was checked prior to treatment period 1 and treatment period 2 of the study. Post-study laboratory tests included complete blood count with a differential, a metabolic panel consisting of urea, creatinine, SGOT, SGPT, total bilirubin, unconjugated and conjugated bilirubin. A chest X-ray (PA view) was performed in all subjects due to the COVID-19 pandemic. A 12 lead EKG was performed in all subjects during screening. Vital signs (blood pressure, heart rate, body temperature and respiratory rate) were obtained prior to the study and at various timepoints post administration of the test or reference drug.

10.4. Safety Results

Deaths

No deaths were reported in the BA studies.

Serious Adverse Events

No SAEs were reported in the BA studies.

Dropouts and/or Discontinuations Due to Adverse Effects

There was a total of 6 subjects who had a discontinuation from the studies, 4 in 21-VIN-0347 and 2 in 21-VIN-0348. Of these, one subject was discontinued due to a treatment emergent adverse event (TEAE) (vomiting), which was considered possibly drug related.

<u>Study 21-VIN-0347:</u>

- Subject No. (b) (6) was withdrawn due to an adverse reaction (vomiting) as noted above
- Subject Nos. (b) (6) and (b) (6) dropped out due to not reporting to the facility in the 2nd treatment period. Subject No. (b) (6) reported an episode of vomiting and abdominal pain one week after administration of the test drug and did not report for the 2nd treatment period. The Applicant reported that the relationship to the study drug was not related.
- Subject No. (b) (6) was withdrawn due to spitting out the drug (reason for spitting out drug was not provided).

<u>Study 21-VIN-0348:</u>

- Subject No. (b) (6) dropped out due to not reporting to the facility in 2nd treatment period (no AE was reported before dropping out)
- Subject No. (b) (6) was withdrawn due to incomplete dosing.

Significant Adverse Events

None.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAE) reported in the individual clinical studies are briefly summarized below.

21-VIN-0347

A total of 48 adult subjects (42 male and 6 female) were enrolled in this study. Forty-four subjects completed the study.

Table 6. TEAEs Experienced by the Subjects in Study 21-VIN-0347

Reported TEAEs in study 21-VIN-0347

	21-VIN-0347		
	REFERENCE-TEST (N=24)	TEST-NOT TREATED (N=2)	TEST-REFERENCE (N=22)
Table Section 1			
Eosinophil count increased	1 (4.2%)	0	0
21-VIN-0347-MEH-(b) (6)	1 (4.2%)	0	0
Vomiting	1 (4.2%)	1 (50.0%)	0
21-VIN-0347-MEH-(b) (6)	0	1 (50.0%)	0
21-VIN-0347-MEH-	1 (4.2%)	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: None.
Table Section 1 - Dataset: Adverse Events; Filter: None

As noted in the discontinuations above, one TEAE of vomiting, leading to withdrawal from the study, was reported in subject (b) (6) after administration of the test drug in the 2nd period.

Two other AEs were reported but were deemed not related to the study drug by the Applicant. Subject (b) (6) was reported to have mild eosinophilia. Screening laboratory testing on this subject showed an eosinophil count of 16% (Reference range 1-6%) with a total white blood cell count of 8390 (Reference range 4000-10,000/µL). A repeat eosinophil count was obtained and found to be 2.3% (total white blood cell count was not reported). This subject was enrolled in the study as this repeat eosinophil percentage fell within the inclusion criteria. The subject tolerated both the reference and test drug doses. Post-study labs were performed on discharge (2 days after test drug administration). On discharge, the subject had no subjective complaints and no abnormal findings on physical exam. The eosinophil count was reported as 22.1% with total WBC count of 8140/ µL. The subject was reported as lost to follow up.

Subject (b) (6) experienced vomiting one week after administration of the test drug. Concomitant abdominal pain was also reported in the case report form (CRF) which was not captured as an AE. The subject failed to report for the second treatment period.

Clinical Reviewer's comment: *Regarding subject (b) (6), it is difficult to ascertain the relationship between eosinophilia and the reference or the test drug. It is also uncertain if there was pre-existing eosinophilia and if the repeat test result was an error. A search of the literature using PubMed did not reveal any evidence of an association between asymptomatic eosinophilia and metronidazole use.*

21-VIN-0348

A total of 48 adult subjects (43 male and 5 female) were enrolled in this study of which 46 subjects completed the study.

Table 7. TEAEs Experienced by Subjects in Study 21-VIN-0348

Reported TEAEs in study 21-VIN-0348

	21-VIN-0348		
	REFERENCE-NOT TREATED (N=1)	REFERENCE-TEST (N=23)	TEST-REFERENCE (N=24)
Table Section 1			
Nasopharyngitis	0	1 (4.3%)	0
21-VIN-0348-MEH- (b) (6)	0	1 (4.3%)	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: None.
Table Section 1 - Dataset: Adverse Events; Filter: None.

This AE of moderate nasopharyngitis was deemed unrelated to the test drug. The subject developed sneezing and runny nose one day after reference drug administration in the first treatment period. He was treated with levocetirizine 5mg BID for 2 days and the symptoms resolved within 24 hours. The subject tolerated the test drug in the second treatment period.

Laboratory Findings

One subject was reported to have eosinophilia as noted above. Other laboratory values were found to be within normal limits or not clinically significant.

Vital Signs

No abnormal vital signs were reported.

Electrocardiograms

Electrocardiograms (ECGs) were performed during screening. No clinically significant baseline ECG abnormality and QT findings were reported.

Immunogenicity

Not applicable.

10.5. Additional Safety Explorations

Human Reproduction and Pregnancy

(b) (4) The LD has a contraindication in pregnancy for use of metronidazole during the first trimester of pregnancy for the treatment of trichomoniasis only. A consultation was requested from the Division of Pediatrics and Maternal Health (DPMH). DPMH noted that upon review of the literature, evidence from published case-control studies, cohort studies, meta-analyses, case series, and case reports over several decades, the evidence does not support an increased incidence of adverse pregnancy or infant outcomes with metronidazole use during pregnancy. Rare earlier reports of such associations were not confirmed by later studies with more modern designs which controlled for a larger number of confounding factors. Thus, DPMH concluded that based on currently available evidence, the contraindication in pregnancy with metronidazole for the first trimester is not applicable (b) (4) (see the consultation review from DPMH by Jane Liedtka, signed into DARRTS on 7/21/2023, for details). This information was communicated to the Applicant in an IR dated 7/25/2023, and the Applicant agreed (b) (4).

Lactation

In the proposed labeling, the Applicant noted the following statement from the LD labeling for the lactating mother: “a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Alternatively, a nursing mother may choose to pump and discard human milk for the duration of metronidazole therapy, and for 24 hours after therapy ends and feed her infant stored human milk or formula.” This was based on tumorigenicity data from mice and rats in non-clinical studies. A consultation from DPMH was obtained where they noted that there are no data on the effects of metronidazole on milk production and that the animal studies showing potential tumorigenicity were after chronic administration. As LIKMEZ is not intended to be administered chronically, the clinical relevance of the findings of the animal studies is unclear. DPMH recommended that the statement be revised in the labeling as follows: “The developmental and health benefits of breastfeeding should be considered along with the

mother's clinical need for metronidazole and any potential adverse effects on the breastfed infant from metronidazole or from the underlying maternal condition. Alternatively, a lactating woman may choose to pump and discard human milk for the duration of LIKMEZ therapy, and for 48 hours after the last dose and feed her infant stored human milk or formula." The recommendation to change "24 hours" to "48 hours" was based on the drug elimination time (6 times the half-life of 8 hours). Please refer to the consultation review from DPMH by Jane Liedtka (signed into DARRTS on 7/21/2023) for additional details.

10.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

See section 10.7 , Integrated Assessment of Safety for a discussion regarding the postmarket safety of the LD. There are no data on the postmarketing experience of LIKMEZ as it is not approved in any country.

10.7. Integrated Assessment of Safety

The safety assessment for this NDA relies predominantly on the Agency's previous findings of safety for the LD. The two BA studies conducted in healthy volunteers are small and provide limited information on safety. The probable adverse reactions (e.g., vomiting) experienced by the subjects in the BA studies are listed in the FLAGYL PI. Additionally, both the Applicant and the clinical reviewer searched the published literature and the safety data reported in FAERS since the last revision of the FLAGYL PI in December 2021, and provided a summary as noted below.

Published Literature Review Submitted by the Applicant

The Applicant conducted a comprehensive literature search following a predefined protocol with the aim of identifying any new safety information regarding the use of metronidazole. This involved a literature search using PubMed and Medline databases from January 1, 1995, to January 24, 2023, using the information provided in English or articles with English translations available to ensure comprehensive coverage of U.S and ex-U.S. sourced published literature. There were 98 papers that were identified as possibly containing relevant information. Based on the title and abstract review, relevant full-text articles were retrieved and reviewed to determine whether they contained data related to metronidazole use in humans. Publications were considered relevant if the following information was included in the title and/ or abstract:

- Any mention of the use of metronidazole not administered with other therapies
- Clinical studies
- Any mention of adverse events, side effects, or safety of metronidazole taken orally
- General statement included about tolerability and/or safety of metronidazole.

Fourteen articles were identified by the Applicant to have relevant information since the last

revision of the FLAGYL PI. After reviewing the available literature, the Applicant concluded that no new relevant safety information was identified when metronidazole was used for the intended indications.

Pharmacovigilance Database (FAERS) review submitted by the Applicant

The Applicant has submitted FAERS data including System organ class (SOC) and Preferred Term (PT). The Applicant did not find any new safety data to be included in the labeling.

In conclusion, the Applicant states that, despite an extensive literature search and examination of adverse event data, no significant new safety information concerning the use of metronidazole for its intended indications was identified. This suggests that the current safety profile of metronidazole remains consistent with the existing knowledge and does not warrant any revisions or additions to the prescribing information (PI).

Clinical Reviewer's Comment: *This reviewer also evaluated the information submitted by the Applicant. Of note, Sun et. al [5]published a phase 3, multicenter, double-blind, randomized clinical trial in 268 adult subjects evaluating the efficacy and safety of ceftolozane/tazobactam (C/T) plus metronidazole versus meropenem plus placebo in Chinese participants with complicated intra-abdominal infections. No statistically significant difference in adverse reactions were noted in either arm. Abdominal distention was noted in the C/T plus metronidazole group and peripheral swelling was reported in both the groups with a higher incidence in the C/T plus metronidazole group. It is difficult to ascertain the causality of these AEs to metronidazole given there was possible confounding by both underlying clinical illness and use of concomitant antibacterial therapy.*

Clinical Reviewer's Search of the Literature and FAERS database:

An independent PubMed search for relevant publications using the keywords "metronidazole" and "adverse events" from December 2021 to present was conducted. Ninety-four publications were identified which included abstracts and full reports. No new safety signals were identified by this reviewer that would require revisions to the PI.

However, this reviewer found a few case reports of tinnitus with or without deafness reported with the use of metronidazole that predated the last revision of the FLAGYL PI in December

[5] Sun Y, Fan J, Chen G, Chen X, Du X, Wang Y, Wang H, Sun F, Johnson MG, Bensaci M, Huntington JA, Bruno CJ. A phase III, multicenter, double-blind, randomized clinical trial to evaluate the efficacy and safety of ceftolozane/tazobactam plus metronidazole versus meropenem in Chinese participants with complicated intra-abdominal infections. Int J Infect Dis. 2022 Oct;123:157-165.

2021. [6] [7] [8] *Upon further review, it was also noted that tinnitus is included as a possible adverse reaction to metronidazole (Flagyl 400 mg tablets) from Sanofi in the drug label from the UK (Electronic Medicine Compendium).* [9] [10]

This reviewer evaluated the FAERS database for metronidazole from December 2021 to present using the preferred term (PT) tinnitus. This generated 12 reports out of which 1 report suggested that metronidazole may have been a suspect drug associated with tinnitus. The case described a 50-year-old female, with a history of allergies to multiple medications who was started on metronidazole 500 mg twice daily for an unknown indication on 2/14/2022. No concomitant medications were reported. She developed sharp abdominal pain, sore lip, headache, dizziness and ringing in her ears.

The majority of the reports were confounded by other concomitant medications, thereby making it difficult to determine causality to the drug.

Clinical Reviewer's Comment: *At this time, tinnitus and ototoxicity will continue to be monitored with routine pharmacovigilance.*

[6] Jafari, G., Hosseini, S.M. & Akhondzadeh, S. Sudden hearing loss subsequent to diarrhea: what is the missing link?. DARU J Pharm Sci 22, 15 (2014).
[7] O'Donnell KL, Barker D. Metronidazole and tinnitus: A potential side effect? Br Dent J. 2016 Mar 25;220(6):289-91.
[8] Iqbal SM, Murthy JG, Banerjee PK, Vishwanathan KA. Metronidazole ototoxicity--report of two cases. J Laryngol Otol. 1999 Apr;113(4):355-7.
[9] https://www.medicines.org.uk/emc/product/9238/smpc
[10] Flagyl 400mg Tablets - Patient Information Leaflet (PIL) - (emc) (medicines.org.uk)

11 Advisory Committee Meeting and Other External Consultations

None.

12 Pediatrics

On 4/29/2022, the Division of Anti-Infectives agreed to the initial Pediatrics Study Plan (Agreed iPSP) submitted by the Applicant under IND 132217, following a PeRC meeting held on 4/5/2022. Of note, the iPSP for this IND was submitted on 6/18/2018 by the previous sponsor, Appili Therapeutics. This iPSP underwent several revisions after meetings and correspondence between Appili Therapeutics and the Agency.

After NDA 216755 was submitted on 11/23/2023 some minor discrepancies were noted in the Agreed iPSP, which were communicated to the Applicant. These included the age range for the partial waiver for the trichomoniasis indication. Although the Applicant had agreed to extend the partial waiver for trichomoniasis to <12 years, they inadvertently did not incorporate this change throughout the iPSP. Additionally, in their proposed phase 2 study designed to evaluate the safety and PK in pediatric patients aged 12 months to < 4 years, the inclusion criteria included (b) (4) , these were brought to attention of the Applicant. The Applicant submitted revisions to the Agreed iPSP on 2/17/23.

The Agreed iPSP included a partial waiver from conducting required pediatric assessments for the treatment of trichomoniasis from birth to <12 years and requests for deferral in certain pediatric populations.

Applicant's Rationale for Partial Waiver
Necessary studies are impossible or highly impracticable because the number of patients in the pediatric age group is very small or treatment with oral metronidazole is not appropriate. Trichomoniasis, which is among the most common sexually transmitted infections in the U.S., has poorly defined epidemiology, especially in the early adolescent and younger populations. There is lack of routine testing, potential for asymptomatic presentation and it is a non-notifiable condition in the U.S. Additionally, *T. vaginalis* infection in children is often associated with suspicion of sexual abuse, thus, making a study in this population infeasible.

The following studies were deferred because the product would be ready for approval for use in adults:

- Deferral from conducting a planned phase 2 pediatric PK and safety study for metronidazole oral suspension to support the use in pediatrics age group 12 months to <4 years of age.

The Applicant acknowledged that the extrapolation model is limited in its utility to effectively extrapolate the PK parameters to all age groups identified in the FDA Pediatric Guidance. This is primarily due to its use of allometric scaling that assumes a linear relationship between metabolic function and body mass that has not been clearly established for metronidazole in

children aged 12 months to < 4 years. Hence, the Applicant proposed to conduct a phase 2 PK and safety study in this age group of pediatric patients with infections that are treated with metronidazole, to collect PK data within this subset of the pediatric population. The Applicant requested a deferral for this study because the product will be ready for approval for use in adults (for indications approved for FLAGYL® tablets in the U.S.) before pediatric studies can be completed.

- Deferral of pediatric assessments from birth to < 12 months for the treatment of amebiasis and anaerobic bacterial infections.

The Applicant plans to submit dosing, safety, and efficacy information for the treatment of amebiasis and anaerobic bacterial infections in the neonate and infant population after the completion of the pediatric PK and safety study, when data in children 12 months to < 4 years of age is available.

- Deferral of pediatric assessment from 4 years to < 18 years of age in anaerobic infections and 12 years to < 18 years in trichomoniasis

The Applicant plans to provide literature support and extrapolate effectiveness from adult populations to children and adolescents ages 4 years to < 18 years of age in anerobic infections and 12 years to < 18 years in trichomoniasis because the courses of the diseases and the effects of the drug are sufficiently similar in adult and pediatric patients and PK has been previously evaluated in children.

In the submitted NDA the Applicant requested approval for the treatment of trichomoniasis and anaerobic infections in adults and for the treatment of amebiasis in both pediatric and adult patients. Thus, although the previous iPSP deferrals included an amebiasis indication, this is not applicable at this point.

A PeRC meeting was held on 7/25/2023. The PeRC agreed with the current request to grant a partial waiver for pediatric patients from birth to <12 years of age for the trichomoniasis indication because necessary studies are impossible or highly impracticable. The PeRC agreed to grant a deferral of studies for pediatric patients 12 years to < 18 years for trichomoniasis and (b) (4) for anaerobic infections. The PeRC agreed that the product has been fully assessed for pediatric patients for the indication for amebiasis and the data from this indication will help inform the modeling for 0-12 months for anaerobic infections. The PMRs that had been generated were discussed during the meeting and were agreed to by the PeRC (refer to PeRC meeting minutes dated July 25, 2023) For details regarding the PMRs, see Section 15.

13 Labeling Recommendations

13.1. Prescription Drug Labeling

Prescribing Information

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes incorporated into the finalized PI (the PI that will be approved or is close to being approved). The finalized PI was compared to the Applicant's draft PI submitted on November 23, 2022 (see table below). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 8. Major Labeling Changes and the Rationale for the Changes

Prescribing Information (PI) Sections	Rationale for Major Changes Incorporated into the Finalized PI
Highlights	The following changes were made in the Highlights based on revisions made in the Full prescribing information (FPI). Please see revisions made in the FPI for additional details. • Boxed warning was updated to contain the same information as in the FPI. "Rejected Applicant's proposal to (b) (4) Added the names of the indications for which the use of LIKMEZ should be reserved. Refer to the labeling recommendations in the FDA Guidance for Industry: "Labeling for Human Prescription Drug and Biological Products-Implementing the PLR Content and Format Requirements" for additional information. • Specified the population (adults or pediatric patients) for which LIKMEZ is indicated as per the FDA Guidance for Industry: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products-Content and Format. • Added that the dosing regimen for trichomoniasis should be individualized. • Added a maximum dose limit of LIKMEZ for pediatric patients with amebiasis. Refer to section 6.2.2 of the Integrated Assessment Review for

Prescribing Information (PI) Sections	Rationale for Major Changes Incorporated into the Finalized PI
	additional details. • Under "Contraindications", replaced the word "(b) (4)" with "metronidazole" in the sentence "Prior history of hypersensitivity to (b) (4)" since this PI is for metronidazole. • Removed (b) (4) from sections, "Contraindications" and "Use in specific populations" because the available evidence (b) (4) • Removed Warning for (b) (4) • Under "Warning and Precautions, Central nervous system", removed the statement stating to (b) (4) and replaced by a statement recommending prompt evaluation of the benefit/risk of continuation of LIKMEZ. This is for consistency with the FPI. • Removed "(b) (4)" and "(b) (4)" subheadings from "Warning and Precautions" because information on (b) (4) section of the Highlights. (b) (4) was removed to align with its removal from the FPI. (b) (4) were removed because it was not considered the most clinically significant safety concern to include in the Highlights. • Removed (b) (4) as these do not describe a clinically significant adverse reaction in patients with (b) (4). • Added information to "Adverse Reactions" as per 21 CFR 201.57) a) (11) because the section was previously left blank by the Applicant. • Modified information on lactation under "Use in Specific populations." Refer to section 10.5 of this

Prescribing Information (PI) Sections	Rationale for Major Changes Incorporated into the Finalized PI
	Integrated Assessment Review and for additional details.
Full Prescribing Information	
BOXED WARNING	• Rejected Applicant's proposal to (b) (4) The title of the Boxed Warning must appear after the word "WARNING:" and must identify the subject(s) of the warning contained in the box as per 21 CFR 201.57 (a)(4). • Specified that LIKMEZ treatment should be reserved for the indications, trichomoniasis, amebiasis and anerobic infections based on current labeling recommendation. This replaced the proposed language by the Applicant where LIKMEZ treatment was (b) (4) for consistency with the preferred presentation for cross-referencing as per the FDA Guidance for Industry: "Labeling for Human Prescription Drug and Biological Products-Implementing the PLR Content and Format Requirements. • Removed the statement " (b) (4) " due to lack of supporting evidence provided in the Applicant's submitted clinical information.
1 INDICATIONS AND USAGE	• Modified proposed language in subsection 1.1, Trichomoniasis to maintain specific information regarding treatment in symptomatic and asymptomatic trichomoniasis. • In subsection 1.2, Amebiasis, added a statement "In amebic liver abscess, treatment with LIKMEZ does not obviate the need for aspiration or drainage of pus." This statement provides clinically relevant information and is also included in LD labeling. • In subsection 1.3, Anerobic Bacterial Infections, renamed (b) (4) to *Parabacteroides distasonis* based on taxonomic nucleic acid analysis

Prescribing Information (PI) Sections	Rationale for Major Changes Incorporated into the Finalized PI
	data. Edits made to reflect that *P. distasonis* is not a member of the *B. fragilis* group.
2 DOSAGE AND ADMINISTRATION	• In subsection 2.1, Recommended Dosage for Trichomoniasis, removed (b) (4) • In subsection 2.2, Recommended Dosage for Amebiasis, added a maximum dose limit for pediatrics patients for treatment of amebiasis to prevent risk of overdose. • In subsection 2.6, Important Administration Instructions, added administration instructions to use a calibrated dosing device to correctly measure the prescribed dose of medication and avoid dosing errors. • Made formatting changes based on FDA Draft Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products-Content and Format
4 CONTRAINDICATIONS	• Removed (b) (4) .
5 Warnings and Precautions	• In subsection 5.1, "Potential for carcinogenicity", removed the Applicant's proposed language (b) (4) due to lack of supporting evidence provided by the Applicant. Added the same risk mitigation statement included in the boxed warning in the Highlights section above as per the labeling recommendations in the FDA Guidance for Industry: "Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling." • In subsection 5.5, Drug -Resistant Bacteria (b) (4) , removed " (b) (4) " from the heading and text to make this regulatory required section consistent with the verbatim statement in 21 CFR 201.24 (c) labeling for systemic antibacterial drug products. • In addition, the Applicant's proposed inclusion of information on " (b) (4) " is not

Prescribing Information (PI) Sections	Rationale for Major Changes Incorporated into the Finalized PI
	required by regulation, is not in the LD (FLAGYL) labeling and was not considered to be necessary for inclusion in this PI by the DAI clinical team. • Moved a regulatory required statement regarding [redacted (b) (4)] • Recommended deletion of [redacted (b) (4)] as noted in the Highlights section of this table.

6 ADVERSE REACTIONS	• Added the following statements at the beginning of the Section 6, Adverse Reactions, for clarity as per the FDA Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products-Content and Format:
	• "The following clinically significant adverse reactions are described elsewhere in the labeling:
	  • Central and Peripheral Nervous System Effects *[see Warnings and Precautions (5.2)]*
	  • [redacted (b) (4)] Blood Dyscrasias *[see Warnings and Precautions (5.4)]*
	• In subsection 6.1, Clinical Trials Experience, added "and Peripheral" to subheading "Central Nervous System" given the description of adverse reactions listed.
	• In subsection 6.1, under "Central and Peripheral Nervous System", [redacted (b) (4)] was moved to Section 17, "Patient Counseling Information" because it is intended to be conveyed to the patient by the health care provider.

7 DRUG INTERACTIONS	In subsection 7.5, the Applicant's proposed recommendation for [redacted (b) (4)] was removed as the language is not noted in the LD PI or supported by the Applicant's provided clinical pharmacology information.
8 USE IN SPECIFIC POPULATIONS	• Revised pregnancy and lactation subsections to

Prescribing Information (PI) Sections	Rationale for Major Changes Incorporated into the Finalized PI
(e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	comply with Pregnancy and Lactation Labeling Rule (PLLR) and the labeling recommendations in the Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format Guidance for Industry. Refer to the guidance above and section 10.5 of the Unireview for additional details regarding the following changes: <u>Under subsection 8.1: Pregnancy</u> • Removed (b) (4) and replaced with information based on currently available evidence. • Removed (b) (4) <u>Under subsection 8.2: Lactation</u> • Revised the statement about tumorigenicity in mouse and rat studies for clarity; (b) (4) • Added a benefit/risk statement for breastfeeding as per 21 CFR 201.57 (c) (9) (ii) (A)(3). <u>Under subsection 8.4: Pediatric Use</u> • Revised the section to clearly state that the safety and effectiveness of LIKMEZ for the treatment of amebiasis has been established in pediatric patients but has not been established for treatment of trichomoniasis and anerobic infection in pediatric patients as per the FDA Guidance for Industry "Pediatric Incorporated into Human Prescription Drug and Biological Product Labeling".
10 OVERDOSAGE	• Removed the (b) (4) since this section should be directed to the providers and not to the patient, and the LD does not contain this statement.

Prescribing Information (PI) Sections	Rationale for Major Changes Incorporated into the Finalized PI
	• Recommended that when describing a dose in this section that is outside the approved recommended dose range for the approved indication, the dosage should be expressed in terms of the maximum recommended dosage to avoid implying or suggesting an unproved dosee or dosing regimen. This revision is based on the recommendation in 21 CFR 201.57 (c)(3). • Applicant's proposed statements to address the above was further revised to replace "(b) (4) " with "single dose" in the parenthetical statement "(3 to 5.2 times the maximum recommended (b) (4)). The revised statement reads as follows "Single oral doses of metronidazole, up to 15 g (7.5 times the maximum recommended dose)..., Neurotoxic effects, including seizures and peripheral neuropathy, have been reported after 5 days to 7 days of doses of 6 g to 10.4 g every other day (3 to 5.2 times the maximum recommended single dose)." This change was based on a maximum dose of 4g/24 hours. This is consistent with the recommendations in the 21 CFR 201.57 (c)(11) regulations, that mentions that the specific information that should be provided in the overdosage section is "the amount of drug in a single dose that is ordinarily associated with symptoms of overdosage..."
12 CLINICAL PHARMACOLOGY	Under Subsection 12.3 Pharmacokinetics the following revisions were made: • Formatting was revised using the labeling recommendations in the FDA Guidance for Industry: Clinical Pharmacology Section of Labeling (final guidance). • Removed (b) (4) and retained relevant PK measures for LIKMEZ that are important for the safe and effective use of the drug. • In subsection 12.3, in support of the presented LIKMEZ PK information from a fed BA study, added

Prescribing Information (PI) Sections	Rationale for Major Changes Incorporated into the Finalized PI
	a description of the food(s) or meal(s) used with respect to total calories and composition (fat, carbohydrate, and protein content) based on the labeling recommendations in the Clinical Pharmacology Section of Labeling (final guidance). • Revised half-life to reflect BA studies data that evaluated LIKMEZ. Under subsection 12.4 Microbiology, the following revisions were made: • This subsection was reformatted to make it consistent with the FDA Guidance for Industry: Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis, and Presentation • Renamed [redacted] (b) (4) to *Parabacteroides distasonis* based on taxonomic nucleic acid analysis data. Edits made to this subsection to reflect that *P. distasonis* is not a member of the *B. fragilis* group as follows:
13 NONCLINICAL TOXICOLOGY	• Added subheadings for Carcinogenesis, Mutagenesis, and Impairment of Fertility.
17 PATIENT COUNSELING INFORMATION	• Made formatting revisions to be consistent with the labeling recommendations in the FDA Guidance for Industry: Patient Counseling Information Section of Labeling (final guidance). For example, (1) Recommended language for the reference statement was changed to "Advise the patient to read the FDA-approved patient labeling (Patient Information)." (2) Command language was used. Instead of "[redacted] (b) (4)", used command language "Advise patient." • Revised this section to reflect revisions included in other sections of the PI • Moved patient counseling statement regarding neurological adverse event from [redacted] (b) (4) to this section under "Central and Peripheral Nervous System Effects" • Moved the antibacterial drug resistance counseling information from section [redacted] (b) (4) to this section as per the labeling recommendations in 21 CFR 201.24 (d). The statement states "Patients should be

Prescribing Information (PI) Sections	Rationale for Major Changes Incorporated into the Finalized PI
	counseled that antibacterial drugs including LIKMEZ should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When LIKMEZ is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by LIKMEZ or other antibacterial drugs in the future". This statement replaced the proposed counseling statement that was included in this section of the proposed PI. "Added Warfarin and other oral" to Anticoagulants to provide more examples. • Removed (b) (4) as it is not considered a Warning in the FPI and also because listing the symptoms alone is not consistent with the FDA Guidance for Industry: Patient Counseling Information Section of labeling. • Removed the Applicant proposed recommendation to (b) (4) in the clinical studies that evaluated LIKMEZ in subsection 12.3 or the LD PI.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Under section 16, How Supplied/Storage and Handling, added the statement "Discard 10 days after opening container" because the Applicant only provided stability data for 10 days after opening. For additional details refer to the OPQ Review, in DARRTS (dated September 8, 2023)

Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Information

- Container label

14 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

15 Postmarketing Requirements and Commitment

Post-Market Requirements (PMRs) for the pediatric indications of treatment of anaerobic bacterial infections and treatment of trichomoniasis were discussed within DAI, Office of Clinical Pharmacology, as well as with DPMH and PeRC. For details regarding the rationale for the following PMRs, see section 6.2, Post-Marketing Requirements.

The following PMRs initially communicated to the Applicant on July 28, 2023, and the milestone dates agreed upon are noted below:

- **PMR 1:** Conduct a phase 2, open-label, single-arm, pharmacokinetic, and safety study in pediatric patients aged 12 months to < 4 years with anaerobic bacterial infections.

  PMR 1 Schedule Milestones
  - Draft Study Protocol Submission: 12/2023
  - Final Study Protocol Submission: 03/2024
  - Study Initiation: 12/2024
  - Study Completion: 01/2026
  - Final Report Submission: 06/2026

- **PMR 2:** Conduct a search and provide a summary of the published literature assessing dosing, safety, efficacy of metronidazole, and the effect of disease state on metronidazole pharmacokinetics in pediatric patients to support an indication for the treatment of anaerobic bacterial infections in pediatric patients aged 0 to < 12 months and 4 years to < 18 years.

  - Additional details regarding PMR 2 sent to the Applicant:

    In your summary, we would like you to clearly identify/specify the pediatric extrapolation plan including identifying a reference adult patient population, targeted exposures, and a justification of the selected exposure target ranges. If you rely on pharmacokinetic (PK) information from healthy adults to select a target exposure range, additional information will be needed with respect to the disease effect on the drug's PK.

  PMR 2 Schedule Milestones
  - Final Report Submission: 06/2025

- **PMR 3:** Conduct a search and provide a summary of the published literature assessing dosing, safety, efficacy of metronidazole, and the effect of disease state on metronidazole pharmacokinetics in pediatric patients to support an indication for the treatment of trichomoniasis in pediatric patients aged 12 years to <18 years.

PMR 3 Schedule Milestones

- Final Report Submission: 06/2025

- Additional details regarding PMR 3 sent to the Applicant:

  In your summary, we would like you to clearly identify/specify the pediatric extrapolation plan including identifying a reference adult patient population, targeted exposures, and a justification of the selected exposure target ranges. If you rely on pharmacokinetic (PK) information from healthy adults to select a target exposure range, additional information will be needed with respect to the disease effect on the drug's PK.

On 8/15/2023, in response to the 8-week PMR communication letter sent to the Applicant, the Applicant submitted a communication noted as "(b) (4)" and informed the Agency that since the submission of the PSP, they have become aware of published evidence from the Medicines and Healthcare Products Regulatory Agency (MHRA) that supports the current marketing of metronidazole suspension for the treatment of anaerobic infections in children aged 12 months to 4 years. The Applicant stated that the information provided (b) (4) The Applicant requested the Agency to review the information, (b) (4)

On 8/18/2023, the Agency responded that due to the limited amount of time remaining in the NDA review cycle, the provided information could not be evaluated, and no determination could be made on their aforementioned requests. The Agency recommended that the Applicant proceed with the plan to conduct the phase 2 study in pediatric patients as noted in the iPSP and in the PMR communication letter. The Agency also advised that further issues related to PMRs could be discussed after the action date. On 8/29/2023, the Applicant submitted their agreement to PMR 1 and the milestone dates noted above. The final proposed PMR language is noted in the Approval letter.

16 Division Director (DAI) Comments

I agree with the review team's assessment and recommendations.

17 Appendices

17.1. References

Please see footnotes.

17.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 21-VIN-0347 and 21-VIN-0348

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

17.3. OCP Appendices (Technical documents supporting OCP recommendations)

17.3.1. Individual Study Review

Study # 21-VIN-0347

Table 9. Study Summary of Study # 21-VIN-0347

STUDY SUMMARY	
Study Design	This was an open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover oral comparative bioavailability study that compared the following two drug products under fasting conditions: • Test Product (T): Metronidazole Oral Suspension, 500 mg/5mL • Reference Product (R): Metronidazole Tablets USP 500 mg After maintaining at least 10 hours of overnight fasting, a single metronidazole 500 mg oral dose either of test product or reference product was administered orally (as per the randomization schedule) in sitting posture to each subject with 240 ± 2 mL of water at ambient temperature in the morning in each period. Overall, two treatment sequences (TR, RT) were evaluated with a washout period of 9 days between Period I and Period II dosing. No carry- over effect between the treatment periods was expected, as the average elimination half-life of metronidazole in healthy adult subjects is eight hours.
Study period	Clinical Phase 02/15/2022 to 02/27/2022 Bioanalytical Phase 03/04/2022 to 03/16/2022
Link to study report	\\CDSESUB1\EVSPROD\nda216755\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\21-vin-0347\study-report-fasting-rpt-body.pdf
Links to bioanalytical validation and performance reports	*Bioanalytical validation report* \\CDSESUB1\EVSPROD\nda216755\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\21-vin-0347\study-report-i-method-validation-report.pdf *Bioanalytical report* \\CDSESUB1\EVSPROD\nda216755\0001\m5\53-clin-stud-rep\531-

STUDY SUMMARY	
	rep-biopharm-stud\5314-bioanalyt-analyt-met\21-vin-0347\study-report-bioanalytical-study-report-21-vin-0347.pdf
Study Objectives	• To compare the metronidazole BA between a single oral dose of the test and reference drug products in healthy human adult subjects under fasting conditions. • To monitor the safety and tolerability of a single oral dose of the test product administered in healthy human adult subjects under fasting conditions.
PK Sampling Schedule	In each period, a total of 20 blood samples were collected at pre-dose and up to 48 hours post-dosing.
Sample Size Determination	The sample size was determined based on the maximum expected (by the Applicant) intrasubject variability of ~20% for metronidazole C_{max}, AUC_{0-t}, $AUC_{0-\infty}$. A sample of 37 subjects was determined to be sufficient to show comparable BA (using traditionally used bioequivalence limits of 80%-125%) between the two formulations under fasting condition with expected T/R ratio of 90-111.1%, significance level of 5%, and a power of 80%. Considering the potential dropout/withdrawals due to adverse events and personal reasons, a total of 48 were randomized and dosed.
PK Assessment	Primary PK parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) as well as secondary PK parameters (T_{max}, $t_{½}$, and K_{el}) and diagnostic parameters ($AUC_{\_\%Extrap\_obs}$, and $R^2_{\_adjusted}$) of metronidazole were computed by noncompartmental analysis using Phoenix WinNonlin® version 8.2. Statistical analysis of ln-transformed pharmacokinetic parameters was performed using the SAS® statistical software version 9.4. Subject/sample exclusions from therapy or assessment: 1. If the subject suffers from significant inter-current illness or undergoes surgery during the study. 2. If the subject found to have entered the study in violation of the protocol. 3. If a subject requires any concomitant medication, which may interfere with the pharmacokinetic property of the study medication. 4. If it is felt in the investigator's opinion that it is not in the subject's best interest to continue in the study. 5. If a subject voluntarily withdraws from the study (i.e., subjects

STUDY SUMMARY	
	who did not complete both periods per protocol). 6. If a subject withdraws from the study due to adverse events, the PK data will not be used for PK or statistical analysis, however, the concentration data will be tabulated in a separate table. 7. Subjects experiencing emesis at or before 2 times median T_{max} (i.e., 2.00 × ~2 hours = 4.00 hours post dose) from the dosing time will be withdrawn from the study. 8. If found pregnant (for female subjects only). 9. Any other justifiable and documented reason/s. Data treatment plan for PK parameter analysis: 1. All concentration values below the limit of quantification (BLQ) will be set to zero for all pharmacokinetic and statistical calculations. 2. Any missing samples will be reported as 'Missing' and will not be included for pharmacokinetic and summary calculations. 3. Any non-reportable sample concentrations will be reported as 'NR' and will not be included for pharmacokinetic and summary calculations. 4. Subjects who missed three or more consecutive blood draws in the elimination phase in a study period will be excluded from estimation of $AUC_{0-\infty}$, $AUC_{\_\%Extrap\_obs}$, $t_{½}$, and K_{el}. 5. For subjects who do not exhibit a terminal log-linear phase in the concentration versus time profile in a study period, $AUC_{0-\infty}$, $AUC_{\_\%Extrap\_obs}$, $t_{½}$, or K_{el} estimates will not be reported. 6. If $AUC_{\_\%Extrap\_obs}$ is greater than 20% or $R^2_{\_adjusted}$ is less than 0.80 for K_{el} estimation, $AUC_{0-\infty}$ will be excluded from statistical analysis. 7. If the pre-dose concentration appears to be > 5% of the C_{max} in any subject at any period, the data of such a subject will be excluded from the statistical analysis for bioavailability.
Reviewer's Assessment	
Overall, the study design, sampling duration, and PK assessment plan are reasonable. The plans to handle subject/PK sample exclusions do not appear to affect study findings and/or overall conclusions.	

Table 10. Subject Summary of Study # 21-VIN-0347

STUDY SUBJECTS	
Demographics	A total of 48 healthy, adult subjects (42 male and 6 female) were enrolled in the study, and 44 subjects completed the study and were included in pharmacokinetics analysis set. All subjects in the study

STUDY SUBJECTS

identified as Asian race. The mean age, height, weight, and BMI of the study subjects were 31.13 years, 158.61 cm, 58.34 kg, and 23.27 kg/m^2, respectively. Demographic information is summarized in tables below.

Demographic data of subjects enrolled in the study (N=48)

Demographic	Age (Yrs)	Height (cm)	Weight (Kg)	BMI (Kg/m²)
Mean	31.13	158.61	58.34	23.27
Standard Deviation	7.12	6.94	8.58	3.73
Median	29.00	160.40	57.40	22.27
Standard Error Mean	1.03	1.00	1.24	0.54
Maximum	44	170.50	74.70	29.73
Minimum	22	145.00	48.80	18.94

Demographic data of subjects completed the study (N=44)

Demographic	Age (Yrs)	Height (cm)	Weight (Kg)	BMI (Kg/m²)
Mean	32.69	157.75	56.95	22.99
Standard Deviation	6.81	6.90	7.96	3.67
Median	31.00	160.50	55.40	22.42
Standard Error Mean	1.03	1.04	1.20	0.55
Maximum	44	168.00	73.30	29.58
Minimum	25	145.00	48.80	18.94

Study Conduct

In total, 48 subjects received the assigned treatment during Period I.

The following is summary of discontinued subjects (dropped out and withdrawn):

- Two subjects (# (b) (6) and # (b) (6)) did not report to the facility hence dropped-out from the study.
- Subjects (# (b) (6)) had adverse event after dosing in period II hence withdrawn from the study.
- Subjects (# (b) (6)) spitted out investigational product hence withdrawn from study.

Consequently, 44 subjects completed both periods of the study.

Protocol Deviations:

- PK sampling deviation: no blood sampling deviations were observed during the study.
- Post Study Safety Assessment deviations: Subjects (b) (6) and (b) (6) did not report to the facility when scheduled for Post Study Safety Assessment per protocol and were considered “Lost to follow-up”.

STUDY SUBJECTS

Reviewer's Assessment

- *A total of 44 subjects completed both periods of the study and were used for determination of bioavailability. A sample of 37 subjects was estimated to be sufficient to establish comparable BA (using traditionally used bioequivalence criteria) between metronidazole formulations under fasting condition.*
- *Only Asian volunteers were enrolled in the study. Per FLAGYL USPI race is not listed as having a clinically meaningful effect on the exposure of metronidazole. Therefore, the enrollment of only Asian volunteers in the study is not a concern from a Clinical Pharmacology perspective.*
- *Post Study Safety Assessment deviations are not expected to have any significant impact on the outcome of the study.*

Table 11. Bioanalytical Method Validation and Performance Reports for Study # 21-VIN-0347

Bioanalytical Method Validation and Performance Reports Summary

Method Type/Matrix	UHPLC-ESI-MS/MS/ K_3EDTA human plasma
Validation report(s)	Provided
Method performance report(s)	Provided
Analytes	Metronidazole
Calibration Range (µg/mL)	0.1 to 40
LLOQ (µg/mL)	0.1
QC Range (µg/mL)	0.1 to 32
Inter-assay Precision Range for QC (CV%)	2.14 to 6.67
Inter-assay Accuracy Range for QC (CV%)	-0.68 to 5.00
% Incurred Sample Reanalysis (ISR) within 20% of the Mean	100
Stability duration at room temperature	22 hours and 47 mins
Long-term stability at -20 ± 5°C and -78 ± 8°C	249 days
Total duration of storage (from date of first sample collection to date of last sample analysis)	29 days at -78 ± 8°C

Reviewer's Assessment

Report Type	Criteria	Assessment
Validation report(s)	Validation reports acceptable	☒ Yes ☐ No

Bioanalytical Method Validation and Performance Reports Summary		
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No

Table 12. Study Results of Study # 21-VIN-0347

STUDY RESULTS

PK Results and Statistical Analyses

Results from statistical comparisons for primary PK parameters (N=44) for metronidazole are summarized below:

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 44)			Intra Subject CV (%)	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
C_{max} (ug/mL)	12.494	11.771	106.14	13.16	101.27% - 111.25%	100.00
AUC_{0-t} (hr*ug/mL)	138.095	136.771	100.97	5.82	98.89% - 103.09%	100.00
$AUC_{0-\infty}$ (hr*ug/mL)	142.156	141.010	100.81	6.73	98.41% - 103.27%	100.00

The statistical results show that the test product and the reference product have comparable BA in healthy adults under fasting conditions.

Reviewer's Assessment

The geometric mean ratios (T/R) and associated 90% confidence intervals for all relevant exposure parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) for metronidazole were within the limits of 80% - 125%. None of the parameters were considered highly variable. Overall, the results of the study demonstrate similarity in the systemic exposures of metronidazole after administration of the test and reference products under fasted condition.

Study # 21-VIN-0348

Table 13. Study Summary of Study # 21-VIN-0348

STUDY SUMMARY	
Study Design	This was an open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover oral comparative bioavailability study that compared the following two drug products under fed conditions: • Test Product (T): Metronidazole Oral Suspension, 500 mg/5mL • Reference Product (R): Metronidazole Tablets USP 500 mg After maintaining at least 10 hours of overnight fasting, a high-fat high-calorie (approximately 800-1000 calories, content breakdown: 26.5% from carbohydrates, 16.5% from protein, and 57% from fat) breakfast was provided to each subject 30 minutes before dosing a single metronidazole 500 mg oral dose either of test product or reference product. The assigned treatment was administered orally (as per the randomization schedule) in sitting posture to each subject with 240 ± 2 mL of water at ambient temperature in the morning in each period. Overall, two treatment sequences (TR, RT) were evaluated with a washout period of 7 days between Period I and Period II dosing. No carry- over effect between the treatment periods was expected, as the average elimination half-life of metronidazole in healthy adult subjects is eight hours.
Study period	Clinical Phase 02/21/2022 to 03/03/2022 Bioanalytical Phase 03/15/2022 to 03/28/2022
Link to study report	\\CDSESUB1\EVSPROD\nda216755\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\21-vin-0348\study-report-fed-report-body.pdf
Links to bioanalytical validation and performance reports	*Bioanalytical validation report* *\\CDSESUB1\EVSPROD\nda216755\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\21-vin-0348\study-report-i-method-validation-report.pdf* *Bioanalytical report* \\CDSESUB1\EVSPROD\nda216755\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\21-vin-0348\study-

STUDY SUMMARY	
	report-bioanalytical-study-report-21-vin-0348.pdf
Study Objectives	• To compare the metronidazole BA between a single oral dose of the test and reference drug products in healthy human adult subjects under fed conditions. • To monitor the safety and tolerability of a single oral dose of the test product administered in healthy human adult subjects under fed conditions.
PK Sampling Schedule	In each period, a total of 20 blood samples were collected at pre-dose and up to 48 hours post-dosing.
Sample Size Determination	The sample size was determined based on the maximum expected (by the Applicant) intrasubject variability of ~20% for metronidazole C_{max}, AUC_{0-t}, $AUC_{0-\infty}$. A sample of 37 subjects was determined to be sufficient to show comparable BA (using traditionally used bioequivalence limits of 80%-125%) between the two formulations under fed condition with expected T/R ratio of 90-111.1%, significance level of 5%, and a power of 80%. Considering the potential dropout/withdrawals due to adverse events and personal reasons, a total of 48 were randomized and dosed.
PK Assessment	Primary PK parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) as well as secondary PK parameters (T_{max}, $t_{½}$, and K_{el}) and diagnostic parameters ($AUC_{\_\%Extrap\_obs}$, and $R^2_{\_adjusted}$) of metronidazole were computed by noncompartmental analysis using Phoenix WinNonlin® version 8.2. Statistical analysis of ln-transformed pharmacokinetic parameters was performed using the SAS® statistical software version 9.4. Subject/sample exclusions from therapy or assessment: 1. If the subject suffers from significant inter-current illness or undergoes surgery during the study. 2. If the subject found to have entered the study in violation of the protocol. 3. If a subject requires any concomitant medication, which may interfere with the pharmacokinetic property of the study medication. 4. If it is felt in the investigator's opinion that it is not in the subject's best interest to continue in the study. 5. If a subject voluntarily withdraws from the study (i.e., subjects who did not complete both periods per protocol). 6. If a subject withdraws from the study due to adverse events, the PK data will not be used for PK or statistical analysis, however, the

STUDY SUMMARY	
	concentration data will be tabulated in a separate table. 7. Subjects experiencing emesis at or before 2 times median T_{max} (i.e., 2.00 × ~2 hours = 4.00 hours post dose) from the dosing time will be withdrawn from the study. 8. Subjects who do not consume at least 800 calories from high-fat high-calorie breakfast will be withdrawn as per the discretion of principal investigator. 9. If found pregnant (for female subjects only). 10. Any other justifiable and documented reason/s. Data treatment plan for PK parameter analysis: 1. All concentration values below the limit of quantification (BLQ) will be set to zero for all pharmacokinetic and statistical calculations. 2. Any missing samples will be reported as 'Missing' and will not be included for pharmacokinetic and summary calculations. 3. Any non-reportable sample concentrations will be reported as 'NR' and will not be included for pharmacokinetic and summary calculations. 4. Subjects who missed three or more consecutive blood draws in the elimination phase in a study period will be excluded from estimation of $AUC_{0-\infty}$, $AUC_{\_\%Extrap\_obs}$, $t_{½}$, and K_{el}. 5. Subjects who do not exhibit a terminal log-linear phase in the concentration versus time profile in a study period, $AUC_{0-\infty}$, $AUC_{\_\%Extrap\_obs}$, $t_{½}$, or K_{el} estimates will not be reported. 6. If $AUC_{\_\%Extrap\_obs}$ is greater than 20% or $R^2_{\_adjusted}$ is less than 0.80 for K_{el} estimation, $AUC_{0-\infty}$ will be excluded from statistical analysis. 7. If the pre-dose concentration appears to be > 5% of the C_{max} in any subject at any period, the data of such a subject will be excluded from the statistical analysis for bioavailability.
Reviewer's Assessment	
Overall, the study design, sampling duration, and PK assessment plan are reasonable. The plans to handle subject/PK sample exclusions do not appear to affect study findings and/or overall conclusions.	

Table 14. Subject Summary of Study # 21-VIN-0348

STUDY SUBJECTS	
Demographics	A total of 48 healthy, adult subjects (43 male and 5 female) were

STUDY SUBJECTS

enrolled in the study, and 46 subjects completed the study and were included in pharmacokinetics analysis set. The mean age, height, weight, and BMI of the study subjects were 32.19 years, 164.73 cm, 63.46 kg, and 23.38 kg/m^2, respectively. Demographic information is summarized in tables below.

Demographic data of subjects enrolled in the study (N=48)

Demographic	Age (Yrs)	Height (cm)	Weight (Kg)	BMI (Kg/m²)
Mean	32.19	164.73	63.46	23.38
Standard Deviation	6.05	6.87	9.37	3.09
Median	31.50	164.95	63.80	23.17
Standard Error Mean	0.87	0.99	1.35	0.45
Maximum	44	178.50	87.10	29.41
Minimum	20	145.00	46.80	18.73

Demographic data of subjects completed the study (N=46)

Demographic	Age (Yrs)	Height (cm)	Weight (Kg)	BMI (Kg/m²)
Mean	32.24	164.77	63.68	23.45
Standard Deviation	6.00	6.98	9.44	3.08
Median	31.50	164.95	63.90	23.17
Standard Error Mean	0.88	1.03	1.39	0.45
Maximum	44	178.50	87.10	29.41
Minimum	20	145.00	46.80	18.73

Study Conduct

In total, 48 subjects received the assigned treatment during Period I. The following is summary of discontinued subjects (dropped out and withdrawn):

- Subject (# (b) (6)) did not report to the facility for period II hence dropped-out from the study.
- Subject (# (b) (6)) spitted out investigational product hence withdrawn from study.

Consequently, 46 subjects completed both periods of the study.

Protocol Deviations:

- PK sampling deviation:
  - Period I, pre-dose sample exceeded prespecified window of 60 minutes prior to dosing for subjects (b) (6). All pre-dose samples were taken within 120 minutes prior to dosing.
  - Period I, 0.25-hour sample for Subject (b) (6) exceeded prespecified window of ± 2 minutes of scheduled timepoint. Sample was taken at 0.25-hour + 4 minutes.
  - Period I, 48-hour sample for Subject (b) (6) exceeded prespecified window of ± 2 minutes of scheduled timepoint. Sample was taken at 48-hour + 4 minutes.

STUDY SUBJECTS	
	○ Period II, 2.67-hour sample for Subject (b) (6) exceeded prespecified window of ± 2 minutes of scheduled timepoint. Sample was taken at 2.67-hour + 3 minutes. • Recording of Vital Signs and Clinical Examination Sitting Blood pressure deviations: clinical Research Nurse had not performed activity of pre dose vital within 60 min prior to dosing in P-01 for Subject No. (b) (6) and (b) (6). Moreover, Subject no. (b) (6) Additional Pre-Dose Vital was Performed and documented in comment section of respective CRF page.

Reviewer's Assessment

- *A total of 46 subjects completed both periods of the study and were used for determination of bioavailability. A sample of 37 subjects was estimated to be sufficient to establish comparable BA (using traditionally used bioequivalence criteria) between metronidazole formulations under fed condition.*
- *Only Asian volunteers were enrolled in the study. Per FLAGYL USPI, race is not listed as having a clinically meaningful effect on the exposure of metronidazole. Therefore, the enrollment of only Asian volunteers in the study is not a concern from a Clinical Pharmacology perspective.*
- *Since actual sampling times were used for PK analysis, PK sampling deviations noted above are not expected to have any significant impact on the outcome of the study.*
- *Recording of Vital Signs and Clinical Examination Sitting Blood pressure deviations are not expected to have any significant impact on the outcome of the pharmacokinetic analysis and bioavailability statistical comparison.*

Table 15. Bioanalytical Method Validation and Performance Reports for Study # 21-VIN-0348

Bioanalytical Method Validation and Performance Reports Summary	
Method Type/Matrix	UHPLC-ESI-MS/MS/ K_3EDTA human plasma
Validation report(s)	Provided
Method performance report(s)	Provided
Analytes	Metronidazole
Calibration Range (µg/mL)	0.1 to 40

Bioanalytical Method Validation and Performance Reports Summary	
LLOQ (µg/mL)	0.1
QC Range (µg/mL)	0.1 to 32
Inter-assay Precision Range for QC (CV%)	2.16 to 3.12
Inter-assay Accuracy Range for QC (CV%)	-0.95 to 1.65
% Incurred Sample Reanalysis (ISR) within 20% of the Mean	100
Stability duration at room temperature	22 hours and 47 mins
Long-term stability at -20 ± 5°C and -78 ± 8°C	249 days
Total duration of storage (from date of first sample collection to date of last sample analysis)	35 days at -78 ± 8°C

Reviewer's Assessment

Report Type	Criteria	Assessment
Validation report(s)	Validation reports acceptable	☒ Yes ☐ No
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No

Table 16. Study Results of Study # 21-VIN-0348

STUDY RESULTS	
PK Results and Statistical Analyses	Results from statistical comparisons for primary PK parameters (N=46) for metronidazole are summarized below:

STUDY RESULTS

PK Parameters (Unit)	Geometric Least Square Means and It's Ratio (N = 46)			Intra Subject CV (%)	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
C_{max} (ug/mL)	9.508	9.625	98.78	6.73	96.48% - 101.14%	100.00
AUC_{0-t} (hr*ug/mL)	137.199	135.893	100.96	4.21	99.48% - 102.46%	100.00
$AUC_{0-\infty}$ (hr*ug/mL)	141.007	139.889	100.80	4.33	99.28% - 102.34%	100.00

The statistical results show that the test product and the reference product have comparable BA in healthy adults under fed conditions.

Reviewer's Assessment

The geometric mean ratios (T/R) and associated 90% confidence intervals for all relevant exposure parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) for metronidazole were within the limits of 80% - 125%. None of the parameters were considered highly variable. Overall, the results of the study demonstrate similarity in the systemic exposures of metronidazole after administration of the test and reference products under fed condition.

17.4. Additional Clinical Outcome Assessment Analyses

Not applicable.

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/

SHABNAM N NASEER
09/21/2023 01:25:16 PM

PETER W KIM
09/22/2023 07:57:07 AM