NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	NDA 209363/S-012
Priority or Standard	Standard
Submit Date(s)	August 31, 2020
Received Date(s)	August 31, 2020
PDUFA Goal Date	June 30, 2021
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	June 29, 2021
Established/Proper Name	secnidazole
(Proposed) Trade Name	SOLOSEC
Pharmacologic Class	nitroimidazole
Applicant	Lupin Pharmaceuticals, Inc.
Dosage form	Granules
Applicant proposed Dosing Regimen	2 grams orally for one dose
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of trichomoniasis caused by *Trichomonas vaginalis* in adults

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMEPA=Division of Medication Error Prevention and Analysis

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Glossary

ACOG	American College of Obstetricians and Gynecologists
AE	adverse event
AT	adenine and thymine
BV	bacterial vaginosis
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
ClinRO	clinician reported outcome
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment
CRF	case report form
CSR	clinical study report
DAI	Division of Anti-Infectives
ECG	electrocardiogram
FAD	flavin adenine dinucleotide
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GCP	good clinical practice
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
IND	Investigational New Drug
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MIC	minimum inhibitory concentration
MLC	minimum lethal concentration
NAAT	nucleic acid amplification test
NDA	new drug application
OCS	Office of Computational Science
OID	Office of Infectious Diseases
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PCR	polymerase chain reaction
PeRC	Pediatric Review Committee
PFOR	pyruvate:ferredoxin oxidoreductase
PI	prescribing information

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
QC	quality control
QIDP	qualified infectious disease product
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SOC	system organ class
TEAE	treatment emergent adverse event
TOC	test of cure
TV	*Trichomonas vaginalis*
VVC	vulvovaginal candidiasis

1 Executive Summary

1.1. Product Introduction

Secnidazole (SOLOSEC™) is an oral, antimicrobial drug in the 5-nitroimidazole class that was initially approved in 2017 for the treatment of bacterial vaginosis (BV) in adult women. This supplemental NDA proposes to add a treatment indication for trichomoniasis in adults. It is currently available as an oral granule formulation. The proposed regimen for the trichomoniasis treatment indication is the same as that approved for BV, namely a single 2-gram packet of granules once orally without regard to the timing of meals.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided adequate information to support the effectiveness of secnidazole for the treatment of adults with trichomoniasis. An adequate and well-controlled trial (SEC-WH-301) compared a single 2 g dose of SOLOSEC to placebo in adult females with trichomoniasis. SOLOSEC was significantly superior to placebo in terms of microbiological cure assessed 6-12 days following treatment (treatment difference 90.7%, 95% CI [80.7%, 96.5%]). Additionally, symptom resolution in patients with vaginal itching, discharge and odor at baseline was significantly higher in the SOLOSEC treatment group than in the placebo group.

Trichomoniasis is a less severe disease in males than females and is often self-limited, therefore the results from trial SEC-WH-301 were extrapolated to males with supporting evidence from the published scientific literature. Four open-label trials assessed a single oral 2 g secnidazole dose in males. The reported cure rates ranged from 91.7% (165/180) to 100% (30/30) at time points ranging from 2 to 20 days (n=437, 211 males and 226 females). The rate of spontaneous resolution was reported to be 36% (5/14) based upon a study of the natural history of trichomoniasis in male patients. From these data, a treatment effect for secnidazole in males was estimated to be 64.3% (exact 95% CI: [35.1%, 87.2%]).

As a part of trial SEC-WH-301, the clinical safety profile of SOLOSEC 2 g was characterized in 147 patients with trichomoniasis (74 patients received SOLOSEC and 73 patients received placebo). The overall rate of adverse events (AEs) was higher in the placebo arm (21.9%) than the SOLOSEC treatment arm (14.9%). There were no deaths or serious AEs. The AEs reported in the SOLOSEC group were of mild severity and no new safety signals were identified. One patient could not tolerate the taste of the medication and discontinued from the trial. The SEC-WH-301 trial data supported and extended the safety database from the original NDA.

Collectively, the data support a treatment effect for secnidazole in adult male and female patients with trichomoniasis. The safety profile was consistent with previous findings for the treatment of bacterial vaginosis, and no new safety signals were identified. The benefit risk assessment for SOLOSEC is favorable for the treatment of adult patients with trichomoniasis.

The indication also includes treatment of partners of infected patients simultaneously in order to prevent reinfection.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk assessment of the information provided in this submission supports the approval of secnidazole oral granules for the treatment of trichomoniasis caused by *Trichomonas vaginalis* (TV) in adults. The indication also includes treatment of partners of infected patients simultaneously in order to prevent reinfection. Secnidazole is a nitroimidazole class antimicrobial drug that was initially approved in 2017 for the treatment of bacterial vaginosis (BV) in adult women.

Efficacy

The evidence to support a new indication includes a single Phase 3 randomized, multicenter, double-blind, placebo-controlled, delayed-treatment study involving 147 subjects (Trial SEC-WH-301). In this study, women aged 15 years and older with suspected trichomoniasis were enrolled and given either a single 2-gram dose of secnidazole or a matched placebo on Day 1 and then asked to return for a Test-of-Cure (TOC) visit 6 to 12 days later. At the TOC visit, subjects had cultures for TV collected and then received the opposite treatment from their initial visit (subjects who received placebo on Day 1 would receive secnidazole at the TOC visit and vice-versa). The primary efficacy endpoint was microbiological cure of trichomoniasis at the TOC visit in the mITT population; the mITT population included all enrolled subjects who had a positive culture for TV at baseline and were negative for other common sexually transmitted infections.

Secnidazole demonstrated statistical superiority to placebo on the primary endpoint. In the secnidazole arm 92% (59/64) of subjects vs. 1% (1/67) of subjects who received placebo had a negative culture at the TOC visit (treatment difference: 90.7% (95% CI [80.7%, 96.5%]; p <.001)). The primary endpoint results are supported by secondary, exploratory analyses involving the resolution of clinical symptoms. In mITT subjects with clinical symptoms at baseline (such as odor, discharge, and itching), 73% of secnidazole subjects (41/56) had both clinical symptom resolution and a negative culture for TV at the TOC visit compared to none of the placebo treated subjects (0/55) (treatment difference: 73.2% (95% CI [59.7%, 84.2%], p<.001)). Similarly, of those placebo arm subjects who remained culture positive for TV at the TOC visit (and then subsequently received secnidazole), 89% (56/63) of such subjects had negative cultures at a follow-up visit roughly a week after the TOC visit. Thus, there is sufficient evidence to support secnidazole as a treatment for trichomoniasis caused by TV.

There were certain limitations to the generalizability of the study results. While the study population was generally representative of the expected clinical population, it should be noted that this study was predominantly conducted in adult African-American women. Though differences in clinical outcome by race are not expected, such differences were not explored in this study. Moreover, only four secnidazole-

treated subjects had HIV at baseline, and while there were successful treatment outcomes with secnidazole in all four subjects, there remains limited information about treatment outcomes in HIV positive patients.

Males were not included in the pivotal Phase 3 study since enrollment was considered impracticable. Males are often asymptomatic, challenging to diagnose, and frequently clear the infection spontaneously. Nevertheless, trichomoniasis is a sexually-transmitted infection and requires the treatment of patients and their sexual partner(s) who are presumed to be infected. The Applicant identified four published studies that evaluated secnidazole treatment of trichomoniasis in males, one of which was a controlled trial in which all 30 subjects in the secnidazole arm were successfully treated [n=30; 95% CI: 88.4%, 100%]. In three open-label, uncontrolled, single-arm studies in males and females, clinical and parasitological evaluations were performed both pre- and post-treatment with secnidazole and the reported cure rates ranged from 91.7% [n=180 (n=76 males and 104 females)] to 97.7% [n=87 (49 males and 38 females)] at time points ranging from 2 to 20 days. The Applicant also cited a small natural history study in which the spontaneous response rate at Day 16 ±12 in untreated men was 36% [n=14, 95% CI: 12.8%, 64.9%]. Based upon this spontaneous response rate, a significant treatment effect for secnidazole in males could be calculated with a difference of 64.3% (exact 95% CI: [35.1%, 87.2%]). The smaller treatment effect calculated for males from the published literature is consistent with the findings in trial SEC-WH-301 in females, considering the potential for spontaneous clearance of trichomoniasis in males. The data collectively support a treatment indication for male patients.

<u>Safety</u>

The safety profile of secnidazole generated from 74 patients treated for trichomoniasis in trial SEC-WH-301 was consistent with the previous safety findings for the treatment of bacterial vaginosis. The overall rate of treatment emergent adverse events (TEAE) was lower in the the SOLOSEC arm (14.9%) than in the placebo arm (21.9%). No deaths, serious adverse events (SAE), or severe intensity adverse events were reported in trial SEC-WH-301. Vulvovaginal candidiasis was the only adverse drug reaction to occur in more than 2% of secnidazole treated subjects. Of note, the current product labeling includes a warning regarding the risk of vulvovaginal candidiasis. Safety data for male subjects were available from studies in healthy volunteers and published scientific literature, which did not reveal any significant safety signals. During the course of this review, post marketing surveillance revealed possible clinical sequelae ((b) (4) nausea, vomiting, diarrhea, abdominal pain, dizziness, and headache) in subjects who concomitantly consumed alcohol with secnidazole. While this safety finding was not evaluated in the SEC-WH-301 trial for the treatment of trichomoniasis, labelling modifications to convey this risk were separately approved on June 14, 2021.

The pediatric study requirement for females and males from birth to less than 12 years of age were waived because the necessary studies are impossible or highly impracticable. Though trichomoniasis can occur in adolescent patients, only two adolescent females were enrolled into the study, and both received placebo. (b) (4) A pediatric PMR will be issued for a pediatric assessment in females and males from 12 years to less than 18 years of age. (b) (4)

(b) (4)

Due to the COVID-19 pandemic, clinical site inspections could not be performed; however, because the Applicant was recently inspected during their original NDA and the trichomoniasis study data appeared to be consistent across sites, it was determined that inspections were not critical for approval and could be waived.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Trichomoniasis is a protozoa-associated sexually transmitted infection typically associated with symptoms of vaginal itching, odor, and discharge in women. Untreated disease is associated with adverse reproductive health consequences such as cervical neoplasia, pelvic inflammatory disease, and infertility. Importantly, TV infection is associated with increased risk of acquisition of HIV, premature rupture of the membranes, preterm birth, and delivery of low birthweight infants for gestational age. Infants born to infected mothers may become infected during delivery which may result in neonatal complications. Males are often asymptomatic, but may experience urethritis and transmit the infection to their sexual partners.	Trichomoniasis a serious disease of public health concern.
Current Treatment Options	• CDC recommendations: a. Tinidazole 2 gram oral single dose, b. Metronidazole 2 gram oral single dose or 500 mg oral twice a day for 7 days	Additional treatment options are needed given the relative paucity of currently available treatments.
Benefit	• Secnidazole successfully treated trichomoniasis in a multicenter, randomized, double-blind, placebo-controlled clinical trial. Statistical superiority was noted on both microbiologic and clinical endpoints. • Uncertainties include limitations in the generalizability of the study	Secnidazole, as a single dose oral therapy, is efficacious in treating trichomoniasis in adults as measured by both microbiologic cure and improvement in patient symptoms.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	results. Males were not included in the clinical trial, and the majority of patients enrolled were African-American.	Since the prevalence of trichomoniasis is greater in African American women than Hispanic or non-Hispanic white women, having Black or African American women as the majority of enrolled subjects is acceptable. The disease presents similarly among patients of different racial and ethnic backgrounds, and the response to therapy is anticipated to be similar. Males present with less severe disease symptoms and may spontaneously clear the disease. It is reasonable to extrapolate the study results to males with trichomoniasis using supporting evidence of secnidazole efficacy from the published scientific literature.
Risk and Risk Management	• The adverse event risk profile of secnidazole for the treatment of TV infection is consistent with its risk profile for the treatment of bacterial vaginosis, including a risk of vulvovaginal candidiasis with treatment as well as adverse events associated with drugs of the nitroimidazole class. • The overall rate of treatment emergent adverse events (TEAE) was lower in the SOLOSEC arm (14.9%) than in the placebo arm (21.9%) in Trial SEC-WH-301. No deaths, serious adverse events (SAE), or severe intensity adverse events were reported.	The risk profile of secnidazole is acceptable compared to the expected benefit and can be adequately addressed through labelling. Overall, there were fewer adverse events in patients with trichomoniasis who were treated with secnidazole than in patients treated with placebo.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	8.1.2 – see note below
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

***CDTL Note**: In clinical Trial SEC-WH-301, symptoms of vaginal discharge, itching and odor were determined and qualified by individual investigators as trichomonal symptoms or non-trichomonal symptoms. This endpoint was exploratory and not formally developed using a clinical outcome assessment tool (source: Applicant response to draft labeling, June 17, 2021).*

2 Therapeutic Context

2.1. Analysis of Condition

Trichomoniasis is a sexually transmitted infection caused by the parasite, *Trichomonas vaginalis (T. vaginalis; TV*), which affects an estimated 3.7 million persons in United States (Satterwhite *et al.*, 2013). TV infection prevalence is disproportionately higher in black women with 13% of individuals estimated to be infected as compared to 1.8% of white women (Sutton *et al.*, 2007). Among women who are 40 years of age or older, TV infection is reported in more than 11% of the population (Ginocchio *et al.*, 2012). In sexually transmitted disease (STD) clinics, rates are higher, where TV infection is reported to be present in 26% of symptomatic women and 6.5% of asymptomatic women (Meites *et al.*, 2013).

Many patients have minimal or no symptoms with TV infection, which may lead to a delay of treatment for months to years (Peterman, 2006; Sutton, 2007; Peterman *et al.*, 2009). More than 75% of males were reported to have asymptomatic infection (Seña *et al.*, 2007) and symptoms of urethritis, epididymitis, or prostatitis are likely to be transient and spontaneously resolve. Women with TV infection are more likely to be symptomatic over time and may experience symptoms ranging from purulent, malodorous vaginal discharge to urethritis, cystitis, and dyspareunia (Workowski *et al.*, 2015). Untreated disease in women is associated with adverse reproductive health consequences such as cervical neoplasia, pelvic inflammatory disease, and infertility (Grodstein *et al.*, 1993). Infected pregnant women are at increased risk of premature rupture of the membranes, preterm birth, and delivery of low birthweight infants for gestational age (Silver *et al.*, 2014). Infants born to infected mothers may become infected during delivery which may result in neonatal complications.

Trichomoniasis is easily transmitted between sexual partners during penile-vaginal intercourse. The rate of reinfection in patients treated for trichomoniasis is high (Peterman *et al.*, 2006). To avoid reinfection, partners are referred for presumptive therapy and advised to abstain from intercourse until they and their sexual partners have been adequately treated and symptoms have resolved. Also, retesting for TV is recommended for all sexually active women within 3 months following the initial treatment regardless of whether they believe their sexual partners were treated (Workowski *et al.*, 2015).

There are epidemiological associations between trichomoniasis and other adverse health outcomes, such as sexually transmitted infections including human immunodeficiency virus (HIV) infection (Kissinger *et al.,* 2013), gonorrhea, human papillomavirus (HPV), and herpes simplex virus (HSV), preterm birth, and other adverse pregnancy outcomes. Of note, TV infection in women with HIV is associated with increased risk of pelvic inflammatory disease (Moodley *et al.*, 2002).

In female patients who have a vaginal discharge, diagnostic testing for TV infection is typically performed. Highly sensitive and specific laboratory tests include nucleic acid amplification tests (NAAT) and antigen-detection tests. The diagnosis of trichomoniasis was classically established by microscopic evaluation of wet preparations of genital secretions where the organism can be directly visualized.

2.2. Analysis of Current Treatment Options

The following table includes the currently available treatment options for trichomoniasis. Single doses of metronidazole and tinidazole are CDC recommended regimens while a 7-day course of metronidazole is listed as alternative regimen. Notably, a recent randomized controlled trial showed that a 7-day course of metronidazole is more effective than a single dose (Kissinger P, 2018).

Table 2-1. Approved Treatments for Trichomoniasis

Product (s) Name	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
FLAGYL (Metronidazole)	1963	2 g orally in a single dose or in two divided doses of 1 g each given in the same day 250 mg orally three times a day for 7 days 500 mg orally twice a day for 7 days (off-label use)	Metallic taste, nausea (in 10 percent of patients), transient neutropenia (7.5 percent), a disulfiram-like effect with alcohol, prolongation of International Normalized Ratio in patients taking vitamin K antagonists (e.g. warfarin), and peripheral neuropathy	Listed as recommended regimen[1] Listed as alternative regimen[1] and recommended treatment regimen[2]
TINDAMAX (Tinidazole)	2004	2 g orally in a single dose	Seizures, neuropathy, leucopenia, vaginal candidiasis, metallic/bitter taste, nausea, weakness/fatigue/malaise, dyspepsia/cramps/epigastric discomfort, vomiting, anorexia, headache, dizziness, and constipation	Listed as recommended regimen[1] and alternative treatment regimen[2]

[1] CDC 2015 Sexually Transmitted Disease Treatment Guidelines (Workowski *et al*, 2015)
[2] ACOG 2020 Clinical Management guidelines (Vaginitis in Nonpregnant Patients: ACOG Practice Bulletin, Number 215. Obstetrics and Gynecology. 2020 Jan;135(1):e1-e17)

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The original NDA 209363 for SOLOSEC (secnidazole) oral granules, 2 g, was approved on September 15, 2017, for treatment of bacterial vaginosis in adult women. The Applicant submitted this efficacy supplement on August 31, 2020, proposing the addition of a new indication to the SOLOSEC labeling for the treatment of trichomoniasis caused by *Trichomonas vaginalis* in adults (b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 117811 was submitted on December 18, 2013, for treatment of bacterial vaginosis. The IND was granted qualified infectious disease product designation (QIDP) on November 18, 2014, and fast track designation on August 12, 2015, for the treatment of bacterial vaginosis. The NDA for SOLOSEC was submitted on January 17, 2017, and was approved on September 15, 2017, for the treatment of bacterial vaginosis.

The Applicant submitted a meeting request on July 31, 2015, to discuss the development of SOLOSEC for a new indication, the treatment of trichomoniasis caused by *Trichomonas vaginalis*. The meeting was held on October 1, 2015. During the meeting, the Division recommended at least one adequate, well-controlled trial be conducted for the treatment of trichomoniasis. The Applicant submitted a synopsis of a protocol, entitled, "(b) (4) " for review on October 8, 2015.

On December 18, 2018, a subsequent meeting was held with the Applicant to discuss a clinical study to support a supplemental NDA for the treatment of trichomoniasis.

On February 13, 2019, protocol SEC-WH-301, entitled, "A Phase 3, Multi-center, Prospective, Randomized, Placebo-Controlled Delayed-Treatment, Double-Blind Study to Evaluate the Effectiveness and Safety of a Single Oral Dose of SOLOSEC Granules Containing 2 grams of Secnidazole for the Treatment of Trichomoniasis" was submitted. Additionally, an agreed initial pediatric study plan for the treatment of trichomoniasis was issued on October 8, 2019.

The Applicant submitted supplement 012 on August 31, 2020, for the treatment of trichomoniasis. The application contains a request for a full waiver for pediatric studies in all boys in all pediatric age groups and girls from birth to less than 12 years of age, (b) (4) The PDUFA due date for Supplemental 012 is June 30, 2021.

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

4.1. Office of Scientific Investigations (OSI)

Clinical site inspections could not be performed due to COVID-19 pandemic related restrictions on Agency travel; however, the Applicant was recently inspected for its bacterial vaginosis trials. No significant issues were identified at that time. The data submitted to support the trichomoniasis indication were consistent across study sites; therefore, the review team concluded that inspections were not critical to approval and inspections could be waived given the circumstances.

4.2. Product Quality

SOLOSEC is a marketed drug. There were no proposed changes to the current chemistry, manufacturing or controls.

4.3. Clinical Microbiology

The clinical microbiology information, based on the nonclinical studies as well as parasitological assessments in the clinical study, is summarized below (for details see Section 15.3).

4.3.1. Nonclinical studies

Mechanism of action
The mechanism by which secnidazole, a nitroimidazole, exhibits activity against *T. vaginalis* is similar to other nitroimidazoles such as metronidazole and tinidazole. Studies with *T. vaginalis* and other protozoans suggest that the nitroreductase enzyme, like for bacteria, plays an important role in the bioactivation of secnidazole resulting in the generation of reactive amines, depleting thiols and damaging DNA and proteins. However, the precise mechanism of action of secnidazole has not been fully investigated. For details see Section 15.3.1.1.

***In vitro* activity**
The *in vitro* activity of secnidazole was measured against laboratory strains and clinical isolates of *T. vaginalis*. The methods for measurement of *in vitro* sensitivity of *T. vaginalis* are not standardized and limited to testing in research laboratories. The results show that secnidazole was effective in inhibiting the motility of the trophozoites of *T. vaginalis*. The minimum lethal concentrations (MLCs), based on absence of motility, ranged between 0.4 – 250 µg/mL. The isolates with increased metronidazole MLCs had increased secnidazole MLCs. Overall, the activity of secnidazole appears to be similar to metronidazole and tinidazole. For details see Section 15.3.1.2.

***In vivo* activity (animal studies)**
Studies in mice infected, subcutaneously or intraperitoneally, with *T. vaginalis* show that the activity of secnidazole was dose-dependent and similar to metronidazole or tinidazole when administered post-infection. Multiple doses of secnidazole or metronidazole were more effective than single doses. A single dose of secnidazole administered prior to infection was more effective than metronidazole; this could be due to the longer half-life of secnidazole compared to metronidazole. For details see Section 15.3.1.3.

Drug resistance and cross-resistance
No studies were conducted to evaluate the potential for development of resistance by *T. vaginalis* to secnidazole. However, like other nitroimidazoles, secnidazole is likely to cause resistance. The mechanism of resistance for nitroimidazoles appears to be multifactorial and includes decreased uptake of the drug, higher efflux activity and/or altered nitroreductase activity.

Studies suggest a potential for cross-resistance between secnidazole and other nitroimidazoles such as metronidazole and tinidazole. For details see Section 15.3.1.4.

4.3.2. Parasitological assessment in clinical studies

The Applicant provided results of a Phase 3 multi-center, double-blind, placebo-controlled clinical trial to support the efficacy of a single oral dose treatment with SOLOSEC in female patients with trichomoniasis (Trial SEC-WH-301). The study was conducted at 10 centers within the US. One of the inclusion criteria for enrollment of patients was based on positive results of one of the following parasitological tests:

- OSOM® *Trichomonas* Rapid test.
- Wet mount.
- *T. vaginalis* nucleic-acid amplification test (NAAT).

OSOM® *Trichomonas* Rapid test and wet mount assessments were performed on vaginal swabs at the investigational sites. The positive *T. vaginalis* NAAT findings were based on information available in the patient chart within 30 days of screening for which treatment had not been initiated. No details on the NAAT method(s) were provided.

Diagnosis was confirmed by culture using the InPouch™ TV device. For culture, vaginal specimens were shipped to a central laboratory. Note that the culture results can take up to 7 days and were not available at the time of study randomization and treatment. Evidence of parasites by wet mount and culture is 100% specific. However, the negative findings should be interpreted with caution. Adequate quality control measures and training of laboratory staff were implemented.

The parasitological tests used by the Applicant were adequate for initial screening and/or diagnosis of trichomoniasis. The sensitivity of the OSOM® *Trichomonas* Rapid test, wet mount technique, and culture using the InPouch TV device, based on testing of clinical trial specimens, was similar to that reported previously. Of the 147 subjects enrolled based on the OSOM® *Trichomonas* Rapid test, wet mount, or NAAT, 135 (91.8%) were confirmed to be culture positive.

The primary efficacy endpoint was parasitological cure based on a negative *T. vaginalis* culture between Days 6-12 of treatment. A majority (92.2%) of the patients in the SOLOSEC group became culture negative whereas only 1 patient (1.5%) in the placebo group became culture negative (Table 8-7 and Table 8-9). There was a good correlation between culture results and clinical cure; 73% of the culture negative patients who were symptomatic at baseline and in the SOLOSEC treatment group were clinically cured whereas none of the placebo group patients were clinically cured.

For details, see Appendix-15.3.2.

4.3.3. Conclusions

Secnidazole, like other nitroimidazoles, is active against *T. vaginalis in vitro* as well as *in vivo*. Studies suggest that the mechanism of action and mechanism of resistance are similar to other nitroimidazoles such as metronidazole and tinidazole. There is a potential for cross-resistance with other nitroimidazoles.

4.4. Devices and Companion Diagnostic Issues

There are no associated devices or companion diagnostics.

5 Nonclinical Pharmacology/Toxicology

There were no nonclinical pharmacology or toxicology data submitted. The reader is referred to Dr. Owen McMaster's review of the pharmacology toxicology data in the original NDA submission.

6 Clinical Pharmacology

6.1. Executive Summary

No clinical pharmacology studies are included in this sNDA. A comprehensive assessment of the Clinical Pharmacology Program for SOLOSEC was provided in the original NDA (Secnidazole oral granules, NDA 209363).

6.2. Summary of Clinical Pharmacology Assessment

The Applicant's proposed dosage regimen for secnidazole for the treatment of trichomoniasis is a single 2-gram packet of granules once orally, without regard to the timing of meals. This regimen is the same as that approved for BV and is supported by the clinical pharmacology studies submitted under the original NDA and efficacy and safety from the Applicant's Phase 3 study in women with trichomoniasis (Trial SEC-WH-301).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Clinical studies relevant to this NDA are listed in the following table.

Table 7-1: Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Study to Support Efficacy and Safety						
SEC-WH-301	03935217	Phase III, multicenter, randomized, double-blind, placebo-controlled, delayed treatment trial	SOLOSEC: 2-gram single oral dose Placebo: After test of cure (TOC) visit (Day 6-12), treatment was switched.	Microbiological cure (a negative *T. vaginalis* culture) at TOC visit	Once/TOC and one follow-up visit (7-12 days post TOC)	SOLOSEC: 74 Placebo: 73	Adult females or post-menarchal adolescent girls ≥ 12 years of age, with positive *T. vaginalis* culture and negative results for other sexually transmitted infections	10 centers in the United States
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
SYM-1219-104		Phase I, randomized, placebo-controlled, single-blind, two part study	Granules, 4 or 6 grams single dose, oral, sprinkled on applesauce	Assess PK and safety of 4 and 6 gram dose in applesauce	Single dose	Part A: 8 Part B: 8 Female: 8 Male: 8	Healthy females and males	Single Center in U.S.

SYM-1219-105		Phase I, double-blind, randomized, placebo-controlled, 4-period, single-dose, crossover trial	Granules, 2 or 6 grams single dose, oral, sprinkled on applesauce, placebo, moxifloxacin	QT/QTC Study	Single dose	Total: 52 Female: 22 Male: 30	Healthy females and males	Single Center in U.S.

Source: Reviewer's analysis. Abbreviation: *T. vaginalis*: *Trichomonas vaginalis*

7.2. Review Strategy

In this sNDA, evidence of clinical efficacy in adult women is based on a single, randomized, double-blind, placebo-controlled trial in patients 15 to 65 years of age with trichomoniasis, which evaluated 64 patients randomized to receive SOLOSEC compared with 67 patients randomized to placebo (Trial SEC-WH-301). Evidence of efficacy in adult men was based on published literature including one controlled trial and three uncontrolled trials. Supporting safety data for use of secnidazole in males included Phase 1 studies in healthy volunteers and published literature.

The efficacy review section will focus on data from Trial SEC-WH-301.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. SEC-WH-301

Trial Design

This trial was a Phase III, multi-center, randomized, double-blind, placebo-controlled, delayed treatment study to evaluate the effectiveness and safety of a single oral dose of SOLOSEC® granules containing 2 grams of secnidazole for the treatment of trichomoniasis.

This trial consisted of a primary study phase (Visit 1 [Day 1, screening/baseline] to Visit 2 [Day 6-12, Test of Cure (TOC)]) and a follow-up phase (Visit 2 to Visit 3 [7-12 days post Visit 2]). Randomization was 1:1 to the two treatment groups, stratified by site and clinical symptoms of trichomoniasis (present or absent).

Study medication [either SOLOSEC (containing 2 grams of single-dose secnidazole) or matching placebo] was orally administered, under direct observation, at Visit 1.

After all Visit 2 study procedures had been completed, patients received the opposite (or switched) treatment. Patients with positive *T. vaginalis* cultures at Visit 2 returned to the clinic for Visit 3 assessments and investigator assessment of need for additional therapy (an additional Visit 4 was scheduled at the investigator's discretion if culture at Visit 3 was positive). Patients with negative cultures at Visit 2 were contacted by phone and discharged from the study (no Visit 3 required). This allowed for the placebo patients to be treated without having to break the study blind.

Inclusion Criteria

Subjects were eligible for enrollment if all of the following inclusion criteria applied:

1. Were adult females or post-menarchal adolescent girls ≥ 12 years of age.
2. Were willing and able to give written informed consent or, if < 18 years of age, were willing and able to give written informed assent with a written informed consent from a parent or legal guardian.
3. Were in good general health including as confirmed by a medical history and physical examination, with no known medical or mental health conditions that, in the Investigator's opinion, may have interfered with study participation.
4. Were willing and able to participate in the study as an outpatient, made required visits to the study center, and complied with all study requirements.
5. Had a negative urine pregnancy test result prior to study treatment initiation. In addition, female patients of childbearing potential must have been using an acceptable form of birth control as determined by the Investigator (e.g., oral contraception, implantable, injectable/transdermal hormonal contraception, intrauterine device, barrier methods), tubal ligation or had a vasectomized partner or were practicing abstinence.
6. Had a diagnosis of trichomoniasis at the screening visit as determined by one of the following:
    - positive *T. vaginalis* nucleic-acid amplification test (NAAT) within 30 days of screening for which treatment had not been initiated.
    - positive OSOM® rapid test.
    - positive wet mount assessment.

    Diagnosis was confirmed by a positive culture for *T. vaginalis* obtained at the baseline visit. (Note: The culture results were not available at the time of study randomization and treatment.)
7. Agreed to abstain from vaginal intercourse until the final study visit.
8. Agreed not to have any vaginal penetration or use any vaginal products for the duration of the study (e.g., spermicides, condoms, diaphragms, vibrators, tampons, etc.).
9. Agreed not to use vaginal douches, lubricants, or similar products for the duration of the study.

Exclusion Criteria

A subject who met any of the following exclusion criteria was not enrolled:

1. Were pregnant, lactating, or planning to become pregnant during the study.
2. Were suspected clinically (or confirmed diagnostically) of having alternative causes of vaginal symptoms including symptomatic vulvovaginal candidiasis, chlamydia, gonorrhea, or an active genital herpes outbreak. (Note: *Chlamydia trachomatis*, *Neisseria gonorrhoeae* [by PCR] results were not available at time of randomization.) Note: patients with bacterial vaginosis (BV) were eligible for this study.
3. Were suspected clinically of having an acute urinary tract infection.
4. Had active genital lesions, including primary syphilitic chancres and herpes simplex virus lesions, or other vaginal or vulvar conditions which could have confounded the

interpretation of the clinical response, as determined by the Investigator (patients with genital warts could be enrolled).

5. Had received systemic antibacterial therapy or topical antimicrobial/antifungal/ immunomodulatory therapies in the genital area (vagina, vulva and surrounding soft tissue), within 14 days prior to the Baseline Visit (Day 1).
6. Had received secnidazole, metronidazole or tinidazole treatment within 30 days prior to the Baseline Visit (Day 1) or any other medication for the treatment of trichomoniasis within 30 days prior to Baseline Visit.
7. Were using NuvaRing® or any other vaginal ring products.
8. Had a history of drug or alcohol abuse within the past 12 months, as determined by the Investigator.
9. Had participated in any investigational trial within 30 days before the Baseline Visit (Day 1).
10. Were participating in any investigational, observational, or non-interventional study (either currently or during the study).
11. Had a known allergy to nitroimidazoles (e.g., metronidazole, tinidazole, nimorazole, secnidazole, etc.).
12. Had an inability to consume apple sauce or comply with study medication dosing instructions.
13. Had any history of cervical carcinoma or other carcinomas of the vagina or vulva or an abnormal Pap smear that may have required colposcopic evaluation within the 3 months following the baseline visit (in the opinion of the investigator).
14. Had undiagnosed abnormal vaginal bleeding.
15. Was planning to undergo a surgical or vaginal procedure during the study.
16. Had any condition that interfered with their ability to understand or comply with the requirements of the study.

Study Endpoints

The primary efficacy point was microbiological cure at the TOC visit. Microbiological cure was defined as a negative *T. vaginalis* culture.

There were no secondary efficacy endpoints. Exploratory efficacy endpoints included trichomoniasis symptom resolution and microbiological cure in the subgroup of patients who had baseline symptoms attributable to trichomoniasis.

Analysis Populations

Intent-to-Treat (ITT): The ITT population included all randomized patients.

Modified Intent-To-Treat (mITT): The mITT population included all randomized patients who were culture positive for *T. vaginalis* and negative for other sexually transmitted infections (STI). This population was used for the primary efficacy analysis.

Per-Protocol (PP): The PP population was composed of patients in the mITT population with consideration of the following criteria: received the study medication as randomized, met inclusion and exclusion criteria, had a TOC visit between Days 6-12, and had no major protocol violations. The composition of the PP population was finalized and documented in a review of the data conducted prior to unblinding the study database. The PP population was used for supportive efficacy analyses by the Applicant.

Statistical Analysis Plan

Sample Size Calculation

Assuming response rates of 75% in the SOLOSEC group and 40% in the placebo group, with a two-sided alpha of 0.05, the sample size of 100 patients in the mITT population would provide approximately 95% power to test the difference in response rates between the two groups. Assuming 70% of randomized patients would meet the mITT criteria, 144 patients were planned to enroll into the study.

Primary Efficacy Analysis

The primary efficacy endpoint was compared between the SOLOSEC and placebo groups using a two-sided Cochran-Mantel-Haenszel (CMH) test (stratified by the presence/absence of clinical symptoms of trichomoniasis at baseline) at the two-sided alpha=0.05 level of significance.

For each treatment group, an exact 95% binomial confidence interval of the cure rate was calculated. Within each stratum, cure rates were compared between the active and placebo treatment groups using a two-sided Fisher's exact test. The reviewer calculated an exact 95% confidence interval for the difference when necessary.

Exploratory Efficacy Analyses

The following exploratory endpoint was evaluated at the TOC visit for the subgroup of patients who had clinical symptoms of trichomoniasis at baseline:

- **Outcome Responder**: complete resolution of trichomoniasis symptoms (i.e., itching, discharge, and odor recorded as normal) and culture results (InPouch™ TV test) negative for *T. vaginalis*

Outcome Responders were compared between the SOLOSEC and placebo treatment groups using a two-sided Fisher's exact test. For each treatment group, an exact 95% binomial confidence interval of the responder rate was calculated.

Protocol Amendments

There was only one amendment before the start of the trial regarding comprehensive and consistent follow-up of adverse events and clarification for the definition of the primary

analysis population (culture negative for other STIs, changed from "culture negative for STIs"), per FDA's request.

8.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in the compliance with Good Clinical Practices (GCPs) including independent quality assurance and archiving of essential documents.

Financial Disclosure

No clinical investigators had any disclosable interests of financial arrangements.

Patient Disposition

The study was conducted between April 23, 2019 and March 18, 2020. A total of 147 patients were enrolled at 10 research centers in the United States. Unless otherwise noted, the following summary of results includes all data reported during the primary phase of the study [Visit 1 (baseline) to Visit 2/TOC (Day 6-12)].

Most enrolled subjects completed the TOC visit. Four patients (2.7%) discontinued the study prematurely: 2 patients voluntarily withdrew, 1 patient was lost to follow-up, and 1 patient was discontinued due to an adverse event (mild nausea and productive cough). Although the protocol stated that all patients should be fully evaluated, if the final assessment for a subject was not performed at the TOC visit, the subject was considered a non-responder for the primary efficacy endpoint. The ITT population included all randomized patients and the mITT population (the primary population for efficacy analyses) included 131 randomized patients who were culture positive for *T. vaginalis* and negative for other STIs. About 97% of mITT patients completed the study.

Table 8-1. Patient Disposition

Disposition	SOLOSEC (N=74)	Placebo (N=73)	All (N=147)
Randomized	74	73	147
ITT Population	74	73	147
Completed TOC visit	73 (98.6)	70 (95.9)	143 (97.3)
mITT Population	64 (86.5)	67 (91.8)	131 (89.1)
Reasons for exclusion from mITT	10* (13.5)	6 (8.2)	16 (10.9)
Not culture positive for *T. vaginalis* at baseline	7 (9.5)	5 (6.8)	12 (8.2)
STIs not negative at baseline	4 (5.4)	1 (1.4)	5 (3.4)
Competed study of mITT subjects			
Yes	63 (98.4)	64 (95.5)	127 (96.9)

No	1 (1.6)	3 (4.5)	4 (3.1)
Reason for discontinuation from study, n(%)			
Adverse event	1 (1.6)	0	1 (0.8)
Loss to follow-up	0	1 (1.5)	1 (0.8)
Withdrawal by subject	0	2 (3.0)	2 (1.5)

Source: Tables 14.1.1, 14.1.2.1 in Study Report
*One subject was excluded for both reasons.
Abbreviations: ITT: Intent-to-treat; MITT: Modified ITT; N: number of subjects; STIs: Sexually transmitted infections

Protocol Violations/Deviations

In the SOLOSEC group, there were 6 major violations. One patient ([(b) (6)]) reported having intercourse between the baseline and TOC visit (Inclusion/Exclusion violation). One patient ([(b) (6)]) took a prohibited concomitant medication, metronidazole, within 30 days of enrolment (Inclusion/Exclusion violation). Four patients ([(b) (6)]) had their TOC visits outside of visit window.

In the placebo group, 5 patients had major violations. One patient ([(b) (6)]) reported having intercourse between the baseline and TOC visit (Inclusion/Exclusion violation). One patient ([(b) (6)]) took a prohibited concomitant medication, oral prednisone, throughout their study participation. Three patients ([(b) (6)]) had their TOC visits completed outside of visit window.

All these subjects were included in the mITT population. We conducted a sensitivity analysis considering these subjects as microbiological failures.

Demographic Characteristics

Demographic and baseline characteristics for the mITT population are displayed in the following table. The mean age was 37.7 years and the range was 15 to 65 years. Only two subjects under 19 were enrolled and the subjects who were 15 and 17 years old were randomized to placebo. About 91% of subjects were Black or African Americans. By study design, all subjects were female (not listed in the table).

Table 8-2. Demographic and Baseline Characteristics (mITT Population)

Characteristic	**SOLOSEC (N=64)**	**Placebo (N=67)**	**All (N=131)**
Age (years)			
Mean (SD)	36.9 (11.3)	38.4 (11.1)	37.7 (11.2)
Median	34.5	39.0	36.0
Range	19, 65	15, 65	15, 65
<20 years, n (%)	1 (1.6)	3 (4.5)	4 (3.1)

≥60 years, n (%)	1 (1.6)	2 (3.0)	3 (2.3)
Body mass index (kg/m^2)			
Mean (SD)	33.8 (9.4)	34.1 (9.3)	34.0 (9.3)
Median	32.2	31.2	31.6
Range	17.7, 63.5	19.5, 62.3	17.7, 63.5
Height (inches)			
Mean (SD)	64.4 (3.1)	64.7 (3.1)	64.6 (3.1)
Median	64.0	65.0	65.0
Range	57.5, 71.0	55.2, 72.0	55.2, 72.0
Weight (lbs)			
Mean (SD)	199.3 (57.2)	203.6 (58.9)	201.5 (57.9)
Median	192.0	190.0	191.0
Range	100.0, 370.0	110.0, 398.0	100.0, 398.0
Race, n(%)			
American Indian or Alaska Native	1 (1.6)	1 (1.5)	2 (1.5)
Asian	1 (1.6)	0	1 (0.8)
Black or African American	59 (92.2)	60 (89.6)	119 (90.8)
White	3 (4.7)	6 (9.0)	9 (6.9)
Ethnicity, n(%)			
Hispanic or Latino	2 (3.1)	2 (3.0)	4 (3.1)
Not Hispanic or Latino	62 (96.9)	65 (97.0)	127 (96.9)

Source: Table 5 of Study Report
Abbreviations: mITT, modified intent-to-treat; N, number of subjects; n, number of subjects in subgroup; SD, standard deviation.

Baseline vaginal assessment results are shown in the following table. Bacterial vaginosis was reported in 29% of patients. The NAAT test was positive in 38.9% of patients. Trichomoniasis symptoms were reported in the majority of patients. Motile trichomonads were present in 85.5% of patients and the OSOM *Trichomonas* Rapid test was positive in 80.9% of patients. Overall, these baseline vaginal assessments were comparable between the two treatment groups.

Table 8-3. Baseline Vaginal Assessments (mITT Population)

Assessment	**SOLOSEC (N=64)**	**Placebo (N=67)**	**All (N=131)**
Bacterial vaginosis, n(%)			
Yes	21 (32.8)	17 (25.4)	38 (29.0)
No	43 (67.2)	50 (74.6)	93 (71.0)
Chlamydia trachomatis, n(%)			
Negative	63 (98.4)	67 (100.0)	130 (99.2)
Missing	1 (1.6)	0	1 (0.8)
NAAT testing, n(%)			

Positive	25 (39.1)	26 (38.8)	51 (38.9)
Not applicable	39 (60.9)	41 (61.2)	80 (61.1)
Trichomoniasis symptoms, n(%)			
Present	56 (87.5)	55 (82.1)	111 (84.7)
Absent	8 (12.5)	12 (17.9)	20 (15.3)
Discharge (trichomoniasis symptom)			
Normal	12 (18.8)	16 (23.9)	28 (21.4)
Abnormal	52 (81.3)	51 (76.1)	103 (78.6)
Itching (trichomoniasis symptom)			
Normal	36 (56.3)	38 (56.7)	74 (56.5)
Abnormal	28 (43.8)	29 (43.3)	57 (43.5)
Odor (trichomoniasis symptom)			
Normal	17 (26.6)	31 (46.3)	48 (36.6)
Abnormal	47 (73.4)	36 (53.7)	83 (63.4)
Clue cells			
<20% of total epithelial cells	36 (56.3)	41 (61.2)	77 (58.8)
≥20% of total epithelial cells	27 (42.2)	26 (38.8)	53 (40.5)
Missing	1 (1.6)	0	1 (0.8)
KOH whiff test			
Missing	0	1 (1.5)	1 (0.8)
Negative	20 (31.3)	27 (40.3)	47 (35.9)
Positive	44 (68.8)	39 (58.2)	83 (63.4)
Motile trichomonads			
Present	54 (84.4)	58 (86.6)	112 (85.5)
Absent	9 (14.1)	9 (13.4)	18 (13.7)
Missing	1 (1.6)	0	1 (0.8)
OSOM *Trichomonas* Rapid test			
Positive	54 (84.4)	52 (77.6)	106 (80.9)
Negative	0 (0)	1 (1.5)	1 (0.8)
Missing	10 (15.6)	14 (20.9)	24 (18.3)
Discharge (non-trichomoniasis symptom)			
Normal	55 (85.9)	59 (88.1)	114 (87.0)
Abnormal	9 (14.1)	8 (11.9)	17 (13.0)
Itching (non-trichomoniasis symptom)			
Normal	63 (98.4)	65 (97.0)	128 (97.7)
Abnormal	1 (1.6)	2 (3.0)	3 (2.3)
Odor (non-trichomoniasis symptom)			
Normal	52 (81.3)	58 (86.6)	110 (84.0)
Abnormal	12 (18.8)	9 (13.4)	21 (16.0)
Vaginal PH			
<4.7	6 (9.4)	4 (6.0)	10 (7.6)

≥4.7	58 (90.6)	62 (92.5)	120 (91.6)
Missing	0 (0)	1 (1.5)	1 (0.8)

Source: Table 7 in Study Report
Abbreviations: KOH: potassium hydroxide. NAAT: *T. vaginalis* Nucleic-acid amplification test.
Determination and qualification of trichomonal symptoms or non-trichomonal symptoms were made by individual investigators.

Other Baseline Characteristics

A summary of medical history, including the index infection, is displayed in the following table. All subjects had a history of trichomoniasis by study design. The most commonly reported medical history conditions (>8%) included bacterial vaginosis, caesarean section, hysterectomy, and hypertension. The two treatment groups were comparable in reported medical history.

Table 8-4. Study Population Past Medical History (mITT Population)

Medical history*	**SOLOSEC (N=64)**	**Placebo (N=67)**	**All (N=131)**
Any medical history	64 (100)	67 (100)	131 (100)
Infections and infestations	64 (100)	67 (100)	131 (100)
Bacterial vaginosis	9 (14.1)	13 (19.4)	22 (16.8)
Trichomoniasis	64 (100)	67 (100)	131 (100)
Investigations	5 (7.8)	10 (14.9)	15 (11.5)
Human immunodeficiency virus	3 (4.7)	3 (4.5)	6 (4.6)
Metabolism and nutrition disorders	8 (12.5)	7 (10.4)	15 (11.5)
Diabetes	1 (1.6)	4 (6.0)	5 (3.8)
Hypercholesterolemia	3 (4.7)	0 (0)	3 (2.3)
Psychiatric disorders	6 (9.4)	12 (17.9)	18 (13.7)
Anxiety	4 (6.3)	6 (9.0)	10 (7.6)
Bipolar disorder	0 (0)	4 (6.0)	4 (3.1)
Depression	3 (4.7)	7 (10.4)	10 (7.6)
Insomnia	0 (0)	3 (4.5)	3 (2.3)
Respiratory, thoracic and mediastinal disorders	3 (4.7)	11 (16.4)	14 (10.7)
Asthma	2 (3.1)	7 (10.4)	9 (6.9)
Chronic obstructive pulmonary disorder	0 (0)	3 (4.5)	3 (2.3)
Social circumstances	3 (4.7)	5 (7.5)	8 (6.1)
Postmenopausal	1 (1.6)	3 (4.5)	4 (3.1)
Surgical and medical procedures	27 (42.2)	29 (43.3)	56 (42.7)
Bilateral tubal ligation	5 (7.8)	4 (6.0)	9 (6.9)
Caesarean section	6 (9.4)	8 (11.9)	14 (10.7)
Hysterectomy	5 (7.8)	10 (14.9)	15 (11.5)
Tubal ligation	4 (6.3)	4 (6.0)	8 (6.1)
Vascular disorders	14 (21.9)	17 (25.4)	31 (23.7)
Hypertension	13 (20.3)	17 (25.4)	30 (22.9)

* Table includes history categories with at least 3 subjects
Source: reviewer's analysis

Treatment Compliance, Concomitant Medications

Study medication was administered under direct observation. Therefore, all randomized patients received study drug on Day 1. One patient ([redacted] (b) (6)) did not take the full dose of study medication within 5 minutes and reported mild nausea and productive cough. The patient was discontinued from the study, as described above, and was considered a failure in the primary analysis.

Prior medication use among at least 3 subjects in a group is reported in the following table. About 60% of patients took a prior medication. The most common medications were hormonal contraceptives for systemic use (13.7%), antidepressants (9.9%), and direct acting antivirals (7.6%). Overall, use of prior medications was comparable between the two treatment groups.

Table 8-5. Prior Medication Use* (mITT Population)

Medications	**SOLOSEC (N=64)**	**Placebo (N=67)**	**All (N=131)**
Any prior medication use	35 (54.7)	43 (64.2)	78 (59.5)
Hormonal contraceptives for systemic use	12 (18.8)	6 (9.0)	18 (13.7)
Drospirenone; ethinylestradiol	1 (1.6)	0 (0)	1 (0.8)
Estradiol; norgestimate	1 (1.6)	0 (0)	1 (0.8)
Ethinylestradiol; iron; norethisterone	1 (1.6)	2 (3)	3 (2.3)
Ethinylestradiol; norelgestromin	1 (1.6)	0 (0)	1 (0.8)
Ethinylestradiol; norethisterone	0 (0)	1 (1.5)	1 (0.8)
Ethinylestradiol; norgestimate	3 (4.7)	0 (0)	3 (2.3)
Etonogestrel	3 (4.7)	1 (1.5)	4 (3.1)
Medroxyprogesterone	2 (3.1)	1 (1.5)	3 (2.3)
Norethisterone	0 (0)	1 (1.5)	1 (0.8)
Antidepressants	4 (6.3)	9 (13.4)	13 (9.9)
Bupropion	0 (0)	3 (4.5)	3 (2.3)
Citalopram	3 (4.7)	1 (1.5)	4 (3.1)
Escitalopram	1 (1.6)	1 (1.5)	2 (1.5)
Fluoxetine	0 (0)	1 (1.5)	1 (0.8)
Sertraline	0 (0)	3 (4.5)	3 (2.3)
Trazodone	0 (0)	2 (3.0)	2 (1.5)
Direct acting antivirals	4 (6.3)	6 (9.0)	10 (7.6)
Bictegravir; emtricitabine; tenofovir	1 (1.6)	3 (4.5)	4 (3.1)
Cobicistat; darunavir	1 (1.6)	1 (1.5)	2 (1.5)
Cobicistat; elvitegravir; emtricitabine; tenofovir	1 (1.6)	0 (0)	1 (0.8)
Emtricitabine; tenofovir	1 (1.6)	1 (1.5)	2 (1.5)
Famciclovir	1 (1.6)	0 (0)	1 (0.8)
Ritonavir	0 (0)	1 (1.5)	1 (0.8)
Valaciclovir	0 (0)	1 (1.5)	1 (0.8)
Blood glucose lowering drugs, excluding insulins	5 (7.8)	5 (7.5)	10 (7.6)
Empagliflozin	1 (1.6)	0 (0)	1 (0.8)

Glimepiride	0 (0)	1 (1.5)	1 (0.8)
Liraglutide	0 (0)	1 (1.5)	1 (0.8)
Metformin	4 (6.3)	4 (6.0)	8 (6.1)
Metformin; sitagliptin	1 (1.6)	1 (1.5)	2 (1.5)
Lipid modifying agents	5 (7.8)	3 (4.5)	8 (6.1)
Atorvastatin	0 (0)	2 (3.0)	2 (1.5)
Ezetimibe	0 (0)	1 (1.5)	1 (0.8)
Pravastatin	1 (1.6)	0 (0)	1 (0.8)
Rosuvastatin	2 (3.1)	1 (1.5)	3 (2.3)
Simvastatin	2 (3.1)	0 (0)	2 (1.5)
Selective calcium channel blockers	5 (7.8)	4 (6.0)	9 (6.9)
Amlodipine	5 (7.8)	4 (6.0)	9 (6.9)
Ace inhibitors	4 (6.3)	2 (3.0)	6 (4.6)
Lisinopril	4 (6.3)	2 (3.0)	6 (4.6)
Anti-inflammatory and antirheumatic products, non-steroidal	4 (6.3)	3 (4.5)	7 (5.3)
Ibuprofen	4 (6.3)	3 (4.5)	7 (5.3)
Adrenergics, inhalants	3 (4.7)	7 (10.4)	10 (7.6)
Budesonide; formoterol	0 (0)	3 (4.5)	3 (2.3)
Salbutamol	3 (4.7)	6 (9.0)	9 (6.9)
Umeclidinium; vilanterol	0 (0)	1 (1.5)	1 (0.8)
Drugs for peptic ulcer and gastro-oesophageal reflux disease	3 (4.7)	3 (4.5)	6 (4.6)
Omeprazole	3 (4.7)	2 (3.0)	5 (3.8)
Pantoprazole	0 (0)	1 (1.5)	1 (0.8)
Other analgesics and antipyretics	3 (4.7)	2 (3.0)	5 (3.8)
Acetylsalicylic acid; caffeine; paracetamol	1 (1.6)	0 (0)	1 (0.8)
Gabapentin	1 (1.6)	2 (3.0)	3 (2.3)
Paracetamol	1 (1.6)	0 (0)	1 (0.8)

* Table includes medication classes with at least 3 subjects
Source: Reviewer's analysis (Study Report page 90 was for safety population)

The most frequently used concomitant medications included hormonal contraceptives, anti-depressants, antiviral, and anti-inflammatory products (non-steroidal).

Table 8-6. Concomitant Medication Use (mITT population)

Medications*	**SOLOSEC (N=64)**	**Placebo (N=67)**	**All (N=131)**
Any concurrent medication use	40 (62.5)	45 (67.2)	85 (64.9)
Hormonal contraceptives for systemic use	8 (12.5)	4 (6.0)	12 (9.2)
Drospirenone; ethinylestradiol	1 (1.6)	0 (0)	1 (0.8)
Estradiol; norgestimate	1 (1.6)	0 (0)	1 (0.8)

Ethinylestradiol; iron; norethisterone	0 (0)	2 (3)	2 (1.5)
Ethinylestradiol; norethisterone	1 (1.6)	1 (1.5)	2 (1.5)
Ethinylestradiol; norgestimate	1 (1.6)	0 (0)	1 (0.8)
Etonogestrel	2 (3.1)	1 (1.5)	3 (2.3)
Medroxyprogesterone	2 (3.1)	0 (0)	2 (1.5)
Lipid modifying agents, plain	2 (3.1)	1 (1.5)	3 (2.3)
Atorvastatin	0 (0)	1 (1.5)	1 (0.8)
Rosuvastatin	2 (3.1)	0 (0)	2 (1.5)
Anti-depressants	4 (6.3)	3 (4.5)	7 (5.3)
Bupropion	0 (0)	1 (1.5)	1 (0.8)
Citalopram	3 (4.7)	1 (1.5)	4 (3.1)
Escitalopram	1 (1.6)	1 (1.5)	2 (1.5)
Anti-inflammatory and antirheumatic products, non-steroids	4 (6.3)	3 (4.5)	7 (5.3)
Ibuprofen	4 (6.3)	3 (4.5)	7 (5.3)
Other analgesics and antipyretics	2 (3.1)	2 (3.0)	4 (3.1)
Acetylsalicylic acid; caffeine; paracetamol	1 (1.6)	0 (0)	1 (0.8)
Gabapentin	0 (0)	1 (1.5)	1 (0.8)
Direct acting antivirals	3 (4.7)	4 (6.0)	7 (5.3)
Bictegravir; emtricitabine; tenofovir	2 (3.1)	2 (3)	4 (3.1)
Cobicistat; elvitegravir; emtricitabine; tenofovir	1 (1.6)	0 (0)	1 (0.8)
Emtricitabine; tenofovir	0 (0)	1 (1.5)	1 (0.8)
Ritonavir	0 (0)	1 (1.5)	1 (0.8)
Bictegravir; emtricitabine; tenofovir	2 (3.1)	2 (3)	4 (3.1)
Cobicistat; elvitegravir; emtricitabine; tenofovir	1 (1.6)	0 (0)	1 (0.8)
Emtricitabine; tenofovir	0 (0)	1 (1.5)	1 (0.8)
Ritonavir	0 (0)	1 (1.5)	1 (0.8)
Drugs for peptic ulcer and gastro-esophageal reflux disease	2 (3.1)	1 (1.5)	3 (2.3)
Omeprazole	2 (3.1)	1 (1.5)	3 (2.3)
Selective calcium channel blockers	3 (4.7)	1 (1.5)	4 (3.1)
Amlodipine	3 (4.7)	1 (1.5)	4 (3.1)

*Table includes medication classes with at least 2 subjects
Source: Reviewer's analysis

Efficacy Results – Primary Endpoint

The primary efficacy endpoint, microbiological cure (i.e., InPouch TV test negative for *T. vaginalis*) at the TOC visit (Day 6-12) for the mITT population, is displayed in the table below. The cure rate was significantly higher in the SOLOSEC group than in the placebo group (p-value <0.001).

Table 8-7. Microbiological Cure at TOC Visit (mITT Population)

	SOLOSEC (N=64)	Placebo (N=67)	Difference (%) [95% CI] p-value
Microbiological cure, n(%) [95% CI]	59 (92.19) [82.70, 97.41]	1 (1.49) [0.04, 8.04]	90.69 [80.68, 96.48]* <0.001
Number imputed (missing as failure)	1	3	

Source: Table 8, Study Report. P-value was from a CMH test adjusted for clinical symptoms (present/absent) of trichomoniasis at baseline

*Reviewer's analysis

Data Quality and Integrity

Web-based, electronic case report form was used for this study. Quality control and data validation procedures were applied.

Efficacy Results – Secondary and other relevant endpoints

Microbiological cure at the TOC visit by baseline trichomoniasis symptom strata (presence/absence) is displayed in the following table. Regardless of the baseline symptom status, there was a statistically significant difference in microbiological cure between the two treatment groups.

Table 8-8. Microbiological Cure at TOC Visit by Baseline Trichomoniasis Symptom Strata (mITT Population)

	SOLOSEC (N=64)	Placebo (N=67)	Difference (%) [95% CI] p-value
Presence of baseline trichomoniasis symptoms†			
Microbiological cure, n(%) [95% CI]	52/56 (92.9) [82.7, 98.0]	0/55 (0) [0.0, 6.5]	92.9 [82.7, 98.0]* <0.001
Number imputed (missing as failure)	0	3	
Absence of baseline trichomoniasis symptoms†			
Microbiological cure, n(%) [95% CI]	7/8 (87.5) [47.4, 99.7]	1/12 (8.3) [0.2, 38.5]	79.2 [32.6, 97.1]* <0.001
Number imputed (missing as failure)	1	0	

† Symptoms of trichomoniasis infection were vaginal itching, discharge, or odor

Source: Table 10, Study Report

*Reviewer's analysis

Among 11 mITT subjects with a major protocol violation, 5/6 in the SOLOSEC group and 0/5 in the placebo group had a microbiological cure. An FDA's sensitivity analysis considering these subjects as failures still demonstrated a significant treatment effect (47/56 versus 0/55) with a difference of 83.9% (exact 95% CI [71.4%, 91.6%], p-value<0.001).

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The following table shows the results of an exploratory analysis for the subgroup of patients who had clinical symptoms of trichomoniasis at baseline (i.e., itching, discharge, and odor) and had complete resolution of symptoms and negative culture results for *T. vaginalis* (outcome responders). In the mITT population, the outcome responder rate at the TOC visit was significantly higher (p <0.001) in the SOLOSEC group than in the placebo group.

Table 8-9. Outcome Responder Rate at TOC Visit for Those with Clinical Symptoms of Trichomoniasis at Baseline (mITT Population)

	SOLOSEC (N=64)	Placebo (N=67)	Difference (%) [95% CI] p-value
Outcome Responder, n/N(%) [95% CI]	41/56 (73.2) [59.7, 84.2]	0/55 (0) [0.0, 6.5]	73.2 [59.7, 84.2]* <0.001
Number imputed (missing as failure)	0	3	

Source: Table 11, Study Report

*Reviewer's analysis

The following table shows the results of exploratory analyses for the complete resolution of symptoms by whether or not clinical symptoms of trichomoniasis were present at baseline (i.e., itching, discharge, and odor) and cross-tabulation of microbiological cure and clinical resolution. For those with symptoms at baseline, complete clinical resolution in the SOLOSEC group was statistically significant higher than in the placebo group, with a 95% CI of [33.0%, 66.4%] for the difference and a p-value <0.001. For 8 subjects in the SOLOSEC group with no symptoms at baseline, 7 subjects continued to not have symptoms, and 1 subject with a missing value at this visit was considered as without clinical resolution. In subjects with no symptoms at baseline in the placebo group, 83.3% of subjects remained without symptoms. As the numbers of subjects with no symptoms at baseline were small and most had no symptoms, there was no significant difference in clinical resolution detected at TOC between the two treatment groups.

Table 8-10. Composite Vaginal Assessments at TOC Visit (mITT Population)

	SOLOSEC (N=64)	Placebo (N=67)	Difference (%) [95% CI]

			p-value
Presence of trichomoniasis symptoms at baseline			
Clinical Resolution (no trichomoniasis symptoms), n/N(%) [95% CI]	43/56 (76.8) [63.6, 87.0]	14/55 (25.5) [13.2, 37.0]	52.8 [33.0, 66.4] <0.001
Number imputed (missing as failure)	0	3	
For those with Microbiological cure:			
Clinical resolution	41	0	
No clinical resolution	11	0	
For those with No microbiological cure:			
Clinical resolution	2	14	
No clinical resolution	2	41*	
Absence of trichomoniasis symptoms at baseline			
Clinical Resolution (no trichomoniasis symptoms), n/N(%) [95% CI]	7/8 (87.5)	10/12 (83.3)	4.2 [-37.8, 40.9] 0.94
Number imputed (missing as failure)	1	0	
For those with Microbiological cure:			
Clinical resolution	7	1	
No clinical resolution	0	0	
For those with No microbiological cure:			
Clinical resolution	0	9	
No clinical resolution	1*	2	

Source: Reviewer's analysis. P-value was from Chi-square test.
*Including 4 subjects with missing values both in microbiological outcome and in symptoms.

Vaginal assessment results at the TOC visit are displayed in the following table. Individual investigators made the determination and qualification of trichomonal symptoms or non-trichomonal symptoms based on their clinical judgement. The proportions of being "normal" at TOC in all trichomoniasis symptoms (itching, discharge, odor) were higher in the SOLOSEC group than in the placebo group. In all non-trichomoniasis symptoms, the proportions of being "normal" at TOC were only slightly better in the SOLOSEC group.

Table 8-11. Vaginal Assessment at TOC Visit, mITT Population

Assessment	SOLOSEC (N=64)	Placebo (N=67)	All (N=131)
Itching (trichomoniasis symptom)			
Normal	59 (92.2)	46 (68.7)	105 (80.2)
Abnormal	4 (6.3)	18 (26.9)	22 (16.8)
Missing	1 (1.6)	3 (4.5)	4 (3.1)
Discharge (trichomoniasis symptom)			
Normal	51 (79.7)	29 (43.3)	80 (61.1)
Abnormal	12 (18.8)	35 (52.2)	47 (35.9)

Missing	1 (1.6)	3 (4.5)	4 (3.1)
Odor (trichomoniasis symptom)			
Normal	59 (92.2)	43 (64.2)	102 (77.9)
Abnormal	4 (6.3)	21 (31.3)	25 (19.1)
Missing	1 (1.6)	3 (4.5)	4 (3.1)
Itching (non-trichomoniasis symptom)			
Normal	60 (93.8)	62 (92.5)	122 (93.1)
Abnormal	3 (4.7)	1 (1.5)	4 (3.1)
Missing	1 (1.6)	3 (4.5)	4 (3.1)
Discharge (non-trichomoniasis symptom)			
Normal	57 (89.1)	57 (85.1)	114 (87)
Abnormal	6 (9.4)	6 (9)	12 (9.2)
Missing	1 (1.6)	3 (4.5)	4 (3.1)
Odor (non-trichomoniasis symptom)			
Normal	59 (92.2)	58 (86.6)	117 (89.3)
Abnormal	4 (6.3)	5 (7.5)	9 (6.9)
Missing	1 (1.6)	3 (4.5)	4 (3.1)

Source: Adapted from Table 14.2.4.1, Study Report
Determination and qualification of trichomonal symptoms or non-trichomonal symptoms were made by individual investigators.

Microbiological cure at Visit 3 for those with positive culture at Visit 2 (TOC)

At TOC, there were 4 and 63 subjects with a positive culture for TV at TOC in the two treatment groups, respectively. After completion of TOC procedures, all subjects received the opposite treatment. Culture positive subjects at TOC were followed up at Visit 3. Microbiological cure at Visit 3 is shown in the following table. The sequence of SOLOSEC-placebo represents subjects who received SOLOSEC at Visit 1 and placebo at Visit 2 and vice-visa for placebo-SOLOSEC subjects. The subjects receiving delayed SOLOSEC treatment showed a comparable microbiological cure rate of 88.9% (56/63), when compared to the 92% cure rate for the initially SOLOSEC treated subjects.

Table 8-12. Microbiological Cure at Visit 3 for Those with Positive Culture and Receiving Opposite Treatment at Visit 2 (TOC), mITT Population

	SOLOSEC-placebo (N=4)	**Placebo-SOLOSEC (N=63)**
Microbiological cure, n(%) [95% CI]	1 (25.0) [0.6, 80.6]	56 (88.9) [78.4, 95.4]
Number imputed (missing as failure)	0	5

Source: Reviewer's analysis.

Additional Analyses Conducted on the Individual Trial

Subgroup Analyses by Age and Race

The following table shows the analysis results of microbiological cure by age and race. In the two age groups (<40 and ≥40 years), there was a statistically significant difference between the two treatment groups. One subject was in the ≥60 group at age 65 years in the SOLOSEC group. This subject remained trichomonas test positive during the study. However, the 2 placebo subjects ≥60 years of age who treated with delayed SOLOSEC were microbiological cures 7-12 days after treatment with SOLOSEC. Among subjects of Black or African American race, the difference between the two treatment groups was also statistically significant. For other races, the numbers of subjects were too small to make a valid comparison.

Table 8-13. Microbiological Cure at TOC Visit by Age and Race, mITT Population

Microbiological cure, n(%) [95% CI]	**SOLOSEC (N=64) n/N (%)**	**Placebo (N=67) n/N (%)**	**Difference (%) [95% CI] p-value**
Age			
<40 years	40/42 (95.2) [83.8, 99.4]	1/36 (2.8) [0.0, 14.5]	92.4 [79.4, 98.3] <0.001
≥40 years	19/22 (86.4) [65.09, 97.09]	0/31 (0) [0.00, 11.22]	86.4 [65.1, 97.1] <0.001
<20 years	1/1 (100)	0/3 (0)	
≥60 years	0/1 (0)	0/2 (0)	
Race			
American Indian or Alaska Native	1/1 (100)	0/1 (0)	
Asian	1/1 (100)	0/0	
Black or African American	54/59 (91.5)	0/60 (0)	91.5 [81.3, 97.2] <0.001
White	3/3 (100)	1/6 (16.7)	
After receiving the opposite treatment (delayed SOLOSEC for placebo subjects)			
Age			
<40 years	1/1 (100)	30/32 (93.8)	
≥40 years	0/3 (0)	26/31 (83.9)	
<20 years	0/0	2/2 (100)	
≥60 years	0/1 (0)	2/2 (100)	
Race			
Black or African American	1/4 (25.0)	51/58 (82.3)	
White	0/0	5/5 (100)	

*Reviewer's analysis

Subgroup Analyses by Study Site

Microbiological cure at TOC visit by study site is displayed in the following table. All sites were in the United States. The range of differences in proportions of microbiological cure was 79.8% to 100%. Site 1011 only included one subject; therefore, the difference was not applicable. All other sites showed consistent treatment effects.

Table 8-14. Microbiological Cure at TOC Visit by Study Site, mITT Population

Site	SOLOSEC (N=64) n/N (%)	Placebo (N=67) n/N (%)	Difference (%)
1001	9/10 (90)	0/11 (0)	90.0
1002	8/8 (100)	0/8 (0)	100.0
1003	10/11 (90.9)	0/10 (0)	90.9
1004	10/11 (90.9)	1/9 (11.1)	79.8
1006	4/5 (80)	0/3 (0)	80.0
1007	8/8 (100)	0/11 (0)	100.0
1009	5/6 (83.3)	0/8 (0)	83.3
1011		0/1 (0)	
1013	1/1 (100)	0/2 (0)	100.0
1014	4/4 (100)	0/4 (0)	100.0

Source: Reviewer's analysis

Subgroup Analyses by HIV infection

A total of 9 patients reported "HIV test positive" or "HIV infection" at baseline (mITT population). The microbiological cure rate at the TOC visit was higher in the SOLOSEC group (4/4 subjects; 100%) as compared to the placebo group (0/5 subjects; 0%).

Clinical Reviewer Comment: *Only a small number of subjects with HIV infection were enrolled in this study. Information regarding immune status/CD4 count was not collected on these subjects. The efficacy in this subgroup analysis was not significantly different as compared with the overall population.*

8.1.3. Assessment of Efficacy Across Trials

It is not applicable, as there is only one study submitted in this NDA.

8.1.4. Integrated Assessment of Effectiveness

One Phase 3, multicenter, randomized, double-blind, placebo-controlled trial was conducted in women aged between 19 and 65 years of age with trichomoniasis to evaluate the efficacy and safety of a single oral dose of 2-gram secnidazole (SOLOSEC®).

There was a significantly greater proportion of subjects with microbiological cure at TOC in the SOLOSEC group (92.2%, 95% CI: 82.7%, 97.4%) than in the placebo group (1.5%, 95% CI: 0.0%, 8.0%) (treatment difference: 90.7% (95% CI [80.7%, 96.5%]; p-value <0.001). Significant treatment effects were also seen for a combined clinical and microbiological response and for trichomoniasis symptoms. In addition, no single site provided an unusually large fraction of subjects or a disproportionate favorable effect. The microbiological cure of placebo subjects who received delayed SOLOSEC after the TOC assessment was comparable to those with initial SOLOSEC treatment (88.9%, 95% CI: 78.4%, 95.4%)

A stringent p-value is required for approval of an indication with a single trial. This trial met this criterion. Therefore, adequate evidence of efficacy was provided to support the indication for the treatment of trichomoniasis.

Regarding efficacy in males, a thorough search of the published literature identified 4 studies (Dyudyun *et al*., 2016; Özbilgin *et al*, 1994; Siboulet *et al.*, 1977; Videau *et al.*, 1978) in which a single oral 2 gm secnidazole dose was used for the treatment of trichomoniasis in men. The studies are summarized in Table 8-15, below.

Table 8-15 Published Clinical Studies of Secnidazole for Treatment of Trichomoniasis in Males

Publication (Country)	Treatment(s)	Study Design	Demographics		Clinical Endpoint(s)
			M / F	Age Range	
Actively Controlled					
Özbilgin *et al*., 1994 (Turkey)	Secnidazole, 2 g SD, PO	Open label, comparative study of SD secnidazole, MD metronidazole, and MD ornidazole	30 / 0	18 - 50[a]	Cure rate 5 days after treatment (100%)
	Metronidazole, 250 mg TID × 7 days PO		29 / 0	18 - 50[a]	Cure rate 5 days after treatment (100%)
	Ornidazole, 500 g BID × 5 days, PO		26 / 0	18 - 50[a]	Cure rate 5 days after treatment (100%)
Uncontrolled					
Videau *et al*., 1978 (France)	Secnidazole, 2 g SD, PO	Open label, SD, uncontrolled study	56 /84	15 - 54	Cure rate at 48 hours (97.1%) Day 15 relapse/reinfection rate (4.4%)
Siboulet *et al*., 1977 (France)	Secnidazole, 2 g SD, PO	Open label, SD, uncontrolled study	76 /104	12 - 54	Clinical symptom score Microbiological cure rate: • Immediate, 2-3 days after treatment (95.6%) • Long-term, 5-20 days after treatment (91.7%)
Dyudyun *et al*., 2016	Secnidazole, 2 g SD, PO ("fresh" trichomoniasis[b])	Open label, SD or MD, uncontrolled study	49 /38	18 - 57	Clinical and microbiological cure rate (97.7%)

(Ukraine)	Or Secnidazole, 2 g given on Day 1, 3, and 5 (chronic trichomoniasis)				

BID=twice daily; F=female; M=male; MD=multiple dose; NR=not reported; PO=by mouth; SD=single dose, TID=three times daily

[a] Age range for study population (n=415) is 18-50 years.

[b] Article originally published in Ukrainian. "Fresh" is interpreted to mean a patient with first occurrence of *T. vaginalis* infection.

Source: Adapted from Applicant's supporting document, "efficacy-men-082820.pdf" (Module 5.4, Table 2.2)

Of these studies, one open-label, randomized controlled study from Turkey evaluating secnidazole treatment compared to metronidazole and ornidazole was identified (Özbilgin *et al.*, 1994). Out of 415 males, ages 18 to 50 years, with symptoms of urethral discharge, dysuria, polyuria, 85 males were found to have trichomoniasis. These subjects were divided into 3 groups of secnidazole 2 gram, metronidazole 250 mg three times a day for 7 days, and ornidazole 500 gram twice a day for 5 days. This study showed 100% efficacy in clinical and parasitological cure of trichomoniasis 5 days after treatment in all 3 groups of secnidazole [n=30; 95% CI: 88.4%, 100%], metronidazole [n=29], and ornidazole [n=26].

In three open-label, uncontrolled, single-arm studies in males and females, ages ranging from 12 to 57 years, conducted in France and Ukraine, clinical and parasitological evaluations were performed both pre- and post-treatment and reported cure rates ranged from 91.7% [n=180 (n=76 males +104 females)] to 97.7% [n=87 (49 males + 38 females)] at time points ranging from 2 to 20 days (Dyudyun *et al*., 2016; Siboulet *et al.*, 1977; Videau *et al.*, 1978). Two of these studies reported results at two time points for males and females combined. Videau *et al.* reported a response rate of 97.1% at 48 hours with a 4.4% relapse/reinfection rate at Day 15, which gives an approximate response rate of 92.9% at Day 15. Siboulet *et al.* reported a 95.6% response rate at 48 hours and a 91.7% response rate at 5-20 days. One study (Siboulet *et al*., 1977) reported symptomatic response rate after secnidazole 2 gram treatment for subjects with symptoms at baseline. Symptomatic response was graded as very good (in the case of total disappearance of the urethral leukorrhea secretion, all signs of inflammation, clear urine), good (disappearance of signs of inflammation, but sometimes persistence of a slight morning moisture), average (decrease in signs of inflammation, persistence of a small secretion or some leukorrhea), and failure (no favorable action noted). Symptomatic response was similar for males and females. About 80 percent of males and females reported having a very good or good symptomatic response to the secnidazole treatment. This finding is consistent with the symptomatic resolution reported in the trial SEC-WH-301.

In addition, one natural history study of trichomoniasis in men evaluated disease progression (Krieger *et al.*, 1993). Response rate at Day 16 ±12 in untreated men was 36% [n=14, 95% CI: 12.8%, 64.9%]. Compared with this spontaneous response rate, secnidazole from Özbilgin *et al.*, 1994 showed a significant treatment effect with a difference of 64.3% (exact 95% CI: [35.1%, 87.2%]). Though the timing of the assessment in untreated males was variable, the studies that

included secnidazole-treated males had success rates greater than 90% at all timepoints assessed.

Statistical Reviewer Comment:
Though the use of historical/external controls has limitations due to the potential differences between the treated and control groups at baseline and the differences in follow-up and assessment of study subjects, the results seen in males appear strong and unlikely to be caused by these potential differences alone. Additionally, these results are supported by the randomized placebo-controlled trial in females.

Clinical Reviewer Comment:
The Applicant did not recruit male subjects in the trichomoniasis study because males are typically asymptomatic and have higher spontaneous cure rates which could affect the study endpoints and sample size. The evidence to support the use of secnidazole in males is provided by four open-label trials in the published literature which show a response rate of greater than 90% at all timepoints for parasitological and clinical response. By considering the difference between the treated and untreated response rates (Özbilgin et al., 1994; Krieger et al., 1993), a conservative estimate of the treatment effect in males is at least 35.1% based upon the lower limit of the 95% confidence interval. There are limitations to the use of published data, such as a lack of access to source data, open-label trials and differences in timepoints; nevertheless, the disease process of trichomoniasis is not expected to be different in other countries, races, or ethnicities. Therefore, even though these published studies were not conducted in the United States, the findings are relevant to the United States patient population.

Overall, the results in adult males from the published literature are consistent with the findings in adult females in clinical trial SEC-WH-301. The robust efficacy demonstrated in SEC-WH-301 and the lesser disease severity in males is also notable. Given the public health importance of treating all sexual partners of patients with trichomoniasis, and based on our review of the published literature, we determined that extending the indication to include both women and men was appropriate.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of secnidazole was previously reviewed in the original NDA application for the bacterial vaginosis (BV) treatment indication. The current safety review primarily focuses on the safety findings from the Phase 3 trial (SYM-WH-301) to support the proposed trichomoniasis treatment indication. Safety analyses were performed using datasets submitted by the Applicant with JMP version 15.0 and JReview 13.2 analytical software. Where relevant, data are compared to the original NDA, in which the safety population received a similar one time dose of 2 g secnidazole for the treatment of BV.

8.2.2. Review of the Safety Database

Overall Exposure

For the treatment of trichomoniasis, 74 subjects were exposed to a single 2 g of secnidazole, and 73 subjects were given placebo.

Adequacy of the safety database

Overall, the safety database provided an adequate number of exposed subjects at the proposed dose (2 g) and frequency (one-time use) for secnidazole in treatment of trichomoniasis. There were no males enrolled in the trichomoniasis trial as it was considered infeasible, but males were included in the safety database of the initial NDA application (see section 8.2.8 for discussion).

Clinical Reviewer Comment: *About 91% of the safety population in this study was Black or African American. Since the prevalence of trichomoniasis is greater in African American women than Hispanic or non-Hispanic white women, having Black or African American women as the majority of enrolled subjects is acceptable. Also, the disease process of trichomoniasis is not expected to be different between races and ethnicities. Therefore, the results from this study can be extrapolated to other racial groups.*

These data augment the safety information provided in the original NDA, in which 783 subjects were exposed to secnidazole, 589 subjects in the BV trials and 194 subjects in the healthy volunteer trials. A total of 518 subjects were exposed to 2 g of secnidazole in the BV trials (197 subjects in the controlled trials and 321 in the open label safety trial).

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

A data fitness assessment was performed on February 2, 2021 in collaboration with the Office of Computational Science (OCS). Five of 147 (3.4%) subjects were assigned to a different actual arm than planned. These subjects were categorized as unplanned treatment. 19 of 52 (36.5%) adverse events found in the SDTM Adverse Events (AE) dataset were not present in ADAE dataset since these AEs occurred after the TOC visit when the treatment was switched. Details of these AEs after the TOC visit are discussed in section 8.2.4. Other than this, the submission was well organized.

Case report forms were reviewed to assess the consistency of the data submitted. The reported terms for Adverse Events (AEs) mostly matched the MedDRA dictionary terms used during the trial.

Categorization of Adverse Events

Clinical Reviewer Comment: *The Applicant's categorization of AEs were acceptable.*

Routine Clinical Tests

A schedule of tests and observations are provided in Table 8-16. The timing of clinical assessments in the safety population appear to be adequate.

Table 8-16: Schedule of Assessments

Assessment	Screening/ Baseline Visit	Visit 2 Test of Cure (TOC)	Visit 3/4[6] (only for Patients culture + at Visit 2)[8]
	Day 1/Visit 1	Day 6 -12	7-12 days post Visit 2 visit
Informed consent	X		
Inclusion/exclusion	X		
Demographics	X		
Medical history	X		
Vital signs	X	X	X
Height/weight	X		
Urine pregnancy test	X[1]	X[1]	X[1]
Physical examination	X	X[7]	X[7]
Pelvic examination	X	X	X
Clinical assessment of trichomoniasis symptoms (e.g., itching, discharge, odor)	X	X	X
OSOM® Trichomonas Rapid Test[2]	X		
Vaginal wet mount	X		X[5]
KOH Whiff Test	X		
pH of vaginal fluid	X		
T. vaginalis culture (BioMed InPouch™ TV test)	X[3]	X[3]	X[3]
STI Assessments	X		
IWRS Randomization	X		
Drug dosing	X	X[4]	
Concomitant medication review	X	X	X
Adverse events query	X	X	X
Investigator's clinical assessment of the need for further treatment			X

1. Performed by site personnel (not sent to central laboratory).
2. OSOM® test not needed if patient has positive NAAT test within 30 days of screening for which treatment has not been initiated. The manufacturer of OSOM® Trichomonas Rapid Test, Sekisui Diagnostics, does not recommend the test be used as a test of cure.
3. Results will not be available at the time of visit.
4. Patients who received placebo at first visit will receive Solosec and those who received Solosec at first visit will receive placebo.
5. For assessment of trichomonas only.
6. At the discretion of the investigator a patient who is culture positive at visit 3 may return for an additional visit (Visit 4) for further evaluation and treatment (assessments may include all those listed but at the discretion of the investigator).
7. A targeted physical examination is only needed per the Investigator's discretion if a reported AE requires further evaluation.
8. Patients with cultures that are negative at V2 or V3 will be contacted by phone and discharged from the study. Note: The telephone contact will include an assessment of safety and well-being. Subjects reporting any complaints, or an adverse event will be asked to return for an unscheduled visit for evaluation and safety assessment.

Source: Obtained from Table 1. Schedule of Assessments Page 11 of the Clinical Trial Protocol of SEC-WH-301 (version: March 29, 2019)

8.2.4. Safety Results

Deaths

No deaths were reported in the trial.

Serious Adverse Events (SAEs)

There were no SAEs reported in the trial.

Dropouts and/or Discontinuations Due to Adverse Effects

One subject in trial SEC-WH-301 (1/174) discontinued study treatment due to TEAEs.

The narrative of the discontinuation is presented below:

- A 36-year-old Black female was diagnosed with trichomoniasis and was randomized to receive secnidazole. The patient was not able to tolerate the taste of the medication/applesauce mix and reported TEAEs of mild nausea and expectoration [productive cough (preferred term)]; both were considered related to the study drug by the Investigator. The AEs resolved on the same day and no concomitant medication was taken. The patient was discontinued from the study due to these AEs.

Clinical Reviewer Comment: *This reviewer concurs that the event could be related to the study drug. The intolerable taste of the mediation/applesauce mix may induce nausea and cough.*

Significant Adverse Events

No other significant adverse events were reported in the study.

Treatment Emergent Adverse Events and Adverse Reactions

The TEAEs that occurred in trial SEC-WH-301 are listed in Table 8-17. Approximately 15% of patients in the SOLOSEC arm experienced at least one AE as compared to 22% of placebo patients. The most frequent TEAEs were in the Gastrointestinal disorder SOC (5.4%) followed by the Infections and Infestations SOC (4.1%); however, gastrointestinal TEAEs were more frequent in the placebo arm than the SOLOSEC arm. The most common TEAEs were vulvovaginal candidiasis and nausea which occurred in >2% of patients in the SOLOSEC arm.

Table 8-17. Trial SEC-WH-301 TEAE by Treatment arm (Safety Analysis Population)

System Organ Class Preferred Term	SOLOSEC 2 grams (N=74)		Placebo (N=73)	
	Subject n (%)	Events n	Subject n (%)	Events n
Any Adverse Event	**11 (14.9)**	**13**	**16 (21.9)**	**20**
Gastrointestinal disorders	**4 (5.4)**	**5**	**6 (8.2)**	**7**
Nausea	2 (2.7)	2	3 (4.1)	3
Abdominal pain	1 (1.4)	1	1 (1.4)	1
Diarrhoea	1 (1.4)	1	2 (2.7)	2

Vomiting	1 (1.4)	1	1 (1.4)	1
Infections and infestations	**3 (4.1)**	**3**	**2 (2.7)**	**2**
Vulvovaginal candidiasis	2 (2.7)	2	0	0
Vulvovaginal mycotic infection	1 (1.4)	1	0	0
Trichomoniasis	0	0	2 (2.7)	2
Respiratory, thoracic and mediastinal disorders	**2 (2.7)**	**2**	**0**	**0**
Productive cough	1 (1.4)	1	0	0
Upper-airway cough syndrome	1 (1.4)	1	0	0
Musculoskeletal and connective tissue disorders	**1 (1.4)**	**1**	**1 (1.4)**	**1**
Myalgia	1 (1.4)	1	0	0
Back pain	0	0	1 (1.4)	1
Nervous system disorders	**1 (1.4)**	**1**	**5 (6.8)**	**5**
Headache	1 (1.4)	1	5 (6.8)	5
Reproductive system and breast disorders	**1 (1.4)**	**1**	**3 (4.1)**	**3**
Vulvovaginal pruritus	1 (1.4)	1	0	0
Dysmenorrhoea	0	0	2 (2.7)	2
Menstruation irregular	0	0	1 (1.4)	1
General disorders and administration site conditions	**0**	**0**	**1 (1.4)**	**1**
Thirst	0	0	1 (1.4)	1
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (1.4)**	**1**
Pruritus	0	0	1 (1.4)	1

Source: Clinical reviewer generated, Trial SEC-WH-301 ADAE dataset

Clinical Reviewer Comment: *The TEAEs of nausea, vomiting, diarrhea, abdominal pain, and headache were seen more frequently in the secnidazole arm compared to placebo arm in the BV studies. In contrast, in the trichomoniasis study, these TEAEs were more frequently seen in the placebo arm. The range of adverse events in the trichomoniasis trial associated with secnidazole are expected and consistent with the current product labeling; moreover, these AEs have been observed with other drugs of the nitroimidazole class, such as metronidazole and tinidazole.*

To further assess TEAEs for causality, Table 8-18 presents the treatment emergent AEs probably or possibly related to the study drug:

Table 8-18: TEAE related to study drug administration (Safety Analysis Population):

System Organ Class Preferred Term	SOLOSEC 2 grams N=74		Placebo N=73	
	Subject n(%)	Events n	Subject n(%)	Events n
Any Adverse Event	**8 (10.8)**	**10**	**8 (10.9)**	**10**
Gastrointestinal disorders	**4 (5.4)**	**5**	**4 (5.4)**	**5**
Nausea	2 (2.7)	2	2 (2.7)	2
Abdominal pain	1 (1.4)	1	1 (1.4)	1
Diarrhoea	1 (1.4)	1	1 (1.4)	1
Vomiting	1 (1.4)	1	1 (1.4)	1
Infections and infestations	**3 (4.1)**	**3**	**0**	**0**
Vulvovaginal candidiasis	2 (2.7)	2	0	0
Vulvovaginal mycotic infection	1 (1.4)	1	0	0
Respiratory, thoracic and mediastinal disorders	**1 (1.4)**	**1**	**0**	**0**
Productive cough	1 (1.4)	1	0	0
Nervous system disorders	**1 (1.4)**	**1**	**5 (6.8)**	**5**
Headache	1 (1.4)	1	5 (6.8)	5

Source: Clinical reviewer generated, Trial SEC-WH-301 ADAE dataset

The most frequent TEAEs related to secnidazole administration were nausea (2.7%) and VVC (2.7%).

The severity of TEAEs, assessed by the study investigator as either mild, moderate, or severe TEAEs is presented below in Table 8-19. Most TEAEs experienced during the study were of mild severity as reported by 14.9% and 19.2% of subjects in the SOLOSEC and placebo arms, respectively. Two patients (2.7%) in the placebo arm experienced moderate AEs which were abdominal pain and headache. There were no TEAEs reported with severe intensity.

Table 8-19: Trial SEC-WH-301 TEAEs by Severity (Safety Analysis Population)

System Organ Class Preferred Term	SOLOSEC 2 grams (N=74)	Placebo (N=73)
	Subject n (%)	Subject n (%)

Any Adverse Event	**11 (14.9)**	**16 (21.9)**
Mild	11 (14.9)	14 (19.2%)
Moderate	0	2 (2.7%)
Severe	0	0

Source: Clinical reviewer generated, Trial SEC-WH-301 ADAE dataset

Adverse Events after the TOC visit
For the SEC-WH-301 trial, after the TOC visit, subjects received the opposite treatment (placebo patient receive SOLOSEC and vice-versa). Therefore, it is difficult to assign which treatment is responsible for the AEs after the TOC visit.

For the SOLOSEC group (received placebo at TOC visit), bacterial vaginosis (1 event), vulvovaginal mycotic infection (1 event), herpes simplex (1 event) were reported.
For the placebo group (received SOLOSEC 2 grams at TOC visit), headache (2 events), nausea (3 events), bacterial vaginosis (2 events), urinary tract infection (1 event), pain in extremity (1 event), vulvovaginal discomfort (1 event), vulvovaginal candidiasis (1 event), upper respiratory infection (1 event), vulvovaginal mycotic infection (moderate 1 event), dry mouth (1 event) and fungal infection (1 event) were reported.

All post-TOC AEs were reported as mild and non-related to study drug except vulvovaginal mycotic infection (moderate 1 event), headache (1 event related) and nausea (2 events related) in the placebo group.

Clinical Reviewer Comment: *Compared to the SOLOSEC group, AEs within the Infection and Infestation SOC (vulvovaginal candidiasis, vulvovaginal mycotic infection, and fungal infection) were more frequently reported in the placebo group after the TOC visit. Since the placebo group received SOLOSEC at the TOC visit, this finding is consistent with the TEAEs reported.*

Laboratory Findings

No safety laboratory tests were reported other than urine pregnancy test. No positive pregnancy tests were reported in the trial SEC-WH-301 .

Vital Signs

Vital signs, including temperature, pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were monitored for clinically significant changes. No meaningful differences were reported for mean changes from baseline values between treatment arms. No vital sign abnormalities were reported as adverse events.

Electrocardiograms (ECGs)

Electrocardiograms were not performed in the trichomoniasis and BV trials. According to the original NDA review, the *in vitro* cardiac toxicity studies and safety ECGs in the clinical pharmacology studies did not show significant ECG abnormalities.

Immunogenicity

No immunogenicity safety issues were reported in the trial SEC-WH-301.

8.2.5. Analysis of Submission-Specific Safety Issues

Vulvovaginal candidiasis (VVC) is a known AE for SOLOSEC and is a warning in the currently approved prescribing information. There were two patients in the present study who experienced VVC as a TEAE of mild severity that resolved with fluconazole treatment.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No clinical outcome assessment data were collected for safety.

8.2.7. Safety Analyses by Demographic Subgroups

TEAEs were generally mild and infrequent. There was no association between any particular TEAE with any age group, race, or ethnicity. For a discussion of safety data in male subjects, the reader is referred to the following section, 8.2.8

8.2.8. Specific Safety Studies/Clinical Trials

There were no males included in trial SEC-WH-301; however, males are proposed to be included in the indication for the treatment of trichomoniasis. The safety of secnidazole in males was supported by clinical data in the initial NDA consisting of two safety/PK studies with secnidazole that included healthy male volunteers. There were no serious adverse events reported.

In study SYM-1219-104, 8 healthy males received doses of secnidazole ranging from 4 grams to 6 grams. One male subject who received 6 grams of secnidazole reported an adverse event of upper respiratory infection which was mild, not related to the treatment, and resolved.

In study SYM-1219-105, 30 healthy males received doses of secnidazole ranging from 2 grams to 6 grams. The observed secnidazole plasma concentrations and exposures in males appeared to be slightly lower than those observed in females. In male subjects, after a 2 gram dose of secnidazole, cough (not related) occurred in 2 subjects. Diarrhea (treatment related), hematoma (not related), and pyrexia (not related) were reported in 1 subject each. In the 6 gram dose group of secnidazole, cough (not related), oropharyngeal pain (not related), presyncope (not related), viral infection (not related), and vomiting (treatment related) were reported in 1 subject each. No SAEs or deaths were reported. All AEs were mild in intensity and

resolved.

Furthermore, in section 8.1.4, four studies were cited from the scientific literature regarding the use of secnidazole in male patients for the treatment of trichomoniasis. In the four clinical studies, a total of 211 males received secnidazole. In three out of four studies, patients received a single, oral 2 gram dose of secnidazole. In the fourth study, two dosing regimens were evaluated: a single, oral 2 gram dose or a 2 gram dose given on Days 1, 3, and 5.

In the publication of one controlled study which enrolled only male subjects, adverse events were not discussed (Özbilgin *et al.*, 1994). There were three uncontrolled studies that enrolled both male and female subjects and the following adverse events were reported in each study; Study 1: nausea in 4% of the patients; Study 2: nausea/gastralgia in 16 patients (8.9%), and gastric burning in 2 patients (1.1%); Study 3: dyspeptic disorders in 4 patients (0.5%) and metallic taste in the mouth (number of patients not specified). This is generally consistent with the adverse events reported following treatment with SOLOSEC for bacterial vaginosis in the current labeling. It is not anticipated that the safety profile of secnidazole would significantly differ between males and females.

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new information regarding carcinogenesis and mutagenesis was submitted.

Human Reproduction and Pregnancy

No new information regarding human reproduction and pregnancy were submitted. Trial SEC-WH-301 excluded women who were pregnant, attempting to conceive, or lactating. No positive pregnancy tests were reported in trial SEC-WH-301.

Pediatrics and Assessment of Effects on Growth

Though trichomoniasis can occur in adolescent patients, only two adolescent females were enrolled into the study, and both were enrolled in the placebo arm. (b) (4)

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

With a single dose, no withdrawal or rebound effects have been observed; no such effects are anticipated. No known overdoses occurred in the trichomoniasis trial. As patients were

provided with a single unit dose that was typically administered in the clinic, there was minimal potential for abuse or misdose.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

During the course of the review of this sNDA, a new safety signal regarding the potential for drug-drug interactions between secnidazole and ethanol was reviewed and the product labeling was revised. Secnidazole is a nitroimidazole antimicrobial. Other nitroimidazoles, such as metronidazole, tinidazole, and benznidazole have been associated with disulfiram-like reactions in patients concomitantly exposed to alcohol and the PIs for these other nitroimidazoles include information regarding drug interactions with alcohol.

The Office of Pharmacovigilance and Epidemiology (OPE) performed a review of case reports from the FDA Adverse Event Reporting System (FAERS) database (Dr. Timothy Jancel, February 20, 2019) that identified adverse events associated with secnidazole after ingestion of alcohol (ethanol). The emerging safety signal became a tracked safety issue (TSI) and Dr. Jancel conducted further analysis to evaluate these potential adverse events (October 19, 2020). Seventeen FAERS cases supported a possible causal association between the use of secnidazole and alcohol intolerance (nausea, vomiting, diarrhea, abdominal pain, dizziness, and headache). One additional supportive case was identified by the Applicant to make a total of 18 cases that support a possible causal association. Four of the 18 cases were categorized asserious. Two of the four cases resulted in treatment in the emergency room and the other two cases described repetitive episodes of vomiting. No fatal outcomes were reported.

On February 26, 2021, the Agency requested revisions to the prescribing information that were ultimately approved on June 14, 2021 as labeling supplement 15.

The following changes to product labeling were agreed:

> (1) The **DOSAGE AND ADMINISTRATION (2)** section, **Instructions for the Preparation and Administration of SOLOSEC (2.2)** subsection**,** was updated to include the following text: *Avoid consumption of alcoholic beverages and preparations containing ethanol or propylene glycol during treatment with SOLOSEC and for at least 2 days after completing therapy.*
>
> (2) The **ADVERSE REACTIONS (6)** section, **Postmarketing Experience (6.2)** subsection was revised to state that *Nausea, vomiting, diarrhea, abdominal pain, dizziness, and headache have been reported when SOLOSEC was taken concomitantly with alcohol.*
>
> (3) Under the **DRUG INTERACTIONS (7)** section, an **Alcohol (7.2)** subsection was added to state *Alcoholic beverages and preparations containing ethanol or propylene glycol should be avoided during SOLOSEC therapy and for 2 days after treatment is stopped*.

Nausea, vomiting, diarrhea, abdominal pain, dizziness, and headache have been reported when SOLOSEC was taken concomitantly with alcohol.

(4) In the **CLINICAL PHARMACOLOGY (12)** section, **Pharmacokinetics (12.3)** subsection, under the Drug Interaction Studies subheading, *Ethanol Metabolism*, was updated to state that *However, postmarketing observations of adverse reactions of nausea, vomiting, diarrhea, abdominal pain, dizziness, and headache with concomitant use of SOLOSEC and alcohol have been reported.*

(5) In the **PATIENT COUNSELING INFORMATION (17)** section, the Alcohol subheading was added to state *Advise patients to avoid consumption of alcoholic beverages and preparations containing ethanol or propylene glycol during SOLOSEC therapy and for 2 days afterward because nausea, vomiting, diarrhea, abdominal pain, dizziness, and headache may occur.*

Additionally, the **PATIENT INFORMATION** and **INSTRUCTIONS FOR USE** were updated to be consistent with the PI.

Expectations on Safety in the Postmarket Setting

No additional safety issues have been identified in the course of this review. Routine postmarket safety surveillance is recommended.

8.2.10. Integrated Assessment of Safety

The clinical safety profile of SOLOSEC 2 g has been characterized in 147 patients with trichomoniasis (74 patients received SOLOSEC and 73 patients received placebo) in one Phase 3 clinical trial (SEC-WH-301). SOLOSEC 2 g in patients with trichomoniasis was well tolerated and there were no reported deaths, SAEs or severe TEAEs. The overall incidence rate of TEAEs was 14.9% in the SOLOSEC 2 gram group compared to 21.9% in the placebo group. The most frequently reported TEAE in the SOLOSEC group compared to placebo was vulvovaginal candidiasis (2.7%). All TEAEs in the SOLOSEC group were of mild intensity. One patient discontinued from the study due to a TEAE (mild nausea and productive cough) relating to intolerance to the taste of the medication in applesauce.

The safety profile of secnidazole in the trichomoniasis trial appears to be similar to the findings from the previous bacterial vaginosis studies. The safety of the drug for use in male patients with trichomoniasis is supported by safety studies in healthy male volunteers and clinical experience in the scientific literature.

In summary, this randomized, multicenter, double-blinded, placebo-controlled, delayed-treatment trial for trichomoniasis was performed in a population of females with trichomoniasis. The trial data were analyzed independently from the existing safety database for the bacterial vaginosis indication, but are complimentary since a single 2g dose of secnidazole was used for both indications. A comprehensive review of safety shows

that SOLOSEC was well tolerated and has an acceptable safety profile as a treatment for adults, diagnosed with trichomoniasis, and per CDC guidelines (Workowski, 2015), for partners of infected patients in order to prevent reinfection.

8.3. Statistical Issues

There were no major statistical issues. The study was conducted in women aged 15 to 65 years old and only one subject in the SOLOSEC group was younger than 20 years old and one older than 60 years. The number of adolescent subjects and geriatric subjects was not large enough to provide efficacy data for adolescent and geriatric subjects. Most subjects were Black or American Africans. Only a few subjects were from other races. But there is no evidence to suggest that the drug may work differently among different races.

The evidence of efficacy in males was supported by studies in the literature and an analysis using an untreated control from a separate study (i.e., an external control). Though patient-level data from a randomized controlled trial was not provided, the results in males showed a large effect and were supported by the strong efficacy seen in women from the randomized controlled trial.

8.4. Conclusions and Recommendations

The efficacy of SOLOSEC was demonstrated in an adequate and well-controlled trial (SEC-WH-301). A single 2 g dose of SOLOSEC was shown to be superior to placebo in terms of microbiological cure at 6-12 days after treatment with a treatment difference of 90.7% and a 95% confidence interval of 80.7%, 96.5%. Additionally, microbiological cure with symptom resolution at TOC was also significantly higher in the SOLOSEC group, compared to the placebo.

A single oral 2 g secnidazole dose was also assessed in four open-label trials in males published in the scientific literature that reported cure rates ranging from 91.7% (165/180) to 100% (30/30) at time points ranging from 2 to 20 days (n=437, 211 males and 226 females). Of note, the rate of spontaneous resolution in men was reported to be 36% (5/14) based the natural history of trichomoniasis from the scientific literature.

Secnidazole was generally well tolerated in patients with trichomoniasis. There were no reported deaths, SAEs or severe TEAEs. The overall rate of AEs was higher in the placebo arm than the SOLOSEC-treated arm. No new safety signals were identified based upon the trichomoniasis treatment trial. The trial data support and extend the prior safety database for the bacterial vaginosis indication.

9 Advisory Committee Meeting and Other External Consultations

Not applicable. An Advisory Committee was not convened and there were no external consultations.

10 Pediatrics

The Applicant requested a partial waiver for all males and in females ages birth to <12 years because studies would be highly impractical. This request was reviewed and discussed during the Pediatric Review Committee (PeRC) meeting on May 4, 2021. PeRC agreed to granting the partial waiver for all males and females <12 years of age.

The study population of the pivotal Phase 3 clinical trial (SEC-WH-301) included post-menarchal adolescent girls ≥ 12 years of age. However, the study enrolled only 2 adolescents and both were assigned to the placebo arm. (b) (4)

The Applicant was issued PMR 3249-1 with the initial NDA approval to "conduct an open label, multicenter, safety study of SOLOSEC (secnidazole) oral granules in healthy postmenarchal adolescent females ages 12 years to less than 18 years of age with bacterial vaginosis." In response, the Applicant submitted clinical study SYM-1219-401, "A multi-center, open-label study to evaluate the safety of a single oral dose of SOLOSEC (secnidazole) 2g oral granules in 40 post menarchal adolescent women with bacterial vaginosis" on March 29, 2021. To address the PREA requirement for a new trichomonas treatment indication, a PMR 4113-1 will be issued for an assessment in adolescent females and males aged 12 years to less than 18 years (see Section 13 of this review). (b) (4)

11 Labeling Recommendations

11.1. Prescription Drug Labeling

In addition to the post-marketing safety changes described in Section 8.2.10 of this review, the following significant labeling changes were made to the proposed labeling:

Section	Applicant Proposed Labeling	Labeling Modifications
HIGHLIGHTS	• For recent major changes section, only listed the new indications and usage of trichomoniasis.	• In addition to the Applicant's proposal, added recommended dosage for trichomoniasis and instructions for preparation and administration of SOLOSEC in the recent major changes.
INDICATIONS AND USAGE	• (b) (4) indication for treatment of trichomoniasis (1.2).	• (b) (4) the indication for treatment of trichomoniasis (b) (4) adults and partners of infected patients to prevent reinfection (1.2).
Clinical Reviewer comment: (b) (4)		
DOSAGE AND ADMINISTRATION	• Added SOLOSEC dosage information for trichomoniasis (2.2).	• Added information about concomitant use of alcoholic beverages with SOLOSEC, per labeling supplement 15 (2.3), which was approved during the course of the review.
CONTRAINDICATIONS		• Removed (b) (4) "
Clinical Reviewer comment: (b) (4)		
WARNINGS AND PRECAUTIONS	• Updated vulvovaginal candidiasis warning with information from trichomoniasis clinical trial (5.1).	
ADVERSE REACTIONS	• Added clinical trial information for trichomoniasis (6.1). (b) (4)	• Refer to trial SEC-WH-301 as "Trial 4." (b) (4)

	(b) (4)	(b) (4) • Added adverse reactions associated with concomitant use of alcoholic beverages, per labeling supplement 15 (6.2).
Clinical Reviewer comment: (b) (4)		
USE IN SPECIFIC POPULATIONS	(b) (4)	
Clinical Reviewer comment: (b) (4)		
CLINICAL PHARMACOLOGY	• Added mechanisms of action of SOLOSEC for trichomoniasis treatment, anti-protozoal activity, and cross-resistance to metronidazole (12.4).	• Made edits based on the information reviewed and current Division practice (12.4).
CLINICAL STUDIES	• Added clinical trial information to support the use of SOLOSEC in adults for the treatment of trichomoniasis (14.2). • Added published literature to support the use of SOLOSEC in male adults for the treatment of trichomoniasis (14.2).	(b) (4)
Clinical Reviewer comment: (b) (4)		

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13 Postmarketing Requirements and Commitment

The following PMR was proposed to address PREA requirements, and was accepted by the Applicant on June 29, 2021:

4113-1: Deferred pediatric assessment under PREA for SOLOSEC (secnidazole) oral granules for the treatment of trichomoniasis in adolescent females and males ages 12 years to less than 18 years of age. In your submission, provide a rationale for extrapolating efficacy from clinical trials of SOLOSEC for the treatment of trichomoniasis in adults and safety data from the completed clinical study in adolescent women for the treatment of bacterial vaginosis: SYM-1219-401, "A multi-center, open-label study to evaluate the safety of a single oral dose of SOLOSEC (secnidazole) 2-gram oral granules in 40 post-menarchal adolescent women with bacterial vaginosis."

Final Report Submission: 08/30/2021

For more information, please see Section 10 of this review.

14 Office Director Comments

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

15 Appendices

15.1. References

1. Benazet F and Guillaume L. Amoebecide and trichomonacide activities of secnidazole in the laboratory. Bulletin de la Societe de Pathologie Exotique et de Ses Filiales. 1976 Jul 1;69(4):309-19.

2. Chapman A, Cammack R, Linstead D, and Lloyd D. The generation of metronidazole radicals in hydrogenosomes isolated from *Trichomonas vaginalis*. Microbiology. 1985 Sep 1;131(9):2141-4.

3. Cudmore SL, Delgaty KL, Hayward-McClelland SF, Petrin DP, and Garber GE. Treatment of infections caused by metronidazole-resistant *Trichomonas vaginalis*. Clinical microbiology reviews. 2004 Oct 1;17(4):783-93.

4. Dyudyun AD, Polyon NM, Gorbuntsov VV. Secnidazole in complex treatment of patients with urogenital trichomoniasis. Dermatovenerology Cosmetology Sexopathology. 2016;1(4): 287-292.

5. Edwards DI. Mechanisms of selective toxicity of metronidazole and other nitroimidazole drugs. Sexually Transmitted Infections. 1980 Oct 1;56(5):285-90.

6. Ghosh AP, Aycock C, and Schwebke JR. In vitro study of the susceptibility of clinical isolates of *Trichomonas vaginalis* to metronidazole and secnidazole. Antimicrobial Agents and Chemotherapy. 2018 Apr 1: 62 (4) e02329-17.

7. Ghosh A and Schwebke J. 2017. Study Report Schwebke Research Laboratory: In vitro study of secnidazole and metronidazole against vaginal isolates of *Trichomonas vaginalis.*

8. Gillis JC and Wiseman LR. Secnidazole. Review of its antimicrobial activity, pharmacokinetic properties and therapeutic use in the management of protozoal infections and bacterial vaginosis. Drugs. 1996 Apr;51(4):621-38.

9. Ginocchio CC, Chapin K, Smith JS, et al. Prevalence of Trichomonas vaginalis and coinfection with Chlamydia trachomatis and Neisseria gonorrhoeae in the United States as determined by the Aptima *Trichomonas vaginalis* nucleic acid amplification assay. Journal of Clinical Microbiololgy 2012 Aug;50(8):2601–8.

10. Grodstein F, Goldman MB, Cramer DW. Relation of tubal infertility to history of sexually transmitted diseases. American Journal of Epidemiology. 1993 Mar 1;137(5):577.

11. Howes Jr HL, Lynch JE, and Kivlin JL. Tinidazole, a new antiprotozoal agent: Effect on *Trichomonas* and other protozoa. Antimicrobial Agents and Chemotherapy. 1970. 261-266.

12. Kissinger P, Adamski A. Trichomoniasis and HIV interactions: a review. Sexually Transmitted Infections. 2013 Sep;89(6):426–3.

13. Kissinger P, Muzny CA, Mena LA, Lillis RA, Schwebke JR, Beauchamps L, et al. Single-dose versus 7-day-dose metronidazole for the treatment of trichomoniasis in women: an open-label, randomised controlled trial. Lancet Infect Disease. 2018 Nov;18(11):1251–9.

14. Knox RJ, Knight RC, Edwards DI. Misonidazole-induced thymidine release from DNA. Biochemical Pharmacology. 1981 Jul 15;30(14):1925-9.

15. Krieger JN, Verdon M, Siegel N, Holmes KK. Natural history of urogenital trichomoniasis in men. Journal of Urology. 1993 Jun;149(6):1455-8.

16. Lamp KC, Freeman CD, Klutman NE, and Lacy MK. Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. Clinical Pharmacokinetics. 1999 May;36(5):353-73.

17. Leitsch D, Kolarich D, Binder M, Stadlmann J, Altmann F, and Duchêne M. *Trichomonas vaginalis*: metronidazole and other nitroimidazole drugs are reduced by the flavin enzyme thioredoxin reductase and disrupt the cellular redox system. Implications for nitroimidazole toxicity and resistance. Molecular Microbiology. 2009 Apr;72(2):518-36.

18. Lossick JG, Miklos Müller BL, and Gorrell TE. In vitro drug susceptibility and doses of metronidazole required for cure in cases of refractory vaginal trichomoniasis. Journal of Infectious Diseases. 1986 May 1;153(5):948-55.

19. Mandel M and Honigberg BM. Isolation and characterization of deoxyribonucleic acid of two species of *Trichomonas Donne*. The Journal of Protozoology. 1964 Feb;11(1):114-6.

20. Meites, E. Trichimoniasis the “neglected” sexually transmitted disease. Infectious Disease Clinics of North America. 2013 Dec; 27(4): 755–764.

21. Moodley P, Wilkinson D, Connolly C, et al. *Trichomonas vaginalis* is associated with pelvic inflammatory disease in women infected with human immunodeficiency virus. Clinical Infectious Diseases. 2002 Feb 15;34(4):519–22.

22. Moreno SN, Mason RP, Muniz RP, Cruz FS, and Docampo R. Generation of free radicals from metronidazole and other nitroimidazoles by *Trichomonas foetus*. Journal of

Biological Chemistry. 1983 Apr 10;258(7):4051-4.

23. Özbilgin A, Özbel Y, Alkan MZ et al. Trichomoniasis in non-gonococcic urethritis among male patients. Journal of the Egyptian Society of Parasitology. 1994; 24(3):621-625.

24. Peterman TA, Tian LH, Metcalf CA, et al. High incidence of new sexually transmitted infections in the year following a sexually transmitted infection: a case for rescreening. Annals of Internal Medicine. 2006 Oct 17;145(8):564–72

25. Peterman TA, Tian LH, Metcalf CA, et al. Persistent, undetected *Trichomonas vaginalis* infections? Clinical Infectious Disease. 2009 Jan 15;48(2):259–60

26. Ray DK, Tendulkar JS, Shrivastava VB, Datta AK, and Nagarajan K. A metronidazole-resistant strain of *Trichomonas vaginalis* and its sensitivity to Go 10213. Journal of Antimicrobial Chemotherapy. 1984 Oct 1;14(4):423-6.

27. Reeves RE, Lushbaugh TS, and Montalvo FE. Characterization of deoxyribonucleic acid of Entamoeba histolytica by cesium chloride density centrifugation. The Journal of Parasitology. 1971 Oct 1:939-44.

28. Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. Sexually Transmitted Disease. 2013 Mar;40(3):187–93

29. Schwebke JR and Barrientes FJ. Prevalence of *Trichomonas vaginalis* isolates with resistance to metronidazole and tinidazole. Antimicrobial Agents and Chemotherapy. 2006 Dec 1;50(12):4209-10.

30. Sena AC, Miller WC, Hobbs MM, et al. *Trichomonas vaginalis* infection in male sexual partners: implications for diagnosis, treatment, and prevention. Clinical Infectious Disease. 2007 Jan 1;44(1):13–22

31. Siboulet A, Catalan F, Videau D, Niel G. Urogenital trichomoniasis. Trials with a long half-life imidazole: secnidazole. Médecine et Maladies Infectectieuses. 1977;7(9):400-409.

32. Sigma Product Information: https://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Sigma/Product_Information_Sheet/d4522pis.pdf

33. Silver BJ, Guy RJ, Kaldor JM, Jamil MS, Rumbold AR. *Trichomonas vaginalis* as a cause of perinatal morbidity: A systematic review and meta-analysis. Sexually Transmitted Diseases. 2014 Jun;41(6):369.

34. Sutton M, Sternberg M, Koumans EH, et al. The prevalence of *Trichomonas vaginalis*

infection among reproductive-age women in the United States, 2001-2004. Clinical Infectious Diseases. 2007 Nov 15;45(10):1319–26

35. Videau D, Niel G, Siboulet A, and Catalan F. Secnidazole. A 5-nitroimidazole derivative with a long half-life. British Journal of Venereal Diseases. 1978 Apr 1;54(2):77-80.

36. Wiese W, Patel SR, Patel SC, Ohl CA, and Estrada CA. A meta-analysis of the Papanicolaou smear and wet mount for the diagnosis of vaginal trichomoniasis. *The American Journal of Medicine.* 2000, 108(4):301-8.

37. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. Morbidity and Mortality Weekly Report. 2015 Jun 5;64(RR-03):1-137.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): A Phase 3, Multi-center, Prospective, Randomized, Placebo-Controlled, Delayed Treatment, Double-Blind Study to Evaluate the Effectiveness and Safety of a Single Oral Dose of SOLOSEC® Granules Containing 2 grams of Secnidazole for the Treatment of Trichomoniasis (Trial SEC-WH-301)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 75		
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)

15.3. Clinical Microbiology

15.3.1. Nonclinical studies

15.3.1.1. Mechanism of Action

The mechanism of action of secnidazole against *T. vaginalis* is similar to other nitroimidazoles such as metronidazole or tinidazole (Gillis and Wiseman, 1996; Lamp *et al*., 1999). For example, generation of free radicals was reported after incubation of trophozoites of *Trichomonas foetis*, a cattle pathogen, with secnidazole or metronidazole (Moreno *et al*., 1983). Similar observations were reported after incubation of isolated *T. vaginalis* hydrogenosomes with metronidazole (Chapman *et al*., 1985).

Some investigators (Cudmore *et al*., 2004; Edwards, 1980; Gillis and Wiseman, 1996) suggest that the nitro radical anions target sections of DNA rich in adenine and thymine (AT) leading to the release of certain thymine and thymidine phosphates and cellular cytotoxicity. Some of the protozoans and bacteria have high AT content. For example, *T. vaginalis* and *Entamoeba histolytica,* have AT content of 71% and 62-78%, respectively (Mandel *et al*., 1964; Reeves *et al*., 1971). *Bacteroides species, Clostridium perfringens,* and *Escherichia coli* have AT content of about 59-61%, 71%, and 50%, respectively (Edwards, 1980; Knox et al., 1981). Note that calf thymus has an AT content of 60% (*Knox et al., 1981*; Sigma Product Information).

Leitsch *et al*. (2009) reported the formation of covalent adducts with proteins and thiols after reduction of metronidazole, by flavin enzyme thioredoxin reductase (a nitroreductase), to reactive intermediates leading to depletion of thiols that are important in conferring defense. A metronidazole-resistant cell line of *T. vaginalis*, generated in vitro, displayed only minimal thioredoxin reductase activity that was associated with the lack of its co-factor, flavin adenine dinucleotide (FAD); FAD is important for maintaining hemoglobin in its functional reduced state. Radical interaction with additional intracellular targets in *T. vaginalis*, such as hydrogenosomal iron- sulfur proteins, may also result in a breakdown of cellular metabolism and contribute to the rapid lethal effect on the parasite. Secnidazole was not tested.

Overall, the studies suggest that secnidazole, like other nitroimidazoles, such as metronidazole and tinidazole, enters *Trichomonas* and bacterial cells where the nitro group is reduced to form radical anions and other toxic intermediates leading to DNA damage of susceptible isolates of *T. vaginalis* in addition to Gram positive and Gram negative bacteria.

15.3.1.2. In vitro activity

Few studies reported the in vitro activity of secnidazole against laboratory strains and clinical isolates of *T. vaginalis*; one of the studies was conducted by the Applicant and included testing of 100 clinical isolates. The experimental design for different studies varied. The published studies suggest that secnidazole MLCs and minimum inhibitory concentrations (MICs) varied between 0.5-250 µg/mL and 0.4 and 6 µg/mL, respectively, and that the activity appears to be similar to metronidazole or tinidazole (Table 15-1).

Table 15-1: Summary of published studies supporting the in vitro activity of secnidazole against *T. vaginalis* clinical isolates/strains

Study Summary (Reference)	**MIC (µg/mL)**	**MLC (µg/mL)**
The MIC and MLC (MCC) were determined for 11 isolates/strains from Paris; one was a reference standard maintained in the laboratory for 20 years and 10 were fresh clinical isolates. Metronidazole and tinidazole were included as comparators. Testing was performed using Diamond medium. Other details of the method including definitions of MIC and MLC were not provided. From the cross-reference cited (Howes *et al*., 1970, it appears that for MIC and MLC determination, 4-10 × 10^4 and 5-20 X 10^5 trichomonads were incubated for 48 h. The MIC was defined as the lowest concentration (µg/mL) which produced a ratio ≤0.5; the MLC was defined as the lowest concentration in which no viable organisms (<1.25 X 10^3 /ml) were detected. Ratios of cidal activity to static activity were calculated by dividing the MLC by the MIC. The mean metronidazole and tinidazole MICs were 0.60 µg/mL and 1.125 µg/mL, respectively; the mean metronidazole and tinidazole MLCs were 0.42 µg/mL and 0.75 µg/mL, respectively. (Videau *et al*., 1978)	Mean: 0.7 Range: 0.53-0.86 (n=11)	Mean: 0.63 (Range: 0.44-0.81) (n=11)
Details of the method were not available for review. Metronidazole MLC was 6 µg/mL. (Benazet and Guillaume, 1976)	Not determined	6 (Not specified)
Approximately, 5 x 10^5 trichomonads of 3 isolates (CG1, CG2, SARA) from Bombay, India and one strain (MRS, metronidazole resistant strain) from Sandoz Ltd, Switzerland were incubated with different concentrations of the drug for 72 h in CPLM medium at 37°C in aerobic environment and MIC determined. The criteria for determining MICs were not specified. The secnidazole, metronidazole and tinidazole MICs for the MRS strain were 250, 200 and 150 µg/mL, respectively. The MIC for all 3 drugs for the 3 isolates from India were 10 µg/mL. (Ray *et al*., 1984)	Mean: 70 Range: 10-250 (n=4)	Not determined
Abbreviations: MIC, minimum inhibitory concentration; MLC, minimum lethal concentration; h, hours; MCC, minimum cidal concentration		

Source: Prepared by the reviewer based on information in the NDA.

The Applicant measured the in vitro activity of secnidazole against 100 clinical isolates of *T. vaginalis*, obtained between 2015-2016 (Ghosh *et al*., 2017; 2018). Testing was performed in a CLIA (Clinical Laboratory Improvement Amendments) certified laboratory (Dr. Schwebke's Research Laboratory, The University of Alabama at Birmingham). Quality control strains tested included CDC 252 (resistant), CDC 520 (sensitive) and 009 (an archived strain). Based on a previous study (Schwebke *et al*., 2006), the authors stated that these strains exhibited *in vitro*

resistance to both metronidazole and tinidazole. For resistance criteria, the authors refer to a study by Lossick *et al*. (1986).[1]

Briefly, parasite suspension of 10^4 viable trichomonads (based on trypan blue staining) in Diamond's growth media was incubated under aerobic conditions in triplicate with different concentrations of secnidazole (0.2-400 µg/mL), metronidazole (0.2-400 µg/mL) or clindamycin (0.03- 32 µg/mL) for 48 hours. The motility of trichomonads was assessed microscopically using a 100x objective and the MLC was defined as the lowest drug concentration that resulted in no motility; all trichomonads in control cultures with DMSO were 3+ based on the following scoring key:

0	=	No motile trichomonads
1+	=	10% or less motile trichomonads
2+	=	20%-50% motile trichomonads
3+	=	50%-100% motile trichomonads
4+	=	Motile and **reproductive** trichomonads **(anaerobic only)**

The activity of secnidazole against the quality control strains was within acceptable limits.

The results show that the secnidazole MLC_{90} (MLCs for 90% of the isolates) and mean values were 12.5 µg/mL and 5.9 µg/mL, respectively. These values were about 1-dilution lower than that of metronidazole; however, the secnidazole median value was 4-fold lower than metronidazole (Table 15-2).

Table 15-2: In Vitro Sensitivity of clinical isolates and control strains to secnidazole, metronidazole and clindamycin

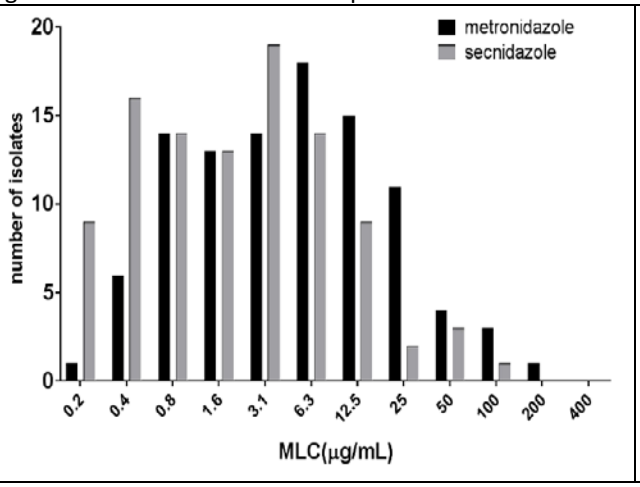
Drug	Clinical Isolates - MLC (µg/mL) (n=100)				Three Quality Control Strains - MLC (µg/mL)		
	Range	MLC_{90}	Mean	Median	009[2]	CDC 252[3]	CDC 520[4]
Secnidazole	0.4 - 200	12.5	5.9±13.2	1.6	100	200	1.6
Metronidazole	1.6- 400	25.0	13.5± 26.9	6.3	400	400	3.1
Clindamycin[1]	No sensitivity seen at <32 µg/mL. Higher concentrations not tested						

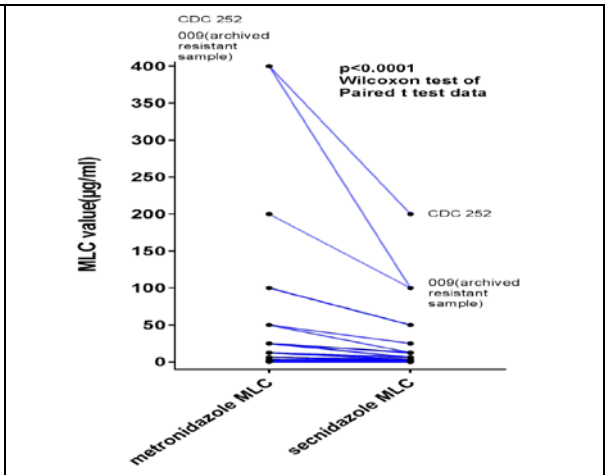
[1]Clindamycin was used as a negative control. No sensitivity to clindamycin at a concentration of <32 µg/mL for all isolates; higher concentrations not tested.
[2]Archived sample
[3]Resistant control strain provided by the CDC; criteria for resistance not specified.
[4]Sensitive control strain provided by the CDC; criteria for sensitivity not specified.
Abbreviation: MLC, minimum lethal concentration
Source: Prepared by reviewer based on information in the NDA - study report (Ghosh *et al*., 2017; 2018).

There was a strong correlation between secnidazole and metronidazole MLCs *(r* = 0.9496; *P* < 0.0001; Figure 15-1).

[1] Note that the resistance levels based on aerobic MLCs were defined as low, moderate or high for the MLC of 50 to 100 µg/mL, 200 µg/mL, and >400 µg/mL, respectively.

Figure 15-1: Distribution and comparison of secnidazole and metronidazole MLCs for 100 clinical isolates.





The MLCs for metronidazole were consistently higher than for those for secnidazole (P < 0.0001, Wilcoxon signed-rank test). The MLCs for metronidazole were strongly correlated with the MLCs for secnidazole *(r* = 0.9496; *P* < 0.0001).

Sensitivity to metronidazole and secnidazole was defined as MLCs of <25 µg/mL, low-level resistance as MLCs of 50 to 100 µg/mL, moderate-level resistance as MLCs of 200 µg/mL, and high-level resistance as MLCs of >400 µg/mL.
Abbreviations: MLC, minimum lethal concentration

Source: NDA - Ghosh *et al*., 2017; 2018

Reviewer comments

The methods for measurement of in vitro sensitivity of T. vaginalis are not standardized and are limited to testing in research laboratories. Overall, the studies show that the secnidazole MLCs and MICs, under aerobic experimental conditions, ranged between 0.5-250 µg/mL. The MLCs are likely to be lower under anaerobic conditions. The isolates with increased metronidazole MLCs had increased secnidazole MLCs. Overall, the activity of secnidazole is similar to metronidazole and tinidazole.

The Applicant states that several clinical isolates that were resistant to metronidazole were sensitive to lower concentrations of secnidazole. The criteria used for characterizing resistance should be interpreted with caution as there are no susceptibility testing interpretive criteria for metronidazole, secnidazole, or tinidazole against Trichomonas.

15.3.1.3. In vivo activity

The activity of secnidazole was reported in mice infected subcutaneously or intraperitoneally with *T. vaginalis*; while the activity was based on absence of parasites, the experimental design in different studies varied (for details see Table 15-3). Overall, the results show that multiple doses of secnidazole or metronidazole were more effective than single doses in clearing the parasites. Additionally, secnidazole was more effective when administered prior to infection compared to metronidazole. One study (Ray *et al*. , 1984) reported the activity of secnidazole to

be similar to metronidazole or tinidazole under the experimental conditions tested. For details see Table 15-3.

Table 15-3: Summary of studies supporting the activity of secnidazole in subcutaneous or peritonitis murine models of *T. vaginalis*.

<table>
<tr><th>Reference</th><th>Study Summary</th></tr>
<tr><td colspan="2">Subcutaneous abscess model</td></tr>
<tr><td>Benazet and Guillaume, 1976</td><td>Mice were infected SC with a 24-h culture of T. vaginalis (5 x 10^5 parasite cells/mouse). Animals were treated orally with secnidazole or metronidazole, daily for 5 days. It appears that the treatment was initiated PI, however, the time of initiation of treatment was not specified. Autopsy was conducted 7 days PI and the dose of drug required to deparasitize 50% of the test animals (DC_{50}) was calculated. The tissues processed for presence of parasites were not specified. The results in Table A show that the of activity secnidazole and metronidazole was similar (DC_{50} values of 5 and 6 mg/kg, respectively).

Table A: Effect secnidazole and metronidazole in mice infected with T. vaginalis
<table>
<tr><th rowspan="2">Dose (mg/kg, by mouth per day)</th><th colspan="2">Ratio of activity[a]</th></tr>
<tr><th>Secnidazole</th><th>Metronidazole</th></tr>
<tr><td>25</td><td>12/12</td><td>12/12</td></tr>
<tr><td>10</td><td>11/12</td><td>11/12</td></tr>
<tr><td>5</td><td>6/12</td><td>4/12</td></tr>
<tr><td>2.5</td><td>2/12</td><td>0/12</td></tr>
<tr><td>0</td><td>0/12</td><td>0/12</td></tr>
<tr><td>DC_{50} (mg/kg, by mouth per day)</td><td>5</td><td>6</td></tr>
</table>
[a] Ratio of activity = Number of animals disparasitized/Total number of animals at dose considered

In another experiment, the effect of single dose of secnidazole administered at 6 or 16 h prior to infection, was measured. The results show that secnidazole was 2-times more active than metronidazole when administered 6 h prior to infection (DC_{50} values of 150 and 300 mg/kg, respectively). However, when administered at 16 hours prior to infection, secnidazole DC_{50} value was 2-times higher (300 mg/kg); metronidazole was not active up to a dose of 50 mg/kg (Table B). This may be due to a longer half-life of secnidazole compared to metronidazole.

Table B: Activity of a single dose of secnidazole and metronidazole administered 6 or 16 hours prior to infection with T. vaginalis
<table>
<tr><th rowspan="3">Dose (mg/kg, by mouth per day)</th><th colspan="4">Ratio of activity[a]</th></tr>
<tr><th colspan="2">Administration 6 h prior to infection</th><th colspan="2">Administration 16 h prior to infection</th></tr>
<tr><th>Secnidazole</th><th>Metronidazole</th><th>Secnidazole</th><th>Metronidazole</th></tr>
<tr><td>500</td><td></td><td></td><td>4/6</td><td>0/6</td></tr>
<tr><td>300</td><td>6/6</td><td>3/6</td><td>3/6</td><td>0/6</td></tr>
<tr><td>175</td><td>4/6</td><td>0/6</td><td>2/6</td><td>0/6</td></tr>
<tr><td>100</td><td>1/6</td><td>0/6</td><td>0/6</td><td>0/6</td></tr>
<tr><td>0</td><td>0/0</td><td>0/0</td><td>0/6</td><td>0/6</td></tr>
<tr><td>DC_{50} (mg/kg, by mouth per day)</td><td>150</td><td>300</td><td>300</td><td>Inactive at 500</td></tr>
</table>
[a] Ratio of activity = Number of animals disparasitized/Total number of animals at dose considered</td></tr>
<tr><td>Ray et al., 1984</td><td>Briefly, Swiss mice were infected SC, into the nuchal region with 3 to 4 x 10^6 parasites of the MRS strain of T. vaginalis. Treatment with single or multiple doses of secnidazole and other nitroimidazoles was initiated 24 h prior to infection, by gavage. Animals were euthanized on Day 5 and the neck region exposed. The scrapings of the infected region were examined microscopically for the presence of motile parasites. If negative, mice were confirmed by subculture of the scrapings for 24 h. The results show that the</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study Summary</th></tr>
<tr><td></td><td>secnidazole 100% curative dose after treatment with single (80 mg/kg) or multiple doses (20 mg/kg/day for 4 days) were 2.5-fold and 2 to 3-fold lower than tinidazole and metronidazole, respectively (Table C).

Table C: Comparative activity of single (x1) and multiple (x4) dosage regimens of secnidazole, metronidazole, and tinidazole against the MRS* of T. vaginalis
<table>
<tr><th rowspan="2">Dosage Frequency</th><th colspan="3">CD100[b] for Test Agent at Dosing Frequency</th></tr>
<tr><th>Secnidazole</th><th>Metronidazole</th><th>Tinidazole</th></tr>
<tr><td>x 1</td><td>80</td><td>200</td><td>200</td></tr>
<tr><td>x 4</td><td>20</td><td>60</td><td>40</td></tr>
</table>
[a] T. vaginalis MRS in vitro MIC values: secnidazole, 250 µg/mL; metronidazole, 200 µg/mL; tinidazole, 150 µg/mL
[b] CD_{100}, curative dose for 100% of mice</td></tr>
<tr><td colspan="2">Peritonitis model</td></tr>
<tr><td>Benazet and Guillaume, 1976</td><td>Mice were infected IP with a 24-h culture of T. vaginalis (5 x 10^5 parasites/mouse) and treated orally with secnidazole or metronidazole daily for 4 days. Autopsy was conducted 7 days PI and the DC_{50} value calculated. The tissues processed for the presence of parasites were not specified. The results in Table D show that the activity of secnidazole and metronidazole was similar (DC_{50} values of 9 and 10 mg/kg, respectively).

Table D: Effect on peritonitis of the mouse due to T. vaginalis
<table>
<tr><th rowspan="2">Dose (mg/kg, by mouth per day)</th><th colspan="2">Ratio of activity*</th></tr>
<tr><th>Secnidazole</th><th>Metronidazole</th></tr>
<tr><td>25</td><td>8/8</td><td>8/8</td></tr>
<tr><td>10</td><td>4/8</td><td>4/8</td></tr>
<tr><td>5</td><td>2/8</td><td>0/8</td></tr>
<tr><td>2.5</td><td>0/8</td><td>0/8</td></tr>
<tr><td>0</td><td>0/8</td><td>0/8</td></tr>
<tr><td>DC_{50} (mg/kg, by mouth per day)</td><td>9</td><td>10</td></tr>
</table>
* Ratio of activity = Number of animals disparasitized/Total number of animals at dose considered</td></tr>
<tr><td colspan="2">Abbreviations: SC, subcutaneously; IP, intraperitoneally; MRS, metronidazole-resistant strain; PI, post-infection; MRS, metronidazole resistant strain.
DC_{50} (ratio of activity). Number of animals deparasitized/Total number of animals at dose considered; h, hours; PI, post-infection.</td></tr>
</table>

Source: Prepared by the Reviewer based on information in the NDA

15.3.1.4. Resistance and Cross-resistance

The potential for development of resistance by *T. vaginalis*, in vitro or in vivo, to secnidazole was not examined. As the mechanism of action of secnidazole is similar to that of other nitroimidazoles, there is a potential for development of resistance and cross-resistance of *T. vaginalis* to secnidazole. Induction of anaerobic metronidazole resistance was reported in vitro by trophozoites incubated with sublethal increasing concentrations of metronidazole for 12 to 21 months; resistance was associated with reduced or absent pyruvate:ferredoxin oxidoreductase (PFOR) activity and decreased uptake of the drug (Cudmore *et al*., 2004).

In vitro studies showed higher secnidazole MLC values for *T. vaginalis* isolates with higher metronidazole MLC (Figure 15-1; Table 15-2) suggesting a potential for development of cross-

resistance among nitroimidazoles (for details see Section 15.3.1.2). However, the clinical relevance of these findings is not known.

The mechanism of resistance to nitroimidazoles appears to be multifactorial that include decreased uptake of the drug (Cudmore *et al*., 2004), higher efflux activity (Cudmore *et al*., 2004) and altered nitroreductase activity (Leitsch *et al*., 2009).

15.3.2. Parasitological assessments in the clinical study

The Applicant provided results of a Phase 3 multi-center, double-blind, placebo controlled clinical trial to support the efficacy of a single dose treatment with SOLOSEC in 147 female patients with trichomoniasis (Trial SEC-WH-301). The study was conducted at 10 centers within the US. One of the inclusion criteria for enrollment of patients was positive parasitological findings by one of the following tests:

- *T. vaginalis* NAAT.
- OSOM® *Trichomonas* Rapid test.
- Wet mount.

Diagnosis was confirmed by culture as the culture results were not available at the time of study randomization and treatment.

Patients with bacterial vaginosis were eligible for the study. However, patients suspected clinically or confirmed diagnostically of having alternative causes of other vaginal symptoms including vulvovaginal candidiasis, chlamydia, gonorrhea, or an active genital herpes outbreak were excluded. Note that the PCR results for *C. trachomatis*, *N. gonorrhoeae* were not available at the time of randomization.

The primary efficacy endpoint was parasitological cure between Days 6-12 [Visit 2 - Test of Cure (TOC)] and based on a negative *T. vaginalis* culture result. The exploratory efficacy endpoints included symptom resolution and microbiologic cure in the subgroup of patients who had baseline symptoms attributable to trichomoniasis.

For details of the Study protocol see Section 8.

15.3.2.1. Description of the Parasitological Tests

The vaginal specimens were collected using sterile Dacron or cotton swabs, at different visits, for parasitological testing (Table 15-4). OSOM® *Trichomonas* Rapid test and wet mount were performed at the investigational sites. The NAAT results were based on information in the patient chart. For culture, the specimens were shipped to a central laboratory ((b) (4) using InPouch® TV device. Adequate oversight and training of laboratory staff were implemented.

Table 15-4: The laboratory testing schedule

Phase	Treatment				
Study Visit	Screening/ Baseline Day 1/Visit 1	Test of Cure (TOC) Visit 2 Day 6 – Day 12	Follow Up Visit Visit 3[4] 7-12 Days post V2	Follow Up Visit[1] Visit 4 Investigator Discretion	Unscheduled
Test Name					
Chlamydia trachomatis and Neisseria gonorrhoeae, Amplified (PCR)	X				X
OSOM Trichomonas Rapid Test[2]	X (on-site)				X (on-site)
Vaginal Wet Mount	X (on-site)		X (on-site)[3]	X (on-site)[3]	X (on-site)
KOH Whiff Test	X (on-site)				X (on-site)
pH of Vaginal Fluid	X (on-site)				X (on-site)
Urine Pregnancy[5]	X (on-site)	X (on-site)	X (on-site)	X (on-site)	X (on-site)
Kits Only[6/7]					
T. Vaginalis[5] Culture ambient culture kits (for shipping)	X	X	X	X	X
Kit Type:	A/B[7]	B[7]	B[7]	B[7]	B[7]/A

1. At the discretion of the investigator a patient who is culture positive at Visit 3 may return for an additional visit (Visit 4) for further evaluation and treatment (assessments may include all those listed but at the discretion of the investigator). Patients with negative cultures for *T. Vaginalis* at V2 will be contacted by phone and discharged from the study, no V3 will be required.
2. OSOM test not needed if patient has positive NAAT test within 30 days of screening for which treatment has not been initiated.
3. For assessment of trichomonas only.
4. A follow-up visit (V3) will be scheduled for all patients who have positive cultures for *T. Vaginalis* (i.e., positive InPouch™ TV test) at Visit 2.
5. Performed by site personnel (not sent to central laboratory).
6. Results will not be available at the time of visit.
7. Kit B will be for *T. Vaginalis*; this is "kit only" and will be tested by (b) (4)
8. Patients are allowed to re-screen once, if not previously randomized. If rescreened, the patient ID will not change.
9. Repeat visits will not be allowed for this study.
10. Unscheduled visits are allowed for this study.
11. Patients who withdraw, are discontinued, or are lost to follow-up may be replaced upon review/approval from the Sponsor.
12. (b) (4) will provide additional supplies for on-site testing.

After all Visit 2 study procedures were completed, patients received the opposite treatment (placebo patients received SOLOSEC and vice versa). Patients with culture positive findings for *T. vaginalis* returned to the clinic for Visit 3 assessments and investigator assessment of need for additional therapy; an additional Visit 4 was scheduled at the Investigator's discretion if culture at Visit 3 was positive. Patients with negative cultures at Visit 2 were contacted by phone and discharged from the study.

OSOM® Rapid test was not needed if patient had positive NAAT within 30 days of screening for which treatment had not been initiated.

Source: NDA

15.3.2.1.1. Nucleic-Acid Amplification Test

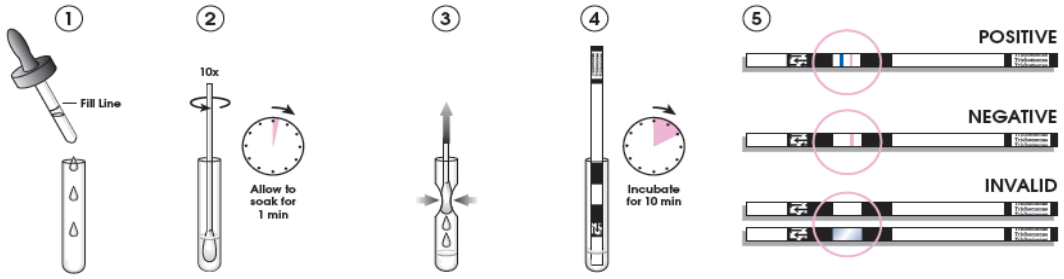
Positive *T. vaginalis* NAAT results were based on information available from the patient chart, performed within 30 days of screening and treatment had not been initiated. No details of the method(s) were provided for review.

15.3.2.1.2. OSOM® *Trichomonas* Rapid Test

OSOM® *Trichomonas* Rapid test (Sekisui Diagnostics, MA), an immunochromatographic assay, is FDA cleared. The test is intended for use in patients with symptoms of vaginosis/vaginitis or suspected exposure to the *Trichomonas* pathogen. Briefly, the *Trichomonas* antigens from vaginal swabs in buffer, if present, form a complex with the conjugated anti-*Trichomonas*

antibody that is visible as a blue line. The test detects antigens derived from 2500 organisms/mL. A positive control forms a red line. A negative finding is based on the presence of a red control line but no blue test line. The test is considered invalid, if no red control line appears or background color makes reading of the red control line impossible. The results are obtained within 10 minutes. For details see Figure 15-2.

Figure 15-2: OSOM® *Trichomonas* Rapid test



Principle of the assay
The OSOM® *Trichomonas* Rapid Test uses color immunochromatographic, capillary flow, "dipstick" technology. The test procedure requires the solubilization of *Trichomonas* proteins from a vaginal swab by mixing the swab in sample buffer. The OSOM® *Trichomonas* Rapid Test Stick is then placed in the sample mixture and the mixture migrates along the membrane surface. If *Trichomonas* is present in the sample, it forms a complex with the primary anti-*Trichomonas* antibody conjugated to colored particles (blue). The complex then binds by a second anti-*Trichomonas* antibody coated on the nitrocellulose membrane. The appearance of a visible blue test line along with the red control line indicates a positive result.

Assay cut-off:
The assay detection limit is 2500 organisms/mL.

Specimen collection and preparation
Specimens from the vaginal cavity should be collected with a sterile rayon swab from the kit. Use of the swabs supplied in the kit or BD BBL™ CultureSwab™ is recommended. Swabs from other suppliers have not been validated. Swabs with cotton tips or wooden shafts are not recommended.

Quality control
The following *internal and external quality control* (QC) are included:
Internal Procedural Controls
1. The appearance of the control line in the results window is an internal positive procedural control.
2. The clearing of the background in the results area may be documented as an internal negative procedural control.
External Controls
Positive and negative external controls should be run with each new lot and with each new untrained operator. One positive control swab (pink shaft) is included with each kit. For a negative control, one of the sterile swabs, supplied with the kit, should be run. The controls should be run in the same manner as patient swabs.

Interfering Substances (Cross-reactivity)
- *Staphylococcus aureus* in specimens at concentrations >$1x10^8$ organisms/mL may interfere with the test results in negative samples.
- Preparations containing douche medicated with iodine may interfere with negative samples.

Source: Prepared by the reviewer based on information in the test package insert included in the NDA.

The sensitivity of the OSOM® *Trichomonas* Rapid Test compared to wet mount microscopy and wet mount + InPouch test was 96% and 83%, respectively (Table 15-5). The specificity was

≥95%. A comparison of the performance of the OSOM® *Trichomonas* Rapid Test with culture was not assessed.

The test was used for rapid diagnosis at the time of screening and testing was performed at investigational sites.

Table 15-5: OSOM® *Trichomonas* Rapid test – Assay performance

Comparison of tests	**Sensitivity**	**Specificity**	**Agreement**
OSOM® *Trichomonas* Rapid test vs. wet mount	69/72 (96%) 95% CI: 91 – 100%	345/365 (95%) 95% CI: 92 – 97%)	414/437 (95%) 95% CI: 93 – 97%
OSOM® *Trichomonas* Rapid test vs. a composite reference standard i.e., wet mount + InPouch test*	85/102 (83%) 95% CI: 76 – 91%	331/335 (99%) 95% CI: 98 – 100%	416/437 (95%) 95%CI: 93 – 97%

Sensitivity of Each Method vs. Composite Reference Standard*

Method	Sensitivity
OSOM® Trichomonas Rapid Test (vaginal swab)	83%
OSOM® Trichomonas Rapid Test (saline from wet mount)	75%
Wet Mount Microscopy	71%
Culture (InPouch™ TV)	99%

*Composite reference standard was based on wet mount + InPouch test
- Any sample with a positive result from either wet mount or culture was defined as positive.
- Samples that were negative in both wet mount and culture tests were defined as negative.

Of the 20 samples negative by wet mount, 16 were positive by culture - 4 were negative.
Abbreviation: CI, confidence interval

Source: Prepared by the reviewer based on information in the test package insert provided in the NDA

15.3.2.1.3. Wet mount

Wet mounts were prepared using vaginal swabs placed in a tube containing 6 drops of saline (~100 µL), enough to keep the swabs moist but do not dilute the sample. The swabs were removed and the vaginal specimens in saline were placed on 2 glass slides and examined microscopically at 100X and 400X magnification for motile trichomonads. Wet mounts were performed at the study sites.

The specificity of wet mount compared to OSOM® *Trichomonas* Rapid Test and culture is 95% and ≥99%, respectively (Table 15-5 and Table 15-6). The sensitivity of wet mount microscopy compared to OSOM® *Trichomonas* Rapid Test was 96% (Table 15-5; for details see Section 15.3.2.1.1). However, some of the published studies suggest a lower sensitivity of wet mounts compared to cultures. For example, Wiese *et al*. (2000) reported mean sensitivity of 58% (range 15% and 98%) based on meta-analysis of 30 studies, published between 1976 and 1998, that included culture results for the diagnosis of trichomoniasis (Table 15-6). The variability in sensitivity could be due to the differences in study designs and frequency of testing.

Table 15-6: Accuracy of the wet mount technique to diagnose *Trichomonas* vaginitis

First Author (Reference)	Prevalence of Trichomoniasis	Sensitivity (Percent)	Sensitivity (n/n)	Specificity (Percent)	Specificity (n/n)	Likelihood Ratio Positive†	Likelihood Ratio Negative
Level I studies							
Sharma (49)	7%	81%	(55/68)	100%	(932/932)	∞	0.19
Beal (28)	9%	66%	(41/62)	100%	(648/648)	∞	0.34
Briselden (32)	9%	80%	(12/15)	100%	(155/155)	∞	0.20
Krieger (41)	15%	60%	(53/88)	99%	(511/512)	308	0.40
Wolner-Hanssen (55)	15%	60%	(71/118)	100%	(661/661)	∞	0.40
Schmid (47)	27%	64%	(65/102)	100%	(273/273)	∞	0.36
Fouts (38)	33%	50%	(66/131)	100%	(269/269)	∞	0.50
Bickley (11)	37%	66%	(25/38)	100%	(66/66)	∞	0.34
de Carli (35)	38%	53%	(40/75)	100%	(125/125)	∞	0.47
Watt (53)	47%	37%	(31/84)	98%	(91/93)	17	0.64
Philip (45)	49%	38%	(33/86)	100%	(91/91)	∞	0.62
Spence (51)	50%	56%	(28/50)	100%	(50/50)	∞	0.44
Weighted mean	19%	58%‡		99.8%‡			
95% confidence interval		51%–66%		99.5%–100%			
Range	7%–50%	37%–81%		98%–100%		17–∞	0.19–0.64
Level II studies							
Weinberger (54)*	6%	83%	(5/6)	100%	(94/94)	∞	0.17
Yule (56)	9%	73%	(32/44)	100%	(438/438)	∞	0.27
Lin (42)	10%	56%	(9/16)	100%	(149/149)	∞	0.44
Carney (33)	11%	74%	(31/42)	100%	(353/353)	∞	0.26
Borchardt (31)	13%	15%	(2/13)	100%	(87/87)	∞	0.85
DeMeo (36)	15%	80%	(76/95)	100%	(520/520)	∞	0.20
Draper (37)	15%	85%	(29/34)	100%	(198/198)	∞	0.15
Chintana (34)	17%	93%	(185/198)	100%	(999/999)	∞	0.07
Lopez-Brea (44)	17%	83%	(15/18)	100%	(88/88)	∞	0.17
Schwebke (48)	26%	69%	(18/26)	100%	(74/74)	∞	0.31
Imandel (40)	30%	59%	(22/37)	100%	(88/88)	∞	0.41
Smith (50)	30%	68%	(21/31)	100%	(74/74)	∞	0.32
Gelbart (39)	32%	67%	(35/52)	100%	(111/111)	∞	0.33
Borchardt (30)	35%	68%	(32/47)	100%	(87/87)	∞	0.32
Thomason (52)	42%	92%	(34/37)	100%	(51/51)	∞	0.08
Weighted mean	17%	72%‡		100%			
95% confidence interval		62%–81%		100%			
Range	6%–42%	15%–93%		100%		∞	0.07%–85%
Level III studies							
Bhatt (29)	14%	88%	(45/51)	100%	(319/319)	∞	0.12
Satapathy (46)	55%	81%	(47/58)	100%	(48/48)	∞	0.19
Lisi (43)	55%	61%	(22/36)	—	—	—	—
Weinberger (54)*	73%	98%	(43/44)	100%	(16/16)	∞	0.02
Weighted mean	31%	82%‡		100%			
95% confidence interval		67%–97%		100%			
Range	14%–73%	61%–98%		100%		∞	0.02–0.19
Pooled Total	19%	68%		99.90%			
95% confidence interval		62%–74%		99.8%–100%			
Range	6%–73%	15%–98%		98%–100%		17–∞	0.02–0.85

* Same article using two study designs.
† ∞ Denotes infinity (division by zero).
‡ Denotes heterogeneity of data ($P < 0.05$).

The results are based on meta-analysis of 30 studies, published between 1976 and 1998, that included culture results for the diagnosis of trichomoniasis.

Source: Wiese *et al*. (2000)

15.3.2.1.4. InPouch® TV

Cultures were performed using a commercially available, FDA cleared, InPouch® TV device (Biomed Diagnostics, Oregon). The InPouch® TV test, a broth media device, consists of a high-barrier, oxygen-resistant, plastic with two V-shaped-chambers connected by a narrow passage. It allows for the direct inoculation, immediate observation, transportation, culture, and detection of *T. vaginalis* in vaginal, cerebrospinal fluid, and urethral/urine samples. The medium is selective for *T. vaginalis* and contains antimicrobial agents that inhibit the growth of yeasts, molds and bacteria. The quality controls (QC) include testing of strains of *T. vaginalis* and yeast (*Candida albicans*) and bacteria (*Escherichia coli, Enterococcus faecalis,* and *Staphylococcus aureus*). The *T. vaginalis* trophozoites show growth whereas growth of fungi and bacteria is inhibited.

The kits were provided to the investigational sites. The vaginal samples obtained from the posterior fornix of the vagina using Dacron applicator swabs, by the Investigator or trained designee, were inoculated immediately to the InPouch® TV device according to the manufacturer's instructions. The inoculated InPouch TV device was shipped on the day of collection to arrive at the central laboratory ([redacted] (b) (4)) within 24 hours of collection. A TempTale 4 USB Ambient Monitor was included during transport. The TempTale® 4 USB Ambient Monitor, with time-temperature alarm settings, provided recorded transport history information including average temperature, highest and lowest temperature and total time above high or low temperature limit.

In the central laboratory, the InPouch® TV device was incubated at 37°C within 48 hours of collection in order to keep any *Trichomonas* alive; otherwise false negative results can occur. The samples were concentrated by letting the cellular materials settle to the bottom of the chamber before microscopic examination at 100X-400X magnification using a plastic microscopic viewing clip.

Immediate observation based on live motile trichomonads was a presumptive positive result. The cultures were incubated at 37°C for up to 7 days for accurate negative findings. The results were available between Days 2 and 7 from receipt of specimens at the central laboratory.

An inoculum containing 1-10 organisms is sufficient to cause a positive test. The sensitivity is between 81-94% and specificity 100%.

Quality Control

- *Visually check TV pouches:* The device was checked to ensure that it was free of any signs of precipitation and bacterial and/or fungal contamination. Pouches containing a cloudy medium or precipitate were not used.
- *Parallel QC:* A known positive *T. vaginalis* strain was included for testing for the purpose of media quality control when new media was received in the laboratory and to ensure that the media supported the growth of *T. vaginalis.*

- lnPouch TV device received by the central laboratory past 48 hours of collection were rejected.

Limitations
Patient specimens contaminated with birth control foams or jellies leads to decreased recovery.

Reviewer comments:
Parasitological tests used by the Applicant are adequate for the intended context of use, i.e., initial screening, diagnosis of trichomoniasis, and/or measuring efficacy. Culture of vaginal secretions is the gold standard for the diagnosis and inoculum containing 1-10 organisms is sufficient to cause a positive test; the sensitivity is between 81 and 94%. Cultures can take up to 7 days.

The OSOM® Trichomonas Rapid test and wet mount are quick and easy to perform with specificity of 95% and ≥99%, respectively. However, the sensitivity may be low. No information was available for the NAA tests.

The Applicant implemented adequate quality control measures.

15.3.2.2. Study Results

- **Parasitological assessments prior to treatment**

Of the 147 patients enrolled, 135 were confirmed to be culture positive at baseline (Table 15-7; for more details see Table 8-1). Of the 12 culture negative subjects, 4 had evidence of motile trichomonads based on wet mount, 2 were positive by OSOM Rapid test, and 9 were positive by NAAT test (Table 15-8). Of the 9 patients positive by the NAAT, 8 were negative by other tests suggesting low specificity of the NAAT or absence of active *Trichomonas* infection. None of the 12 culture negative patients were included in the mITT population.

Table 15-7: Trial SEC-WH-301 - A Comparison of the performance of different tests

Test	Positive	Negative
InPouch® TV	135/147 (91.8%)	12/147 (8.2%)
NAAT*	60	NA (n=87)
OSOM® *Trichomonas* Rapid test	112/117 (95.7%)	5/117 (4.3%)
Motile *Trichomonas* (Probably based on wet mount)	119/145 (82.1%)	26/145 (17.9%)
*NAAT information for 60 patients was based on their chart; No NAAT results available for 87 patients. Abbreviation: NA, not available		

Source: Reviewer's analysis based on datasets (LB, ADSL, and ADEFF)

Table 15-8: Trial SEC-WH-301 – A comparison of test results in 12 patients that were culture negative at baseline

Unique Subject ID	Group	InPouch® TV	Motile *Trichomonas**	OSOM**	NAAT***
SEC-WH-301 (b) (6)	Placebo	Negative	Positive	Negative	
SEC-WH-301		Negative	Negative	Negative	Positive
SEC-WH-301		Negative	Negative		Positive
SEC-WH-301		Negative	Positive	Positive	
SEC-WH-301		Negative	Negative	Negative	Positive
SEC-WH-301	SOLOSEC	Negative	Negative		Positive
SEC-WH-301		Negative	Negative		Positive
SEC-WH-301		Negative	Negative		Positive
SEC-WH-301		Negative	Positive		Positive
SEC-WH-301		Negative	Positive	Positive	
SEC-WH-301		Negative			Positive
SEC-WH-301		Negative	Negative	Negative	Positive

*Probably wet mount.
**OSOM® *Trichomonas* Rapid test.
***Represents 9 patients positive by NAAT findings (Blue font), based on available information in the patient chart; of the 9 NAAT positive patients, 8 were negative by other tests (Blue font).
All 12 patients were not included in the mITT population.

Source: Reviewer's analysis based on datasets

Reviewer comments:
The parasitological tests used by the Applicant are adequate for initial screening and diagnosis of trichomoniasis. Evidence of parasites by wet mount and culture is 100% specific. However, the negative findings should be interpreted with caution. The sensitivity of the OSOM® Trichomonas Rapid test, wet mount technique, and culture using InPouch TV device, based on testing of clinical trial specimens, was similar to that reported previously (for details see Section 15.3.2.1. above).

- **Parasitological assessment at the end of treatment**

Of the 135 patients confirmed to be culture positive prior to treatment, 131 (64 in the SOLOSEC group and 67 in the placebo group) completed the TOC visit (mITT population). A majority of the patients in the SOLOSEC group [59/64 (92.2%)] became culture negative whereas only 1 patient [1/67 (1.5%)] in the placebo group became culture negative (Table 8-7).

Clinical symptoms of trichomoniasis, prior to treatment, were reported in 111/131 subjects (56 in the SOLOSEC group and 55 in the placebo group). Complete resolution of symptoms and negative culture results were reported in 41 of the 56 patients (73.2%) treated with SOLOSEC; none of the 55 placebo group patients were clinically cured (Table 8-8; Table 8-9).

Reviewer comments:
The results show that a higher proportion (92%) of the SOLOSEC treated patients, compared to the placebo group (<2%), became culture negative at the TOC visit. There was a good correlation between culture results and clinical cure as 73% of the culture negative patients

treated with SOLOSEC were clinically cured whereas none of the 55 placebo group patients were clinically cured.

15.3.2.3. Interpretive Criteria

The Applicant has not requested any interpretive susceptibility testing criteria in the labeling. This is appropriate as the tests to measure in vitro sensitivity of the *T. vaginalis* parasites are not standardized and their use is limited to research laboratories.

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

/s/

DEBORAH WANG
06/29/2021 09:17:51 PM

KAREN M HIGGINS
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SHUKAL BALA
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AVERY C GOODWIN
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CRISTINA M MIGLIS
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DAKSHINA M CHILUKURI
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XIANBIN LI
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JAE H HONG
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EDWARD A WEINSTEIN
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ADAM I SHERWAT
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