Efficacy and Safety of Single Oral Dosing of Secnidazole for Trichomoniasis in Women: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Delayed-Treatment Study

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Summary: A single oral dose of secnidazole vs. placebo significantly increased microbiological cure rates in women with trichomoniasis, including those with HIV and/or bacterial vaginosis.
**Background.** *Trichomonas vaginalis* is the most prevalent non-viral sexually transmitted infection. We evaluated the efficacy and safety of secnidazole vs. placebo in women with trichomoniasis.

**Methods.** Women with trichomoniasis, confirmed by a positive *T. vaginalis* culture, were randomized to single-dose oral secnidazole 2g or placebo. The primary endpoint was microbiological test of cure (TOC) by culture 6–12 days after dosing. At the TOC visit, participants were given the opposite treatment. They were followed for resolution of infection afterward and offered treatment at subsequent visits, if needed. Fifty patients per group (N=100) provided ~95% power to detect a statistically significant difference between treatment groups.

**Results.** Between April 2019 and March 2020, 147 women enrolled at 10 US sites. The modified intent-to-treat (mITT) population included 131 randomized patients (64/67, in secnidazole/placebo). Cure rates were significantly higher in the secnidazole vs. placebo group (92.2% [95% CI: 82.7–97.4] vs. 1.5% [95% CI: 0.0–8.0]) for the mITT population and for the per-protocol population (94.9% [95% CI: 85.9–98.9]) vs. 1.7% [95% CI: 0.0–8.9]). Cure rates were 100% (4/4) in women with HIV and 95.2% (20/21) in women with bacterial vaginosis (BV). Secnidazole was generally well tolerated. The most frequently reported treatment-emergent adverse events (TEAEs) were vulvovaginal candidiasis and nausea (each 2.7%). No serious TEAEs were observed.

**Conclusion.** A single oral 2g dose of secnidazole was associated with significantly higher microbiological cure rates vs. placebo, supporting a role for secnidazole in treating women with trichomoniasis, including those with HIV and/or BV.

**Clinical trial registration.** ClinicalTrials.gov Registration Number: NCT03935217

**Keywords:** *Trichomonas vaginalis*; trichomoniasis; secnidazole; women
Trichomoniasis is the most prevalent non-viral sexually transmitted infection (STI) worldwide, affecting 3.7 million people in the United States.[1] Women with *Trichomonas vaginalis* have a two- to three-fold increased risk for acquiring human immunodeficiency virus (HIV)[2] and other STIs.[3] Trichomoniasis is also associated with infertility[4] and adverse birth outcomes.[5] National guidelines recommend annual screening of women with HIV for trichomoniasis.[6]

The 2015 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases (STD) Treatment Guidelines recommends a single 2-g dose of oral metronidazole (MTZ) or tinidazole (TDZ) for *T. vaginalis*-infected women without HIV; for infected women with HIV, MTZ 500 mg orally twice daily for 7 days is preferred.[6] The 2020 American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on Vaginitis has recently recommended multi-dose MTZ for all non-pregnant women[3], based on new clinical trial data.[7] Updated 2021 CDC STI Treatment Guidelines are pending.

Secnidazole (SEC) is a potent 5-nitroimidazole antibiotic with a longer half-life than MTZ and TDZ.[8] In 2017, SEC was approved by the Food and Drug Administration (FDA) as the first, single-dose oral treatment for bacterial vaginosis (BV) in women.[9, 10] The 2020 ACOG guidance includes SEC 2 g as an alternative treatment for BV, based on a randomized controlled trial, finding it comparable to 7-day MTZ for BV.[3]

As a treatment for trichomoniasis, single-dose SEC had microbiological cure rates of 93–96% after 2–3 days of treatment and up to 100% ≤20 days of treatment in studies conducted outside the US.[11] We aimed to evaluate the efficacy and safety of single-dose SEC in US-based women with trichomoniasis. We hypothesized that microbiological cure rates would be
high after treatment of *T. vaginalis*-infected women with SEC, similar to studies outside of the United States.

**METHODS**

**Study Design**

This phase 3, randomized, double-blind, placebo-controlled, delayed-treatment study received institutional review board approval (IntegReview, Austin, TX; Western Institutional Review Board, Puyallup, WA; Office of Human Research Ethics, Chapel Hill, NC, USA) for 10 clinical sites in the United States (ClinicalTrials.gov Registration Number: NCT03935217). It was designed and monitored in accordance with FDA recommendations and the sponsor’s standard operating procedures, which comply with the International Conference on Harmonisation’s Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent or parental/legal guardian consent (when appropriate) before engaging in study-related procedures.

In contrast to the FDA approval of tinidazole for trichomoniasis, which was based on a literature-focused New Drug Application submission, in this circumstance, the FDA required a single, placebo-controlled trial for the approval of SEC to treat trichomoniasis. To ensure patient safety, the Investigators, in collaboration with the FDA, adopted a delayed-treatment study design, similar to FDA guidance on uncomplicated UTI studies.[12] Because there is no evidence that a one- to two-week delay in treatment for trichomoniasis is associated with significant health risks, the study design was approved by both local (academic) and central IRBs. Out of an abundance of caution, the Investigators agreed on a trial protocol that was more stringent than the current standard of care, which recommends retesting for *T. vaginalis* at 3 months.[6] In the current trial, TOC was performed 6–12 days after treatment, with
further follow-up if needed to ensure successful treatment. In addition, Investigators counseled patients on the need for partner therapy and the importance of abstinence during the study to prevent reinfection.

Participants

Eligible patients were adult females or post-menarchal adolescent girls ≥12 years of age in general good health. An initial diagnosis of *T. vaginalis* was determined by a positive wet mount, positive OSOM® Trichomonas Rapid Test (Sekisui Diagnostics, Burlington, MA, USA), or a positive *T. vaginalis* nucleic acid amplification test (NAAT; within the past 30 days) for which treatment had not yet been initiated. Patients diagnosed with *T. vaginalis* based on a Pap smear were not excluded; however, these patients were required to have *T. vaginalis* confirmed with one of the other diagnostic tests mentioned above. Patients agreed to abstain from vaginal intercourse, vaginal penetration (eg, sex toys), or use of any vaginal products (eg, spermicides, tampons, vaginal douches, lubricants) until after study completion. Patients were counseled to notify all sexual partners within the past 60 days to be treated as contacts to trichomoniasis. Based on data from in vitro studies,[13] and as noted in the Package Insert,[14] SEC does not have an alcohol consumption restriction. Patients were excluded if they were pregnant (owing to placebo-controlled study design) or lactating, had symptomatic vulvovaginal candidiasis or an active genital herpes outbreak, received a course of antibacterial or antifungal therapy within the past 14 days, or had a known allergy to nitroimidazoles. Patients with chlamydia or gonorrhea via positive NAAT test at enrollment were included in the safety population; however, they were not included in the modified intent-to-treat (mITT) analysis, as per the direction of the FDA. Women with HIV and those with BV (based on all four Amsel criteria per FDA trial guidance: presence of homogenous,
white/gray vaginal discharge; ≥20% clue cells per high-power field on wet mount; positive whiff test; vaginal pH ≥4.7)[15] were not excluded.

Procedures

Eligible patients were randomly assigned (1:1) to SEC 2 g or matching placebo in a double-blinded manner. Before study start, biostatisticians generated a randomization list assigning kit numbers to one of the two treatment groups. This list was used by the study sponsor to package study drug into treatment kits. Randomization was stratified by site and clinical symptoms of trichomoniasis at baseline (present/absent).

At Visit 1 (baseline), patients completed assessments including demographics, medical history (including presence of genital symptoms), vital signs, urine pregnancy testing, and a physical examination. A pelvic examination was performed to assess genital signs and to collect vaginal specimens for pH, wet mount, KOH whiff test, InPouch™ T. vaginalis culture (BioMed Diagnostics, White City, OR, USA), and gonorrhea/chlamydia NAAT (Roche HC/Chlamydia Collection Kit [Cobas PCR Media Uni Swab]). SEC oral granules or matching placebo oral granules were mixed in ~ 4 ounces of unsweetened applesauce and administered under direct observation. The matching placebo contained the same ingredients as the active formulation with the exception of SEC. Both SEC and the placebo were packaged in white packets with blinded packaging and labeling so they were indistinguishable. Patients were evaluated 6–12 days later at Visit 2 for test of cure (TOC).

At Visit 2 (TOC), patients were queried about treatment-emergent adverse events (TEAEs) and assessed for clinical symptoms of trichomoniasis. A provider obtained an additional vaginal specimen for T. vaginalis culture. At this visit, patients received the opposite
treatment from baseline (ie, SEC if they had received placebo at baseline or placebo if they had received SEC at baseline) under direct observation by study staff. Patients with a microbiological cure, defined as negative *T. vaginalis* by InPouch™ culture at Visit 2, were subsequently discharged from the study. Patients with a positive *T. vaginalis* culture from Visit 2 were asked to return for a Visit 3, 7–12 days later, for an additional assessment, including determination of the need for additional therapy. A Visit 4 (7–12 days after Visit 3) was scheduled at the investigator’s discretion if a repeat *T. vaginalis* culture at Visit 3 was positive. Patients who had a positive culture at Visit 3 and Visit 4 were offered treatment, based upon the investigator’s discretion and per standard of care.[6] InPouch™ cultures were examined daily for 5 days over a 7-day period to reduce the possibility of false-negative results.[16]

The primary efficacy endpoint was microbiological cure at Visit 2 (TOC). The trial was designed to limit the possibility of unprotected sex resulting in reinfection, which would become more likely the longer the interval between treatment and TOC. The InPouch™ culture was selected as the diagnostic TOC based on its relatively high sensitivity, 81–94%,[17, 18] allowing for a TOC visit within 1 week. We did not perform a *T. vaginalis* NAAT for TOC as the optimal timing of this highly sensitive test is 3–4 weeks after treatment. Use of this test within 3 weeks after treatment may have detected remnant trichomonal nucleic acid, leading to false-positive test results.[19] In addition, the use of *T. vaginalis* NAAT for TOC would have required patients to remain sexually inactive for as much as 4 weeks, which was considered impractical.
Statistical Analysis

Assuming microbiological cure rates of 75% [7] and 40% [20] with SEC and placebo, respectively, a sample size of 100 patients (50 patients/group) provided ~ 95% power to demonstrate a statistically significant between-treatment-group difference using a two-sided, two-sample comparison of proportions at the $\alpha=0.05$ level of significance. Assuming an attrition rate of 30%, 144 patients needed to be randomly assigned to SEC or placebo.

The primary efficacy endpoint was compared between the active and placebo treatment groups using a two-sided Cochran-Mantel-Haenszel (CMH) test (stratified by the presence/absence of clinical symptoms of trichomoniasis at baseline, HIV status, and BV status) at the $\alpha=0.05$ level of significance. As required by the FDA and determined a priori, the primary efficacy analysis was based on the mITT population, defined as all randomized patients who had a positive $T. vaginalis$ culture at baseline and a negative chlamydia and gonorrhea NAAT at baseline. Secondary efficacy endpoint analysis was based on the per protocol (PP) population, defined as patients in the mITT population who received their assigned study medication and had a TOC visit. Post hoc efficacy analyses of the microbiological cure rate at TOC compared SEC- vs. placebo-treated patients: (1) with trichomoniasis who were symptomatic and those who were asymptomatic, (2) infected with HIV, and (3) with BV at baseline. All analyses were performed using SAS® software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Safety endpoints included the incidence, severity, and relationship to study medication of TEAEs, serious TEAEs, and TEAEs leading to discontinuation. Vital signs, physical examinations, and clinical laboratory tests also were assessed. Safety endpoints were
evaluated using the safety population, defined as all randomized patients who received any study-related medication.

RESULTS

Patient Disposition and Characteristics

Between April 23, 2019 and March 18, 2020, 147 women with trichomoniasis (SEC=74, placebo=73), identified by a positive wet mount (n=119), OSOM® Trichomonas Rapid Test (n=112), or T. vaginalis NAAT (n=60) were enrolled at 10 clinical sites in the United States. One hundred thirty one women (SEC=64, placebo=67) were included in the mITT population (Fig. 1). In the mITT population, 57 patients had positive T. vaginalis InPouch test results at Visit 2, and 54 of these 57 patients had negative T. vaginalis InPouch test results at Visit 3. This corresponds to a 94.7% success rate for SEC.

Eight percent (12/147) of patients were excluded due to a negative T. vaginalis culture at baseline; 3.4% (5/147) patients had a positive gonorrhea/chlamydia NAAT. One hundred and nineteen patients were included in the PP population (SEC=59, placebo=60). In addition to the above-mentioned exclusions, 7.5% (11/147) of patients were excluded from the PP population because their TOC visit did not occur within the 6- to 12-day window (Appendix 1). Of the 12 patients excluded from both the mITT and PP populations due to negative T. vaginalis culture at baseline, 6 had a positive NAAT (within 30 days of Visit 1) at enrollment, 2 had positive wet mounts and positive OSOMs, 1 had a positive wet mount, and 1 had a positive wet mount and positive NAAT. Four patients did not return for TOC at Visit 2. One patient withdrew owing to a TEAE, two withdrew consent, and one was contacted by phone multiple times and sent a certified letter in the mail. She acknowledged receipt of this letter but chose not to return. In the mITT population, the mean ± SD age was 37.7±11.19
years (range, 15–65 years), and 90.8% were African American (Table 1). The majority of patients (84.7%) had genital symptoms, and among those, 43.5% had abnormal genital itching, 78.6% had abnormal vaginal discharge, and 63.4% had abnormal odor.

**Efficacy**

In the mITT population, the microbiologic cure rate at TOC was significantly higher ($P<.001$) in the SEC vs. placebo group (92.2% [95% CI 82.7–97.4]) vs. 1.5% [95% CI 0.0–8.0]) (Table 2). In the PP population, the cure rate at TOC also was significantly higher ($P<.001$) in the SEC vs. placebo group (94.9% [95% CI 85.9–98.9]) vs. 1.7% [95% CI 0.0–8.9]). There were no significant demographic differences between patients who were not cured (i.e., at Visit 2 in the SEC group and at Visit 3 in the placebo group) and those who were cured (data not shown).

In the subgroup of patients with vaginal symptoms at baseline, the microbiological cure rate at TOC was 92.9% (95% CI 82.7–98.0) in the SEC group; no patient in the placebo group had a negative *T. vaginalis* culture at TOC ($P<.001$; Table 3). In women with HIV, 100% (4/4) had a microbiological cure at TOC; no patient in the placebo group had a negative *T. vaginalis* culture at TOC. In patients with BV at baseline, the microbiological cure rate at TOC was 95.2% (95% CI 76.2–99.9) patients in the SEC group; no patient in the placebo group had a negative *T. vaginalis* culture at TOC ($P<.001$).

**Safety**

In the safety population, TEAE rates were lower in the SEC vs. placebo group. All TEAEs were mild. Only one patient in the SEC group discontinued due to mild nausea and productive cough. There were no serious TEAEs (Table 4).
Discussion

The results of this study demonstrate the superiority of SEC vs. placebo for the treatment of trichomoniasis. Importantly, SEC was superior to placebo in patients with trichomoniasis and vaginal symptoms and in those with HIV and/or BV. Although prior studies have shown trichomoniasis is asymptomatic in 70–85% of cases,[21] patients can present with symptoms including yellow-to-green frothy vaginal discharge, abnormal vaginal odor, pruritus, irritation, and/or dysuria.[3] Thus, single-dose SEC may be an effective option for symptomatic and asymptomatic trichomoniasis in women.

National guidelines have traditionally recommended a single, 2-g dose of oral MTZ or TDZ as the preferred treatment of trichomoniasis in women, with oral MTZ 500 mg BID for 7 days as an alternative regimen.[6] In 2010, results of a randomized, open-label trial of a single oral dose of MTZ 2 g vs. the 7-day MTZ 500 mg BID regimen in women with HIV and trichomoniasis demonstrated microbiological cure rates of 83.2% vs. 91.5%, 6–12 days after treatment.[22] These results led to the CDC recommendation to use the multi-dose MTZ regimen for trichomoniasis in women with HIV.[6] In 2018, similar results were reported from a randomized, open-label trial of single- vs. multi-dose MTZ for trichomoniasis in women without HIV. Microbiological cure rates at TOC were 81.4% and 89.1% in the single- and multi-dose MTZ groups.[7] Hence, the 2020 ACOG Practice Bulletin on Vaginitis now recommends the multi-dose MTZ regimen as the preferred regimen for trichomoniasis in non-pregnant women.[3] Updated 2021 CDC STI Treatment Guidelines are anticipated later this year.

As providers move toward multi-dose MTZ as the preferred regimen for all women with trichomoniasis, our findings also support the use of single-dose SEC. With efficacy rates for
the treatment of trichomoniasis comparable to multi-dose MTZ.[7, 22] SEC has favorable attributes that may provide advantages over other options. In vitro studies of *T. vaginalis* isolates[14] showed that the minimal lethal concentration of SEC is 56% lower vs. MTZ. SEC also differs from other nitroimidazoles with a notably longer half-life (17 hours) vs. MTZ (7–8 hours) and TDZ (12 hours).[23] Single-dose options are convenient and likely to improve adherence overall, especially in populations at risk for non-compliance.[24] Of note, compliance with multi-dose MTZ has been low (50–63%) in some studies.[25] Factors that may impact adherence include gastrointestinal complaints, treatment duration, and lifestyle restrictions. In one study, 23% of patients reported nausea in the single- and multi-dose MTZ groups.[7] In our study, 2.7% of patients reported nausea with SEC. Additionally, SEC does not have an alcohol restriction based on data from in vitro studies.[13, 14]

In our study, cure rates were 92–100% in the overall population and in subgroups of women with genital symptoms, HIV, and/or BV. Previous research showed that trichomoniasis treatment significantly decreases HIV viral load and viral shedding and may reduce HIV transmission.[6, 26-28] Although only four patients had HIV, our finding that all were cured is reassuring, and larger clinical trials in this patient population are warranted to confirm these results. Moreover, coinfection of BV and *T. vaginalis* is common, with rates of 60–80%.[29] Thus, a single treatment for BV and trichomoniasis may have multiple benefits.

A potential limitation of this study was the use of *T. vaginalis* culture to achieve a shorter timeframe to TOC. Although InPouch™ may be less sensitive than NAAT,[21] the accuracy in this study was high as supported by the low placebo responder rate (~ 1%). Other limitations include the lack of long-term follow-up and the exclusion of men and pregnant women. However, two non-US-based studies of SEC for trichomoniasis in patients, including
a small subgroup of men, showed cure rates of 91.7–100% two to 20 days after treatment.[30, 31] Although our study did not include pregnant women, and data on the use of SEC during pregnancy are limited, reproductive preclinical toxicology studies have shown no evidence of toxicity, and SEC is not contraindicated during pregnancy.[14, 32] The CDC recommends that trichomoniasis treatment be considered for symptomatic pregnant women, regardless of pregnancy stage.[6] Finally, 5-nitroimidazole susceptibility testing was not performed on trichomonas isolates in the study; thus, we cannot comment on any resistance that potentially may have been present.

Study strengths include high cure rates for SEC (92–95%), low placebo responder rates, minimal dropouts, a favorable TEAE profile, and treatment success in women with and without clinical symptoms, HIV, and/or BV.

In conclusion, this study demonstrated that a single dose of SEC 2 g was efficacious and well tolerated in women with trichomoniasis and in those with trichomoniasis and comorbid HIV and/or BV. If approved by the FDA for the treatment of trichomoniasis, SEC will be the only single oral-dose medication available for the treatment of BV and T. vaginalis. Future studies should be considered in pregnant women and those with persistent T. vaginalis infection, including the use of SEC multi-dose regimens.
Notes

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| Characteristic                      | Secnidazole 2 g (n=64) | Placebo (n=67) | Overall (N=131) |
|------------------------------------|------------------------|----------------|-----------------|
| **Age (y)**                         | 36.9±11.3              | 38.4±11.12     | 37.7±11.19      |
| **Median (range)**                 | 34.5 (19–65)           | 39.0 (15–65)   | 36.0 (15–65)    |
| **Race**                           |                        |                |                 |
| American Indian/Alaska Native      | 1 (1.6)                | 1 (1.5)        | 2 (1.5)         |
| Asian                              | 1 (1.6)                | 0              | 1 (0.8)         |
| Black/African American             | 59 (92.2)              | 60 (89.6)      | 119 (90.8)      |
| Native Hawaiian/Other Pacific      | 0                      | 0              | 0               |
| **Ethnicity**                      |                        |                |                 |
| Not Hispanic or Latino             | 62 (96.9)              | 65 (97.0)      | 127 (96.9)      |
| Hispanic or Latino                 | 2 (3.1)                | 2 (3.0)        | 4 (3.1)         |
| **Weight (kg)**                    | 90.4 (25.9)            | 92.4 (26.7)    | 91.4 (26.3)     |
| **Median (range)**                 | 87.1 (45.4–167.8)      | 86.2 (49.9–180.5) | 86.6 (49.9–180.5) |
| **BMI (kg/m²)**                    | 33.8 (9.4)             | 34.1 (9.3)     | 34.0 (9.3)      |
| **Median (range)**                 | 32.2 (17.7–63.5)       | 31.2 (19.5–62.3) | 31.6 (17.7–63.5) |
| **Trichomoniasis symptoms**        |                        |                |                 |
| Present                            | 56 (87.5)              | 55 (82.1)      | 111 (84.7)      |
| Absent                             | 8 (12.5)               | 12 (17.9)      | 20 (15.3)       |
| BV                                 | 21 (32.8)              | 17 (25.4)      | 38 (29.0)       |
| HIV+                               | 5 (7.8)                | 4 (6.0)        | 9 (6.9)         |

Abbreviations: BMI, body mass index; BV, bacterial vaginosis; HIV+, positive for human immunodeficiency virus; mITT, modified intent-to-treat population; SD, standard deviation.

Data are means ± SDs or n (%).

*Vaginal itching, discharge, and/or odor.
|                           | Secnidazole 2 g (n=64) | Placebo (n=67) |
|---------------------------|------------------------|----------------|
| Microbiological cure\(^a\), n (%) | 59 (92.2)\(^b\) | 1 (1.5)\(^b\) |
| 95% exact binomial CI      | 82.70–97.41            | 0.04–8.04      |
| P-value\(^c\)              | <.001                  |                |

Abbreviations: CI, confidence interval; mITT, modified intent-to-treat population; TOC, test of cure.

\(^a\) InPouch™ *T. vaginalis* test negative for *T. vaginalis*.

\(^b\) Patients with no test results were assumed to be positive (numbers imputed: secnidazole = 1; placebo = 3).

\(^c\) P value vs. placebo from a Cochran-Mantel-Haenszel test adjusted for clinical symptoms (present/absent) of trichomoniasis at baseline.
Table 3. Microbiological Cure by Presence of Clinical Symptoms, HIV, and BV Status at Baseline\textsuperscript{a} (mITT)

|                                      | Secnidazole 2 g (n=64) | Placebo (n=67) | P-value\textsuperscript{d} |
|--------------------------------------|-------------------------|----------------|-----------------------------|
|                                      | Symptoms Present | Symptoms Absent | Symptoms Present | Symptoms Absent |                       |
| Microbiological cure\textsuperscript{b}, % (n/N) | 92.9 (52/56)       | 87.5 (7/8)\textsuperscript{c} | 0 (0/55)\textsuperscript{c} | 8.3 (1/12) | <.001 |
| 95% CI                               | 82.7--98.0          | 47.4--99.7      | 0.0--6.5          | 0.2--38.5 | <.001 |
| Microbiological cure\textsuperscript{b}, HIV, % (n/N) | 100 (4/4)          | 0 (0/4)         | 0 (0/4)           | NC       |
| Microbiological cure\textsuperscript{b}, BV, % (n/N) | 95.2 (20/21)       | 0 (0/17)\textsuperscript{c} |                | <.001     |
| 95% CI                               | 76.2--99.9          | 0.0--19.5       |

Abbreviations: BV, bacterial vaginosis; CI, confidence interval; HIV, human immunodeficiency virus; mITT, modified intent-to-treat population; NC, not calculated.

\textsuperscript{a}Post hoc analysis.

\textsuperscript{b}InPouch™ T. vaginalis test negative for T. vaginalis.

\textsuperscript{c}Patients with no test results were assumed to be positive (numbers imputed: secnidazole [symptoms absent] = 1; placebo [symptoms present] = 3; placebo [symptoms absent] = 1).

\textsuperscript{d}P value vs. placebo from a Cochran-Mantel-Haenszel test adjusted for clinical symptoms (present/absent) of trichomoniasis at baseline.
| TEAE                        | Secnidazole 2 g (n=74) | Placebo (n=73) |
|----------------------------|------------------------|----------------|
| Any TEAE                   | 11 (14.9%)             | 16 (21.9%)     |
| Nausea                     | 2 (2.7%)               | 3 (4.1%)       |
| Abdominal pain             | 1 (1.4%)               | 1 (1.4%)       |
| Diarrhea                   | 1 (1.4%)               | 2 (2.7%)       |
| Vomiting                   | 1 (1.4%)               | 1 (1.4%)       |
| Vulvovaginal candidiasis   | 2 (2.7%)               | 0 (0%)         |
| Vulvovaginal mycotic infection | 1 (1.4%)         | 0 (0%)         |
| Trichomoniasis             | 0 (0%)                 | 2 (2.7%)       |
| Productive cough           | 1 (1.4%)               | 0 (0%)         |
| Upper-airway cough syndrome| 1 (1.4%)               | 0 (0%)         |
| Myalgia                    | 1 (1.4%)               | 0 (0%)         |
| Back pain                  | 0 (0%)                 | 1 (1.4%)       |
| Headache                   | 1 (1.4%)               | 5 (6.8%)       |
| Vulvovaginal pruritus      | 1 (1.4%)               | 0 (0%)         |
| Dysmenorrhea               | 0 (0%)                 | 2 (2.7%)       |
| Menstruation irregular     | 0 (0%)                 | 1 (1.4%)       |
| Thirst                     | 0 (0%)                 | 1 (1.4%)       |
| Pruritus                   | 0 (0%)                 | 1 (1.4%)       |

TEAE, treatment-emergent adverse event; SAF, safety population; TOC, test of cure.

\(^{a}\)Includes all TEAEs during the primary phase (start date on or before the TOC visit).

\(^{b}\)Patients experiencing multiple TEAEs are counted only once within a given cell.
**Figure Legends**

**Figure 1.** mITT population and reasons for exclusion

**Figure 2.** PP population and reasons for exclusion
Figure 1

Patients randomized
N=147

Secnidazole 2 g
n=74

Excluded from mITT* 
n=10
Negative TV culture at BL = 7
STI at BLh = 4

Included in mITT 
N=64

Placebo 
n=73

Excluded from mITT* 
N=6
Negative TV culture at BL = 5
STI at BLh = 1

Included in mITT 
N=67

Abbreviations: BL, baseline; CT, Chlamydia trachomatis; mITT, modified intent-to-treat population; NAAT, nucleic acid amplification test; NG, Neisseria gonorrhoea; STI, sexually transmitted infection; TV, Trichomonas vaginalis.

*Patients could have multiple reasons for exclusion.

hCT/NG by NAAT.
Figure 2

Patients randomized
N=147

Secnidazole 2 g
n=74

Placebo
n=73

Excluded from PP (n=13)
Negative culture for TV at BL =7
TOC visit not during D6–12 =5
STIs at BL =4
Did not complete key vaginal assessments at TOC =1
Did not meet all inclusion/exclusion criteriab =1
Did not take full dose of first study drug within 5 min =1
Disallowed medication =1
Missing InPouchTV result at TOC =1
Major protocol violation affecting primary endpoint =1
Positive post-BL STI assessment =1

Included in PP
n=59

Excluded from PP (n=13)
Negative culture for TV at BL =5
TOC visit not during D6–12 =6
STIs at BL =7
Did not complete key vaginal assessments at TOC =8
Did not meet all inclusion/exclusion criteriaa =1
Disallowed medication =1
Missing InPouchTV result at TOC =3
Major protocol violation affecting primary endpoint =1

Included in PP
n=60

Abbreviations: BL, baseline; CT, Chlamydia trachomatis; D, day; NAAT, nucleic acid amplification test; NG, Neisseria gonorrhoea; PP, per-protocol population; STI, sexually transmitted infection; TOC, test of cure; TV, Trichomonas vaginalis.

aPatient did not abstain from sexual intercourse during the study.

bPatients could have multiple reasons for exclusion.