GYNECOLOGY

A phase-3, double-blind, placebo-controlled study of the effectiveness and safety of single oral doses of secnidazole 2 g for the treatment of women with bacterial vaginosis

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BACKGROUND: A novel single oral dose granule formulation of secnidazole 2 g, a 5-nitroimidazole with a longer half-life (~17 hours) than metronidazole (~8 hours), is being developed to treat bacterial vaginosis.

OBJECTIVE: We sought to evaluate the effectiveness and safety of single-dose secnidazole 2 g compared to placebo for the treatment of women with bacterial vaginosis.

STUDY DESIGN: In all, 189 women with bacterial vaginosis were randomized 2:1 to receive a single oral dose of secnidazole 2 g (N = 125) or matched placebo (N = 64) at 21 centers in the United States. The primary endpoint was the proportion of clinical outcome responders, defined as those with: (1) normal vaginal discharge; (2) negative 10% potassium hydroxide whiff test; and (3) <20% clue cells of total epithelial cell count on microscopic examination of the vaginal wet mount, using saline at the test of cure/end of study visit (study days 21-30). Secondary efficacy analyses included clinical cure rates, defined as: (1) responders with normal discharge or abnormal discharge not consistent with bacterial vaginosis after treatment; (2) negative potassium hydroxide whiff tests; and (3) clue cells <20% assessed at the interim visit (study days 7-14), and test of cure/end of study (study days 21-30). In addition, based on the 2016 US Food and Drug Administration draft guidance, patients with baseline Nugent scores 7-10 were evaluated for clinical cure using the following clinical assessments on study days 7-14: (1) resolution of the abnormal vaginal discharge; (2) a negative potassium hydroxide whiff test; and (3) clue cells <20%. The study was designed and powered to demonstrate the efficacy of single-dose secnidazole 2 g compared to placebo; safety and tolerability were also assessed. Due to a prespecified institutional review board–approved protocol calling for withdrawal of randomized, treated patients with a Nugent score <4 or with a separate sexually transmitted infection, this modified intent-to-treat population was the primary analysis population. Statistical comparisons used a stratified Cochran-Mantel-Haenszel test with a .05 level of significance (2-sided).

RESULTS: Single-dose secnidazole 2 g was superior to placebo for the primary and all secondary efficacy measures in the modified intent-to-treat population, with clinical outcome responder rates of 53.3% (57/107) vs 19.3% (11/57; $P < .001$). Clinical cure rates, based on an alternate definition of responder, which accounted for resolution of abnormal discharge consistent with bacterial vaginosis, were consistent with the clinical outcome responder rate analysis (58.9% vs 24.6%; $P < .001$) for single-dose secnidazole 2 g vs placebo. Clinical cure rates based on the 2016 US Food and Drug Administration guidance were 64.0% vs 26.4% for single-dose secnidazole 2 g vs placebo. Based on the investigator's clinical assessment at the test of cure/end of study visit, significantly more patients receiving single-dose secnidazole 2 g vs placebo required no additional bacterial vaginosis treatment (68.0% [68/100] vs 29.6% [16/54]; $P < .001$). Adverse events considered by the investigator to be related to study drug occurred in only 20.0% of single-dose secnidazole 2 g—treated patients vs 10.9% of placebo patients, and they included diarrhea (4.0% vs 1.6%), headache (4.0% vs 3.1%), nausea (4.8% vs 1.6%), and vulvovaginal candidiasis (4.0% vs 3.1%).

CONCLUSION: Single-dose secnidazole 2 g was superior to placebo on all primary and secondary outcomes and was well tolerated; these results support its role for the treatment of women with bacterial vaginosis.

Key words: bacterial vaginosis, secnidazole, single-dose treatment

Introduction

Bacterial vaginosis (BV) affects >21 million girls and women (29.2%) between the ages of 14-49 years in the United States annually, and it is the most common vaginal infection among girls and women aged 15-44 years.[1,2] BV is associated with a 2-fold increased risk of serious health complications, including susceptibility to and transmission of HIV and herpes simplex type 2 virus; acquisition of other sexually transmitted infections, including *Neisseria gonorrhoeae* and *Chlamydia trachomatis*; and, in pregnant women, preterm delivery and premature rupture of membranes.[3,4]

Currently recommended treatments include a 7-day regimen of twice-daily oral metronidazole 500 mg, a 5-day regimen of intravaginal metronidazole 0.75% gel, and a 7-day regimen of intravaginal clindamycin 2% cream.[5] Poor adherence to antiinfective therapy increases with the length (~7 days for current standard of care) and complexity of the drug regimen, and it contributes to treatment failure, recurrent disease, and possibly more rapid development of resistant microorganisms.[6] For example, studies have shown that ~50% of patients do not comply with a 5- to 7-day treatment regimen.[7,8] These outcomes may lead to higher health care costs, including increased out-of-pocket expenses, increased office visits and tests, additional treatment costs, and lost productivity.[9] Poor adherence to the 7-day regimens may also be contributing to the emergence of an increasing number of

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cases of chronic BV, which require multiple antibiotic treatments.[5,9]

Single-dose secnidazole 2 g (Solosec [secnidazole], Symbiomix Therapeutics LLC, Newark, NJ) is a novel oral granule formulation being developed to treat BV. Secnidazole is a 5-nitroimidazole with demonstrated in vitro antimicrobial activity against many anaerobic Gram-negative and Gram-positive bacterial species, while sparing *Lactobacillus* species.[10,11] Several published clinical studies demonstrated clinical and/or microbiologic evidence of activity of secnidazole in the treatment of BV.[10] Single-dose secnidazole 2 g has a favorable safety profile, has not been shown to have any clinically meaningful drug-drug interactions, has a longer half-life than metronidazole (~17 vs ~8 hours), and can be administered with or without a meal. These characteristics and the single-dose regimen have the potential to improve treatment adherence, which could lead to improved clinical outcomes for women with BV.

The efficacy and tolerability of single-dose secnidazole 2 g for the treatment of BV was demonstrated in a randomized, placebo-controlled, phase-2 hypothesis-generating study in which single-dose secnidazole 1 g and 2 g were investigated vs placebo.[12] The primary efficacy endpoint analysis (clinical cure rate) in the modified intent-to-treat (mITT) population demonstrated significantly greater response rates for both single-dose secnidazole 1 g and 2 g vs placebo ($P < .001$). Secondary efficacy endpoint analyses (microbiologic cure and therapeutic cure rates) were consistent with the primary results.[12] Overall, both levels of single-dose secnidazole were well tolerated compared to placebo. Additionally, it was the first secnidazole efficacy study and evaluated 2 dose levels to answer questions about dose and the degree of cure compared to placebo. Predicated on the enhanced efficacy and tolerability of single-dose secnidazole 2 g over 1 g in the phase-2 study,[12] the 2-g dose was selected for further investigation in this phase-3 confirmatory study.

Materials and Methods

Study design

This was a phase-3, multicenter, prospective, randomized, double-blind, placebo-controlled study that assessed the effectiveness, safety, and tolerability of single-dose secnidazole 2 g in women and postmenarchal adolescent girls with BV. The study is registered with ClinicalTrials.gov, NCT02418845.

All patients provided written informed consent or, when applicable, assent with parental/legal guardian consent before the performance of any study-related procedures. Patients were screened for study eligibility at the baseline visit (day 1). Patients determined to be eligible were centrally randomized at a 2:1 ratio to receive either single-dose secnidazole 2 g or matched placebo. Randomization was stratified by the number of reported episodes of BV in the past 12 months (≤3 vs ≥4 episodes), including the current episode, and race (black vs all others). Study drug was self-administered on day 1 without regard to meals. For administration, study drug granules were mixed in 4 oz of unsweetened applesauce. The matching placebo contained the same ingredients as the active formulation, except for the absence of secnidazole and the addition of sucrose octaacetate as a bittering agent. After receiving study drug or placebo, patients were instructed to immediately drink 8 oz of water.

Patients returned to the study center for an interim visit between study days 7-14 for response assessments and evaluation for adverse events (AEs). A test of cure (TOC) visit was conducted between study days 21-30, at least 10 days after the interim visit. Patients were allowed to withdraw their participation from the study at any time, for any reason. If they chose to withdraw, an end of study (EOS) visit was conducted comprising the same assessments as the TOC visit. If patients withdrew because they were dissatisfied with treatment, they were offered the option to receive any US Food and Drug Administration (FDA)-approved treatment for BV.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines. The study was also performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and later revisions (insofar as such revisions are consistent with US treaty obligations and in accordance with US law). The study was performed in keeping with local legal requirements. Before the start of the study, the study protocol and other appropriate documents were submitted to the institutional review board (IRB) (Schulman Associates IRB, Cincinnati, OH; Western IRB, Puyallup, WA). The IRB confirmed the ethics of conducting a placebo-controlled study that ensured placebo-randomized subjects received effective treatment delayed by 1 week for the patient population and their demographics. Letters documenting the IRB approvals were provided to the sponsor or its representative prior to initiation of the study.

Study population

The mITT was specified as the primary analysis population in the protocol because these patients were confirmed to have BV. The protocol states patient disposition based on the intent-to-treat (ITT) population. It was prespecified in the IRB-approved protocol that patients were to be randomized and treated if they met the clinical criteria for enrollment, but they were then to be withdrawn if centrally analyzed Nugent scoring resulted in a Nugent score <4 or if baseline laboratory tests revealed a positive result for a separate sexually transmitted infection. Adult females or postmenarchal adolescent girls ≥12 years of age were planned to be enrolled at 21 study centers in the United States. All patients had a clinical diagnosis of BV, defined as meeting 4 Amsel criteria for BV (discharge; pH ≥4.7; ≥20% clue cells; and positive 10% potassium hydroxide [KOH] whiff test) and Nugent scores ≥4. Baseline laboratory tests and vaginal sample slides for Gram staining and Nugent scoring were analyzed centrally; thus, results were unavailable at the time of randomization. Accordingly, patients remained in the study until laboratory tests and Nugent scores became available. Baseline scores ultimately were used as criteria for inclusion

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