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Original Research

Effect of 2016 FDA guidance on study population and clinical response rates in patients with bacterial vaginosis: a phase 3 post hoc analysis

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Summary

Purpose of Investigation: In 2016, the US Food and Drug Administration updated the enrollment and clinical response criteria for clinical studies of bacterial vaginosis (BV). The purpose of this post hoc analysis was to determine the effects of these differences on the results of a previously published phase 3 clinical study of the use of a single oral dose of secnidazole 2 grams to treat BV. *Results:* The updated guidelines for enrollment include a more stringent baseline Nugent score cutoff, which reduced the number of subjects from the initial study by 16.8% (secnidazole group) and 7.0% (placebo group). The updated efficacy guidelines changed the clinical outcome responder rates to 64.0% (secnidazole) and 26.4% (placebo) on assessment days 7–14 ($p < 0.001$), and to 58.4% and 24.5%, respectively, on days 21–30 ($p < 0.001$). *Conclusion:* Although the guidelines did not significantly affect efficacy outcomes, future BV studies will need to screen more patients to compensate for the new, more stringent enrollment criteria.

Key words: Bacterial vaginosis; Nugent score; Secnidazole; Single-dose treatment; FDA.

Introduction

Bacterial vaginosis (BV) affects more than 21 million women, 29.2% of the population between the ages of 14 and 49 years in the US annually [1]. BV doubles the risk of certain health complications and can have serious consequences for pregnant women, as it has been associated with preterm delivery and premature rupture of membranes [2, 3].

Guidelines for the clinical development of treatments for BV were first issued by the US Food and Drug Administration (FDA) in 1998 to standardize the approach of clinical trials conducted in the US [4]. In 2016, the FDA updated these guidelines, changing multiple aspects of clinical trials of BV including enrollment, timing of the test-of-cure (TOC) visit, and definitions of cure (Table 1) [4, 5]. The effect of these changes on current clinical trials and the ability to compare them to past trials is currently unknown.

Single-dose secnidazole 2 grams [SOLOSEC™ (secnidazole), Symbiomix Therapeutics, LLC, Newark, NJ] is an antimicrobial agent that has recently been approved by the FDA for the treatment of BV. In two registration studies, a single oral dose of secnidazole 2 grams was shown to be superior to placebo and to have a favorable safety profile with no clinically meaningful drug-drug interactions [6, 7]. The first phase 3 clinical trial of secnidazole provides a unique opportunity to compare outcomes for patients enrolled before and after the availability of the new guidance, as its design facilitates evaluation of results using both the 1998 and 2016 FDA guidelines. The purpose of this post hoc analysis was to apply the new FDA criteria to the enrollment and outcomes parameters in the phase 3 study.

Materials and Methods

This was a post hoc analysis of data from a phase 3, multicenter, prospective, randomized, double-blind, placebo-controlled registration study (ClinicalTrials.gov Identifier NCT02418845) that assessed the safety and efficacy of single-dose secnidazole 2 grams in women and postmenarchal adolescent girls (≥ 12 years of age) with BV [7]. Patients with written informed consent were screened for study eligibility at the baseline visit (day 1), and they were centrally randomized to receive either single-dose secnidazole 2 grams or matched placebo (2:1).

Patients were examined between days 7–14 and again between days 21–30. If patients discontinued due to treatment, an end-of-study (EOS) visit was conducted and they were offered any FDA-approved treatment for BV. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guideline.

In the original phase 3 study, adult females and postmenarchal adolescent girls were enrolled across 21 study centers in the US. All patients had a clinical diagnosis of BV, defined as meeting the following Amsel criteria for BV: an abnormal discharge, pH > 4.5,

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Table 1. — *Key differences between the 1998 and 2016 guidance on overall clinical development and clinical trial designs to support drugs for the treatment of BV.*

	FDA criteria 1998 [4]	FDA criteria 2016 [5]
Enrollment criteria	*Exclusion*: Nugent score < 4	*Exclusion*: Nugent score < 7
Timing of TOC visit	21–30 days after the first day of treatment	Approximately 7–14 days after randomization
Definition of clinical cure	Vaginal pH ≤ 4.7. Normal discharge	pH not included. Resolution of abnormal discharge

BV = bacterial vaginosis; FDA = US Food and Drug Administration; TOC = test of cure.

Table 2. — *Key differences between results from the phase 3 study of secnidazole under the 1998 and the 2016 FDA guidance.*

	FDA criteria 1998 [4]	FDA criteria 2016 [5]
Subjects assessed (n)	164	142
Efficacy, days 21–30 (% COR)	53.3% secnidazole *vs.* 19.3% placebo	58.4% secnidazole *vs.* 24.5% placebo

COR = clinical outcome responder; FDA = US Food and Drug Administration.

> 20% clue cells, and a positive 10% potassium hydroxide (KOH) whiff test. A Nugent score ≥ 4 at baseline was required for confirmation. Patients were excluded if they were pregnant, lactating, menstruating, menopausal, or had suspected or confirmed alternative causes of vaginal symptoms (eg, sexually transmitted infections). Concomitant systemic and topical antimicrobial therapies were not permitted during the course of the study. Alcohol, vaginal intercourse, or use of any vaginal products was not permitted, as previously described [7]. For this post hoc analysis, a clinical diagnosis of BV was defined according to the original study, with the added measure of a baseline Nugent score ≥ 7.

The modified intent-to-treat (mITT) population (164 patients) of the original study included all randomized patients who met the inclusion/exclusion criteria. The primary efficacy endpoint assessed in the original prespecified population for primary analysis, the mITT population, was the clinical outcome responder (COR) rate, defined as those with 1) a normal vaginal discharge, 2) a negative 10% KOH whiff test, and 3) clue cells < 20% of the total epithelial cells on microscopic examination of the vaginal wet mount using saline at the TOC/EOS visit (study days 21–30). An alternate definition was used for the efficacy analysis performed on the mITT population in this post hoc analysis: using the 2016 FDA criteria, patients in the mITT population with baseline Nugent scores of 7–10 were evaluated for COR rate on days 7–14; the TOC visit time frame defined by the new FDA guidelines. An additional change was that women with an abnormal discharge inconsistent with BV were also considered CORs.

A Cochran-Mantel-Haenszel test adjusted for BV and race strata was used to calculate *p* values. For each treatment group, an exact 95% binomial confidence interval (CI) was calculated for the COR rate.

Results

For the initial study, a total of 189 patients were enrolled at 21 study centers between May 4, 2015, and August 26, 2015 [7]. Patients were assigned 2:1 to treatment with single-dose secnidazole 2 grams (n=125) or placebo (n=64). The original mITT population included 85.6% (107/125) of enrolled patients in the single-dose secnidazole 2-gram group and 89.1% (57/64) of enrolled patients in the placebo group. The demographics and baseline characteristics of the mITT population were previously described in the published phase 3 study [7].

In determining the post hoc population based on the 2016 FDA draft guidelines, an additional 22 patients were excluded from the original mITT population for having a baseline Nugent score of 4–6 (single-dose secnidazole 2-gram group, n=18; placebo group, n=4), leaving 83.2% (89/107), and 93% (53/57) of enrolled patients in the single-dose secnidazole 2-gram and placebo groups, respectively (Table 1).

In the original mITT population, the COR rate for single-dose secnidazole 2 grams was superior to that of placebo (53.3% [n=57/107; 95% CI (43.4, 63.0)] *vs.* 19.3% [n=11/57], respectively; $p < 0.001$) at the TOC/EOS visit (days 21–30) (Table 2) [7]. Applying the 2016 FDA definition of clinical cure to the post hoc analysis study population, secnidazole was also found to be superior to placebo at days 7–14 (64.0% [n=57/89; 95% CI (53.2, 73.9)] *vs.* 26.4% [n=14/53], respectively) and at days 21–30 (58.4% [n=52/89] *vs.* 24.5% [n=13/53]; $p < 0.001$) (Table 2). These response rates (at days 7–14 *vs.* days 21–30) were not significantly different ($p = 0.54$). For patients excluded by the 2016 guidance based on intermediate Nugent scores of 4–6, secnidazole also had greater efficacy than did placebo when assessed at days 7–14 (77.8% [n=14/18] *vs.* 25.0% [n=1/4]; $p = 0.042$).

Discussion

The results of this post hoc analysis showed that changes between the inclusion criteria for the original mITT analysis and the 2016 draft FDA guidance, particularly the higher Nugent score threshold (> 7, *vs.* > 4 under the old guidelines), led to the exclusion of more subjects. The timing of COR rate measurement (between 7–14 days under the new guidance), did not significantly change outcomes ($p = 0.54$) from those under the old guidance (days 21–30). However, the COR rate was numerically higher when calculated using the 2016 FDA criteria, despite the exclusion of women with intermediate Nugent scores.

The new FDA guidelines, which are based on recent research suggesting that the Nugent score is a more accurate diagnostic tool, will impact clinical trials in a number of ways [8-11]. First, the Nugent score is not available for sev-

eral days after the clinical exam. Therefore, a greater number of initially enrolled subjects will later be excluded from the study population, impacting the power calculations of future trials. Additionally, in clinical practice, women are diagnosed with BV if they meet Amsel's criteria and have a Nugent score > 4. Moving forward, there will be less available data on treatment effects in the population with Nugent scores of 4–6, as these patients will have been excluded from the analyzed study population [12, 13].

In the 1998 guidelines, the FDA required a normal pH (3.8–4.5) as part of the criteria for clinical cure. This requirement has long been considered controversial, as pH alone is a relatively poor predictor of BV [14], and many normal healthy women who do not have BV can have a pH ≥ 4.7. The FDA has therefore excluded the need for a normal pH in determining COR. Although the previous requirement of pH < 4.7 for the definition of cure likely decreased cure rates in both treatment and placebo groups, a limitation of the present analysis is that the authors were unable to assess the effect of removing this parameter under the newer FDA guidelines. The information was not originally obtained, as it was not established as a study requirement in discussions with the FDA prior to initiating the clinical trial.

Finally, the impact of the timing for the TOC visit was unclear prior to this analysis. An earlier TOC visit, as recommended by the new guidelines, might lead to poorer outcomes if some patients had not yet fully responded to the drug. Conversely, a later visit, as recommended by the old guidelines, might lead to poorer outcomes if an initial cure was not sustained and patients had begun to relapse. The present authors found no significant impact on overall cure rates with regard to the timing of the TOC visit.

Conclusions

In summary, this analysis has shown that future clinical trials will need to enroll more patients to maintain adequate power, as a greater number of women who meet initial entry criteria will be excluded from the mITT population based on their Nugent score. The timing of the return visit does not seem to materially impact the overall expected cure rates.

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