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## A phase 3, randomized, controlled trial of Astodrimmer 1% Gel for preventing recurrent bacterial vaginosis



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### ABSTRACT

**Objective:** The objective of the study was to confirm the efficacy and safety of Astodrimmer 1% Gel to prevent recurrence of bacterial vaginosis.

**Study design:** 864 women with a diagnosis of bacterial vaginosis and a history of recurrent bacterial vaginosis were enrolled in North America and first received oral metronidazole (500 mg twice daily for 7 days). Women successfully treated with metronidazole were randomly assigned 1:1 to Astodrimmer 1% Gel (N = 295) or placebo (N = 291) at a dose of 5 g vaginally every second day for 16 weeks, and followed for a further 12 weeks off-treatment. The primary endpoint was recurrence of bacterial vaginosis (presence of  $\geq 3$  Amsel criteria) at or by Week 16. Secondary endpoints included time to recurrence, and recurrence of subject-reported symptoms. Adverse events were monitored throughout the study.

**Results:** Astodrimmer 1% Gel was superior to placebo for the primary and many secondary efficacy measures. At or by Week 16, bacterial vaginosis recurred in 44.2 % (130/294) of women receiving astodrimmer and 54.3 % (158/291) receiving placebo ( $P = .015$ ). Time to recurrence of bacterial vaginosis was significantly longer for women receiving astodrimmer compared with placebo (Kaplan–Meier survival curves,  $P = .007$ ). Recurrence of subject-reported symptoms at or by Week 16 was also significantly lower in the astodrimmer arm compared with placebo (vaginal odor and/or discharge, 27.9 % [75/269] vs 40.6 % [108/266],  $P = .002$ ). A significantly lower proportion of patients receiving astodrimmer compared with placebo had recurrence of bacterial vaginosis at or by Week 16 by other secondary measures, including individual Amsel criteria (vaginal discharge and clue cells) and Nugent score 7–10. Recurrence of subject-reported vaginal odor and/or discharge was significantly lower in the astodrimmer arm compared with placebo up to 8 weeks after cessation of therapy (36.1 % [97/269] vs 45.5 % [121/266],  $P = .027$ ).

Adverse events were infrequent, and rates were generally similar between placebo and astodrimmer groups. Vulvovaginal candidiasis and urinary tract infection occurred more often in women receiving astodrimmer.

**Conclusions:** Astodrimmer 1% Gel, administered every second day for 16 weeks, was effective and superior to placebo for prevention of recurrent bacterial vaginosis in women with a history of recurrent BV, and was well-tolerated.

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### 1. Introduction

Bacterial vaginosis (BV) is the most common vaginal infection and twice as common as vulvovaginal candidiasis [1]. BV recurrence rates are 43%–52% within 3–6 months of treatment [2]. BV is a risk factor for serious sequelae, including pre-term

birth, and acquisition and transmission of human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs) [3,4]. Recurrent BV has significant psychosocial impacts on women, including severely affecting self-esteem and sex life, and carries a high economic burden [5,6].

There are no therapies with US regulatory approval for prevention of recurrent BV, and there have been no other adequately powered, well-controlled studies of interventions for recurrent BV. Antibiotic therapies are used off-label over extended periods for reducing recurrence of BV, but are associated with increased risk of side effects [7] and potential for antibiotic resistance development [8]. Long-term cure of BV is elusive given the lifestyle factors associated with recurrence [9]. Therefore, therapies suitable for longer-term use for preventing BV recurrence are urgently required [10,11].

Astodrimmer sodium is a polyanionic dendrimer that blocks attachment of bacteria to cells, preventing formation of bacterial biofilms, which are central to the pathogenesis of BV and not targeted by existing therapies [12–16]. Astodrimmer Gel achieved clinical cure in women with BV following a 7-day treatment course, with 50–74 % cured 2–5 days after end of treatment, and was well-tolerated and not systemically absorbed [17,18].

This phase 3 study assessed Astodrimmer 1% Gel for preventing recurrent BV.

## 2. Materials and methods

### 2.1. Study design

This was a phase 3, double-blind, multicenter, randomized, placebo-controlled study assessing the efficacy and safety of Astodrimmer 1% Gel applied vaginally for 16 weeks compared with placebo (hydroxyethyl cellulose placebo gel) to prevent BV recurrence (Fig. 2).

The study complied with the Declaration of Helsinki, was conducted in accordance with Good Clinical Practice, regulatory guidelines, and relevant local legislation, and was approved by an institutional review board on June 20, 2014 (Quorum Review, Inc.). Patient enrolment commenced October 2014 with last follow-up in February 2017.

Patients provided written informed consent and were screened for eligibility at the Screening visit. Eligible patients with a current symptomatic episode of BV and a history of recurrent BV were enrolled in an open-label phase and received oral metronidazole (500 mg), twice daily for 7 days. At the second visit (Baseline), 3–5 days after completion of metronidazole, women with resolution of BV were randomized 1:1 to either Astodrimmer 1% Gel or placebo using a computer-generated randomization list based upon a permutation block procedure.

The active gel and placebo were colorless, clear gels packaged in identical vaginal applicators. Each applicator contained a single dose (5 g) and was individually overwrapped in a sealed pouch. Seventeen applicators (14 doses and 3 spare) were packed in a tamper-evident carton labelled with a unique study medication/patient identification number, allocated using an interactive randomization system. One carton, enough for 4 weeks' dosing, was dispensed at Baseline, and at Week 4, 8 and 12 study visits. Women self-administered a dose vaginally, every second day for 16 weeks (56 doses total) and attended visits for assessment of BV and adverse events (AEs) every 4 weeks during, and for 12 weeks after end of, treatment. Both care providers and patients were unaware of treatment allocations. Women could withdraw from the study at any time.

Women who had a BV recurrence prior to Week 16 stopped treatment, ended the study and were offered BV therapy as per local practice. A woman was considered to have completed the

study if she reached the final follow-up visit (Week 28) recurrence free or had BV recurrence at any time.

### 2.2. Study population

Women aged 18–45 years with a current diagnosis of BV, defined as presence of  $\geq 3$  Amsel criteria (discharge; vaginal fluid pH  $\geq 4.5$ ;  $\geq 20$  % clue cells; and/or positive 10 % potassium hydroxide whiff test) [19], Nugent score (NS) of 4–10 [20] and self-report of characteristic BV symptoms (abnormal vaginal odor and/or discharge), and a history of recurrent BV defined as  $\geq 2$  documented episodes of BV in the past year, were enrolled in the open-label phase.

Women who were pregnant, planning to become pregnant, lactating, or within 3 months of last pregnancy outcome, and women testing positive for urinary tract infection (UTI), or who had signs/symptoms of active genital herpes simplex virus or tested positive for other STIs (*Chlamydia trachomatis*, *Neisseria gonorrhoea* or *Trichomoniasis vaginalis*) at Screening, were excluded.

Women who were asymptomatic and had clinical cure of BV (i.e., negative Amsel criteria for discharge, whiff test and clue cells) following the open-label phase, regardless of Nugent score, were randomized for the double-blind treatment phase.

Concomitant systemic and vaginal antimicrobial therapies, vaginal antifungals, or any other kind of vaginal products were not permitted during the study.

### 2.3. Outcomes

The primary efficacy endpoint was recurrence of BV at or by Week 16, defined as presence of  $\geq 3$  Amsel criteria (Fig. 2). Secondary efficacy endpoints included recurrence of subject-reported BV symptoms, individual Amsel criteria, NS 7–10, and  $\geq 3$  Amsel criteria and a NS  $\geq 4$ , at or by Week 16. Time to BV recurrence and BV recurrence at the follow-up visits after end of the treatment period were also secondary efficacy endpoints.

AEs were monitored throughout the study.

### 2.4. Statistical analyses

Primary and secondary efficacy analyses using logistic regression, with missing BV recurrence data at Week 16 imputed as recurrence, and treatment as the only factor in the model, were performed on the modified intent-to-treat (mITT) population, which comprised all women randomized who administered  $\geq 1$  dose of study product. This population was also used to assess safety.

The primary efficacy endpoint was also analyzed for population subgroups, including Nugent category at screening, method of contraception, race, and sexual activity during the study.

Categorical variables were summarized using frequency counts and percentages of patients in each category. Descriptive statistics were calculated for each continuous variable.

Survival curves for time to recurrence were estimated using Kaplan-Meier methodology. A log-rank test was used to test the difference between survival curves of the treatment arms. Hazard of BV recurrence was analyzed within the framework of the Kaplan-Meier survival analysis.

Statistical analyses were performed using SAS (Version 9.2; SAS Institute, Cary, NC).

### 2.5. Sample size calculation

Assuming BV recurrence rates of 32 % and 45 % for Astodrimmer Gel and placebo, respectively, a sample size of 308 evaluable participants per treatment arm provided 90 % power with a 2-

sided test to detect a treatment difference with alpha significance level of 0.05. Therefore, approximately 310 per arm and 620 participants overall were to be randomized into the double-blind treatment phase of the study.

### 3. Results

#### 3.1. Disposition and demographics

A total of 864 women were enrolled in the open-label phase of the study to receive metronidazole; 586/864 (67.8 %) eligible women entered the double-blind treatment phase and were randomized to either Astodrim 1% Gel (N = 295) or placebo (N = 291) at 67 sites in the US, 4 in Canada, 4 in Mexico and 2 in Puerto Rico. The mITT population included 585 women. Treatment groups were well-balanced with respect to demographic and baseline characteristics (Table 1). The majority of women completed the study and were included in the mITT population (Fig. 1). In the astodrim group, 8.5 % of patients were lost to follow-up compared with 10.3 % of patients in the placebo group. The median compliance with the treatment regimen (administered 80%–120% of expected doses) was >96 % in both groups when adjusted for missing doses due to menses.

#### 3.2. Efficacy

Astodrim 1% Gel was superior to placebo for the primary endpoint, with 44.2 % (130/294) given astodrim compared to 54.3 % (158/291) given placebo experiencing recurrence of BV at or by Week 16;  $P = .015$  (Table 2). The recurrence of subject-reported symptoms of BV at or by Week 16 was also significantly lower in the astodrim arm compared with placebo (Table 2).

Kaplan–Meier survival curves for time to recurrence separated after Week 4 and remained so at Week 16;  $P = .007$  (Fig. 3).

Recurrence of all individual Amsel criteria at or by Week 16 was lower in the astodrim group than in the placebo group, with exception of vaginal fluid pH (Table 2). In addition, a lower proportion of patients receiving astodrim compared with placebo had BV recurrence at or by Week 16 based on NS 7–10, and the composite of  $\geq 3$  Amsel criteria and NS  $\geq 4$  (Table 2).

During the 12-week follow-up phase, recurrence of BV ( $\geq 3$  Amsel criteria) in women given astodrim was lower than in those given placebo but differences were not statistically significant (Table 3).

Recurrence of BV symptoms of vaginal odor and/or discharge was statistically significantly lower in the astodrim arm compared with placebo up to 8 weeks after cessation of therapy (Table 3).

Subgroup recurrence rates were in line with those for the mITT. The Breslow–Day test for homogeneity of odds ratios of astodrim versus placebo was non-significant for each subgroup factor ( $P > .150$ , except Age,  $P = .098$ ); data not shown. Lower recurrence at or by Week 16 for women randomized to astodrim compared to placebo was statistically significant for several subgroup categories, including women with screening NS 7–10 (46.2 % [108/234] vs 57.7 % [128/222],  $P = .014$ ), black women (53.7 % [79/147] vs 68.1 % [96/141],  $P = .013$ ), women who had penile–vaginal sexual acts during the treatment period (38.9 % [96/247] vs 50.6 % [121/239],  $P = .009$ ), and women who used condoms during treatment (33.0 % [29/88] vs 49.4 % [44/89],  $P = .027$ ).

#### 3.3. Safety/tolerability

The overall incidence of AEs was 54.1 % (159/294) for Astodrim Gel and 47.4 % (138/291) for placebo (Table 4). AEs potentially treatment-related occurred in 12.6 % (37/294) of astodrim patients and 11.3 % (33/291) for placebo.

Most AEs were mild or moderate in intensity, and self-limiting. During treatment, 1.7 % (5) women in each group reported severe AEs; none were considered treatment related. In the astodrim group, 1 participant discontinued treatment due to menorrhagia and 1 participant due to vulvovaginal candidiasis, which was considered possibly related to treatment. For placebo, 1 participant discontinued due to each of vulvovaginal candidiasis, type 2 diabetes mellitus, headache and abdominal pain, and 1 participant discontinued after experiencing vaginal inflammation, vulvovaginal burning sensation, vulvovaginal pruritus and BV considered possibly treatment-related.

Serious AEs were reported for 3/294 (1.0 %) women in the astodrim group and 3/291 (1.0 %) in placebo, and none was considered to be potentially treatment related.

**Table 1**  
Screening Characteristics (mITT population), by Treatment Group.

	Astodrim Gel (N = 294)	Placebo (N = 291)
<b>Age (yr)</b>		
Mean [SD]	31.6 [7.23]	31.6 [6.99]
Range	18 to 45	18 to 45
<b>Race, n (%)</b>		
Black	147 (50.0)	141 (48.5)
White	115 (39.1)	113 (38.8)
All Others <sup>a</sup>	32 (10.9)	37 (12.7)
<b>Ethnicity, n (%)</b>		
Not Hispanic or Latino	209 (71.1)	206 (70.8)
Hispanic or Latino	85 (28.9)	85 (29.2)
<b>Screening Nugent score, n (%)</b>		
0–3	3 (1.0)	1 (0.3)
4–6	57 (19.4)	67 (23.0)
7–10	234 (79.6)	222 (76.3)
Missing	0	1 (0.3)
<b>Number of BV episodes in 12 months prior to enrolment<sup>b</sup></b>		
1	2 (0.7)	0
2	187 (63.6)	198 (68.0)
3–4	94 (32.0)	82 (28.2)
$\geq 5$	11 (3.7)	11 (3.8)

BV = bacterial vaginosis; SD = standard deviation.

<sup>a</sup> All Others = American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander, Other.

<sup>b</sup> Not including a current episode.

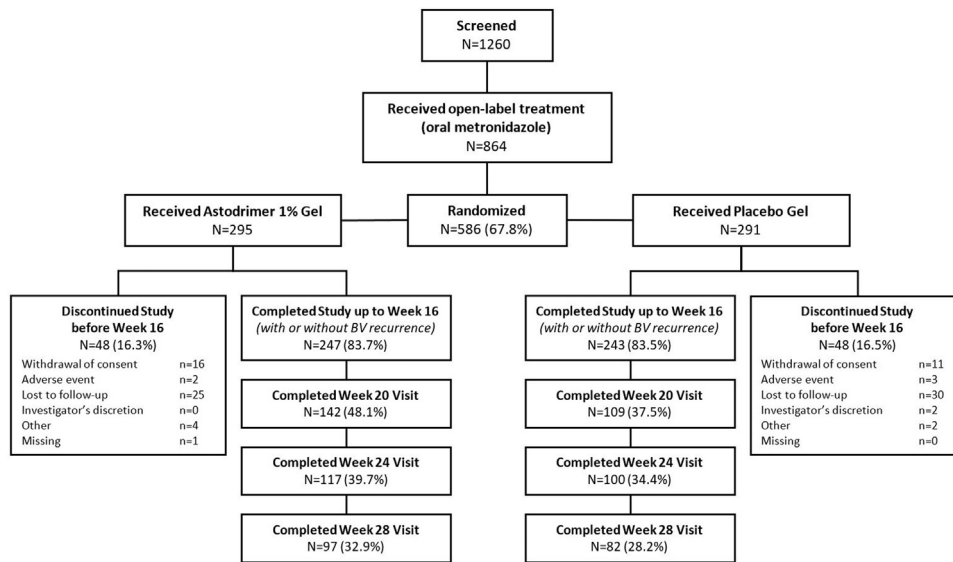


Fig. 1. CONSORT diagram.

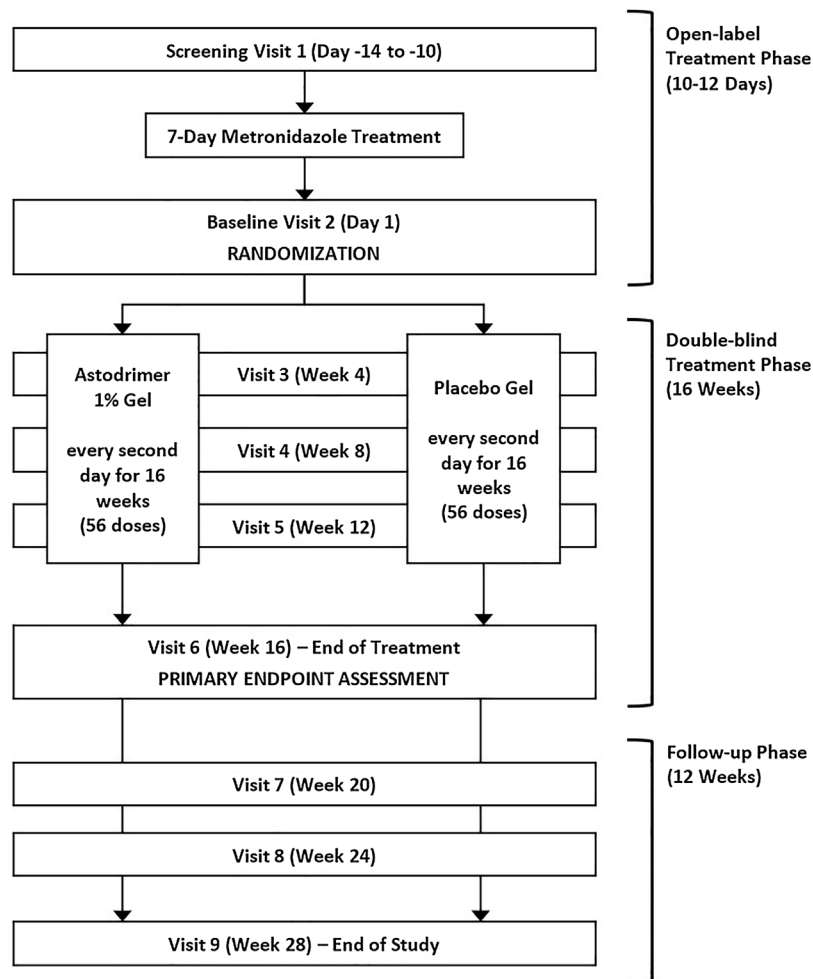


Fig. 2. Study design flowchart.

Vulvovaginal candidiasis was reported in 18.0 % (53/294) and 13.7 % (40/291) women in the astodrimmer and placebo groups, respectively, during treatment and 20.1 % [59/294] vs 17.2 % [50/291] for the overall study period. Vulvovaginal candidiasis

considered potentially treatment-related was reported in 6.8 % (20/294) and 4.8 % (14/291) of women using astodrimmer or placebo, respectively, during treatment. During follow-up, vulvovaginal candidiasis rates were 4.1 % (12/294) for astodrimmer and 5.8 % (17/

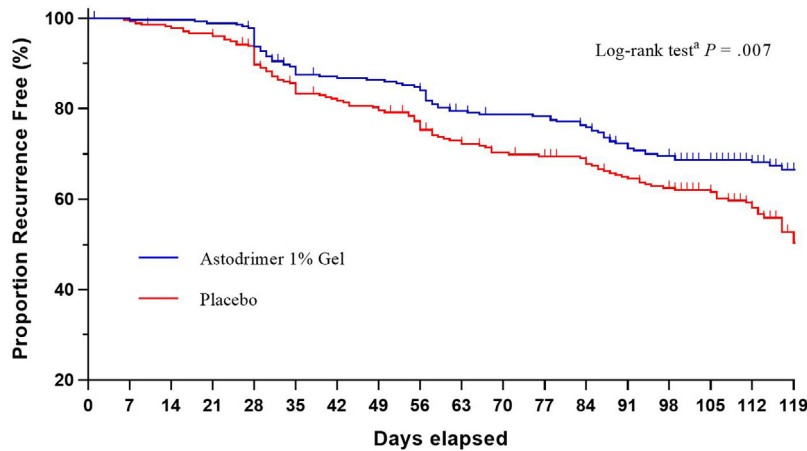
**Table 2**  
Efficacy Outcomes at or by Week 16 (mITT population), by Treatment Group.

BV Recurrence Endpoint	Astodrimmer n/N (%) [95 % CI <sup>a</sup> ]	Placebo n/N (%) [95 % CI <sup>a</sup> ]	RR (95 % CI <sup>b</sup> )	P value <sup>b</sup>
<b>Primary Endpoint</b>				
≥3 Amsel criteria	130/294 (44.2) [38.5, 50.1]	158/291 (54.3) [48.4, 60.1]	0.81 (0.69, 0.96)	0.015
<b>Subject-reported BV Symptoms</b>				
Vaginal Discharge	56/275 (20.4) [15.8, 25.6]	79/276 (28.6) [23.4, 34.3]	0.71 (0.53, 0.96)	0.025
Vaginal Odor	57/275 (20.7) [16.1, 26.0]	87/276 (31.5) [26.1, 37.4]	0.66 (0.49, 0.88)	0.004
Vaginal Discharge and/or Odor	75/269 (27.9) [22.6, 33.6]	108/266 (40.6) [34.6, 46.8]	0.69 (0.54, 0.87)	0.002
<b>Individual Amsel Criteria</b>				
Vaginal Discharge	97/276 (35.1) [29.5, 41.1]	125/276 (45.3) [39.3, 51.4]	0.78 (0.63, 0.95)	0.015
Positive Whiff Test	99/276 (35.9) [30.2, 41.8]	119/276 (43.1) [37.2, 49.2]	0.83 (0.68, 1.02)	0.082
Clue Cells ≥20 %	104/274 (38.0) [32.2, 44.0]	132/273 (48.4) [42.3, 54.5]	0.79 (0.65, 0.95)	0.014
pH >4.5	175/276 (63.4) [57.4, 69.1]	175/276 (63.4) [57.4, 69.1]	1.00 (0.88, 1.14)	1.000
<b>Composite Definition</b>	81/276 (29.3) [24.0, 35.1]	111/276 (40.2) [34.4, 46.3]	0.73 (0.58, 0.92)	0.008
<b>Nugent Score 7–10</b>	95/240 (38.5) [32.4, 44.8]	135/273 (49.5) [43.4, 55.5]	0.78 (0.64, 0.95)	0.012

BV = bacterial vaginosis; CI = confidence interval; RR = relative risk.

<sup>a</sup> Clopper Pearson CI.

<sup>b</sup> Wald CI and P value.



**Fig. 3.** Kaplan-Meier survival curves for time to recurrence of bacterial vaginosis at or by Week 16 (modified intent-to-treat population).

<sup>a</sup> Log-rank test for the difference between the survival curves of the two treatment groups.

**Table 3**  
Efficacy Outcomes During Follow-up (mITT population), by Treatment Group.

Endpoint	Astodrimmer n/N (%) [95 % CI <sup>a</sup> ]	Placebo n/N (%) [95 % CI <sup>a</sup> ]	RR (95 % CI <sup>b</sup> )	P value <sup>b</sup>
<b>BV Recurrence (≥3 Amsel criteria)</b>				
Week 20	191/294 (65.0) [59.2, 70.4]	203/291 (69.8) [64.1, 75.0]	0.93 (0.83, 1.04)	0.217
Week 24	194/294 (66.0) [60.3, 71.4]	213/291 (73.2) [67.7, 78.2]	0.90 (0.81, 1.00)	0.059
Week 28	197/294 (67.0) [61.3, 72.4]	206/291 (70.8) [65.2, 76.0]	0.95 (0.85, 1.06)	0.323
<b>Subject-reported BV Symptoms – Vaginal Discharge and/or Odor</b>				
Week 20	87/269 (32.3) [26.8, 38.3]	110/266 (41.4) [35.4, 47.5]	0.78 (0.62, 0.98)	0.031
Week 24	97/269 (36.1) [30.3, 42.1]	121/266 (45.5) [39.4, 51.7]	0.79 (0.64, 0.97)	0.027
Week 28	107/269 (39.8) [33.9, 45.9]	124/266 (46.6) [40.5, 52.8]	0.85 (0.70, 1.04)	0.111

BV = bacterial vaginosis; CI = confidence interval; RR = relative risk.

<sup>a</sup> Clopper Pearson CI.

<sup>b</sup> Wald CI and P value.

291) for placebo. During treatment, UTI rates were 7.8 % (23/294) for astodrimmer and 2.4 % (7/291) for placebo.

**4. Discussion**

Astodrimmer 1% Gel, administered every second day for 16 weeks, was effective and superior to placebo for the prevention of BV recurrence in women with a history of recurrent BV. The

primary efficacy finding was supported by multiple secondary endpoints, including significantly longer time to recurrence and lower recurrence of symptoms, which was significant up to 8 weeks after end of treatment.

Astodrimmer 1% Gel was well-tolerated, with the incidence of AEs generally similar between the astodrimmer and placebo arms. Rates of candidiasis were generally low. The majority of patients completed the study

**Table 4**  
Tolerability (mITT population), by Treatment Group.

Parameter	Astodrimmer N = 294 n (%)	Placebo N = 291 n (%)
Patients with $\geq 1$ AE	159 (54.1)	138 (47.4)
Patients with $\geq 1$ AE considered by investigator to be potentially related to study treatment	37 (12.6)	33 (11.3)
Patients with $\geq 1$ severe AE during treatment	5 (1.7)	5 (1.7)
Patients with $\geq 1$ serious AE	3 (1.0)	3 (1.0)
Patients who discontinued treatment due to AE	2 (0.7)	5 (1.7)
Most frequent AEs during treatment (incidence $\geq 2\%$ for astodrimmer)		
Vulvovaginal candidiasis	53 (18.0)	40 (13.7)
Urinary tract infection	23 (7.8)	7 (2.4)
Headache	15 (5.1)	18 (6.2)
Abdominal pain (upper, lower, not specified)	11 (3.7)	8 (2.7)
Vaginal discharge	9 (3.1)	4 (1.4)
Nasopharyngitis	8 (2.7)	13 (4.5)
Upper respiratory tract infection	8 (2.7)	6 (2.1)
Vulvovaginal pruritus	7 (2.4)	10 (3.4)

AE = adverse event.

The current study of Astodrimmer 1% Gel represents the largest and first adequately powered, randomized, placebo-controlled study of a therapy for preventing recurrent BV.

Some approved antibiotics or investigational therapies have been shown to reduce recurrence of BV in limited clinical studies that have been generally non-randomized, not placebo-controlled, and/or not adequately powered [7,21–23]. Nevertheless, off-label regimens of products not approved for prevention, including topical metronidazole and topical boric acid over periods of 4–6 months, together with fluconazole to prevent likely secondary candidiasis, are recommended in treatment guidelines for reducing recurrent BV [24].

The proportion of women with known BV recurrence (i.e., missing data not imputed) for Astodrimmer 1% Gel (34.9% [88/252] vs 46.6% [116/249] for placebo) was comparable with that seen in a similarly designed study of topically applied metronidazole gel given for 16 weeks (25.5%) [7].

The difference in recurrence rates between astodrimmer and placebo narrowed progressively after end of treatment, but women in the astodrimmer group recurred later than placebo, and therefore had more recurrence free days. In addition, recurrence of symptoms of BV was statistically significantly lower for astodrimmer compared with placebo up to Week 24, 8 weeks after end of therapy, indicating a clinically meaningful residual benefit.

Treatment with astodrimmer helped maintain normal vaginal flora, with lower BV recurrence rates as determined by Nugent score and the combination of Amsel criteria and Nugent score.

The proportion of women with vulvovaginal candidiasis receiving astodrimmer (18% during treatment, 20.1% overall) was similar to placebo and less than half that reported during a study of 16 weeks' treatment with topical metronidazole 0.75% gel (43.1% vs 20.5% in placebo) [7].

The slightly higher proportion of women with UTI for astodrimmer compared with placebo could be potentially explained by the longer symptom-free period associated with use of astodrimmer allowing a resumption of a more normal frequency of intercourse, consistent with slightly higher sexual functioning scores observed in this study. In any case, the incidence of uncomplicated UTI in young, sexually active women in the US is reported to be approximately 0.5 episodes per person per year [25]. The incidence in women using astodrimmer in this study was 0.37 episodes per person per year.

There were no other notable differences in AEs reported for astodrimmer and placebo.

Astodrimmer is a novel dendrimer administered vaginally and is not systemically absorbed. Data show that it inhibits formation of

and disrupts biofilms due to its ability to block bacterial adhesion. Given this profile, astodrimmer avoids issues typically associated with conventional antibiotics, such as systemic side effects and antibiotic resistance, and is suitable as an effective and safe alternative for the long-term management of recurrent BV, addressing an unmet medical need.

Subgroup analyses showed statistically significant differences in clinical response between astodrimmer and placebo in population groups with recognized risk factors for BV, such as black women, those engaging in penile-vaginal sexual acts during the treatment period, and a high screening NS of 7–10, suggesting benefit of preventive treatment with astodrimmer in these high-risk groups. Subgroup analyses were exploratory in nature and results should be interpreted with caution.

The findings of this Phase 3 study support the clinical utility of Astodrimmer 1% Gel as a novel treatment for prevention of BV recurrence in women suffering from recurrent BV. The product has regulatory approval in Europe, Australia and a number of countries in Asia, and additional safety information will be derived from routine post-market surveillance activities.

The study is the largest randomized, double-blind, placebo-controlled study of a therapy to prevent recurrent BV and was adequately powered to detect a difference in rates of BV recurrence between astodrimmer- and placebo-treated women.

The results of reduced recurrence of BV at Week 16 are consistent with the ability of Astodrimmer 1% Gel to achieve clinical cure of BV at the end of a 7-day treatment period, as demonstrated in phase 2 and 3 clinical studies [17,18].

## 5. Conclusions

The study supports a role for Astodrimmer 1% Gel as an effective long-term therapy to prevent recurrence of BV, with a novel mechanism of action related to blocking of biofilms. The product is not systemically absorbed, and offers patients and clinicians a unique treatment option that avoids potential issues associated with existing antibiotics.

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### Clinical trial registration

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### Paper presentation

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### Declaration of Competing Interest

Dr Schwebke received research funding from Starpharma Pty Ltd for participating in this multicenter study, and is a paid consultant for Starpharma Pty Ltd, Talis One, Toltec, Lupin Pharmaceuticals, and Hologic.

Dr Carter (Women's Physician Group, Memphis, TN, USA) received research funding from Starpharma Pty Ltd for participating in this multicenter study and is a paid consultant for Starpharma Pty Ltd.

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Ms Agnew was a paid consultant for Starpharma Pty Ltd.

Dr Paull is a paid employee of Starpharma Pty Ltd.

Ms Price and Mr Castellarnau were paid employees of Starpharma Pty Ltd and are now paid consultants for Starpharma Pty Ltd.

Dr McCloud and Dr Kinghorn are paid consultants for Starpharma Pty Ltd.

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