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# Journal Pre-proof

Two phase 3, double-blind, placebo-controlled studies of the efficacy and safety of Astodrimmer 1% Gel for the treatment of bacterial vaginosis

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## **Two phase 3, double-blind, placebo-controlled studies of the efficacy and safety of Astodrimmer 1% Gel for the treatment of bacterial vaginosis**

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**CONDENSATION:** These Phase 3 studies demonstrated efficacy and safety of  
Astodrimmer 1% Gel for treatment of bacterial vaginosis (BV).

**SHORT TITLE:** Astodrimmer Gel for Treatment of BV

**ABSTRACT:****Objective:**

Astodrimmer is a dendrimer formulated in a vaginal gel to treat bacterial vaginosis (BV) and prevent recurrence. The objective of these studies was to confirm the efficacy and safety of Astodrimmer 1% Gel for treatment of BV.

**Study Design:**

Women with bacterial vaginosis were randomized 1:1 to Astodrimmer 1% Gel (Study 1 conducted in the United States, N=127; Study 2 conducted in the United States, Germany and Belgium, N=128) or placebo gel (Study 1, N=123; Study 2, N=123) at a dose of 5 g vaginally once daily for 7 days. The primary endpoint was clinical cure, defined as i) absence of bacterial vaginosis vaginal discharge; ii) <20% clue cells; and iii) negative whiff test at day 9-12. Secondary efficacy analyses included clinical cure at day 21-30. Other endpoints at days 9-12 and 21-30 included Nugent cure (Nugent score  $\leq 3$ ), absence of symptoms, and adverse events. The primary analysis in the modified intent-to-treat population used the Cochran Mantel Haenszel test stratified by analysis center with a two-sided significance level of  $\alpha=.05$ .

**Results:**

Astodrimmer 1% Gel was superior to placebo for the primary and selected secondary efficacy measures. Clinical cure rates at day 9-12 were 50.4% (59/117) vs 16.5% (19/115,  $P<.001$ ) (Study 1) and 56.7% (68/120) vs 21.4% (25/117,  $P<.001$ ) (Study 2) for astodrimmer vs placebo. At day 21-30, clinical cure results showed a similar trend but the

difference to placebo was not statistically significant. Nugent cure rates at day 9-12 were 12.8% (15/117) vs 2.6% (3/115,  $P=.004$ ) (Study 1) and 13.3% (16/120) vs 5.1% (6/117,  $P=.030$ ) (Study 2) for astodrimer vs placebo. A greater proportion of women receiving astodrimer reported absence of vaginal discharge and absence of vaginal odor at day 9-12 and day 21-30 compared with placebo. Adverse events were generally mild and self-limiting. For the combined studies, adverse events potentially related to treatment occurred in 14.7% (37/252) of astodrimer patients vs 9.4% (23/244) for placebo, including vulvovaginal candidiasis reported for 2.4% (6/252) of astodrimer patients.

**Conclusion:**

These results support a role for Astodrimer 1% Gel as an effective, safe and well-tolerated treatment for women with bacterial vaginosis.

**Keywords:** Astodrimer Gel; bacterial vaginosis; biofilm; dendrimer; SPL7013; treatment; VivaGel®

**INTRODUCTION:**

Bacterial vaginosis (BV) is a syndromic condition resulting from a heterogeneous dysbiosis.<sup>1</sup> The adverse impact of BV symptoms of vaginal odor and discharge on women's social experiences and broader quality of life is significant.<sup>2</sup> Clinical management of BV focuses on treatment of symptoms and follow-up typically only occurs if patients do not get relief from symptoms or relapse.<sup>3,4</sup>

Conventional antibiotics are not well tolerated by patients due to gastrointestinal side effects, interaction with alcohol and high rates of vulvovaginal candidiasis. Relapse of BV after treatment is common. Current treatment options are inadequate to sufficiently address the condition, and alternate therapies are required.<sup>5,6,7,8</sup>

Astodrimer is a dendrimer molecule and has been shown to inhibit growth of several organisms implicated in the pathogenesis of BV, including *Gardnerella vaginalis* and *Prevotella bivia*. Astodrimer blocks bacterial attachment, and disrupts and prevents formation of bacterial biofilms, so that potential for development of resistance is low. It is not systemically absorbed, helping avoid potential systemic side effects common to antibiotics.<sup>9,10</sup>

The efficacy of Astodrimer 1% Gel for treatment of BV was initially demonstrated in a Phase 2 study of similar design to the current studies, in which the product was superior to placebo by all efficacy measures.<sup>11</sup> The current studies aimed to confirm the utility of Astodrimer 1% Gel for treatment of women with BV.



## MATERIALS AND METHODS:

### Study Design

These were two Phase 3, double-blind, multicenter, randomized, placebo-controlled studies (Study 1 and Study 2) to confirm the efficacy and safety of Astodrimmer 1% Gel compared with placebo (hydroxyethyl cellulose placebo gel)<sup>12,13</sup>, in women with BV.

The studies complied with the Declaration of Helsinki, Good Clinical Practice, regulatory guidelines and relevant local legislation, and were approved by an institutional review board on 24 February 2012 (Quorum Review, Inc.). The studies were registered on [clinicaltrials.gov](http://clinicaltrials.gov) on 12 April 2012 (NCT01577238 and NCT01577537).

All patients provided written informed consent and were screened for eligibility at the baseline visit (study day 1).

Eligible women were randomized in a 1:1 ratio using a computer-generated randomization list to Astodrimmer 1% Gel or placebo gel, which were colorless gels packaged in identical, pre-filled, vaginal applicators, each containing a single dose (5g).

Women self-administered a dose vaginally once daily for 7 days and then attended an end of treatment (EOT) visit between study days 9-12. A 2-3 week follow-up period concluded with a visit between study days 21-30. Both care providers and patients were unaware of treatment allocations throughout the study. Patients could withdraw from the study at any time, for any reason.

Women who reported no improvement in BV symptoms, or who relapsed between EOT and the follow-up visit, could request rescue medication, provided the investigator confirmed the presence of BV. Women who received rescue medication were considered failures with respect to clinical cure and were assessed for safety up to the final study visit (days 21-30).

At each visit, women had a pelvic/gynecological examination, adverse events (AEs) were recorded, BV symptoms were reviewed, and protocol adherence was assessed. Women completed diary cards to capture data on symptoms, sexual activity, menstruation, and AEs.

### **Study Population**

Post-menarchal women aged 12 years or older, with a diagnosis of BV defined as presence of 4 Amsel criteria (discharge; vaginal fluid pH >4.5;  $\geq 20\%$  clue cells; and positive 10% potassium hydroxide whiff test)<sup>14</sup> and Nugent score (NS)  $\geq 4$ <sup>15</sup> were eligible. The protocol allowed enrolment before confirmation of a NS  $\geq 4$  if an OSOM<sup>®</sup> BV Blue<sup>®</sup> test (Sekisui Diagnostics; Burlington MA, USA) returned a positive result.

Women who were pregnant, planning to become pregnant, lactating, or within 3 months of last pregnancy outcome at enrolment, and women testing positive for urinary tract infection, or who had signs/symptoms of active genital herpes simplex virus or other sexually transmitted infection (STI) at screening were excluded from participation.

Women who had received antifungal or antimicrobial therapy (systemic or intravaginal) within 14 days of enrolment were also excluded. *Chlamydia trachomatis*, *Neisseria*

*gonorrhoeae* and *Trichomonas vaginalis* testing was conducted at screening but results were unavailable at the time of randomization.

Concomitant vaginal or systemic antibiotic and vaginal antifungal therapies were prohibited during the study and use of other vaginally administered products was discouraged.

### **Outcomes**

The primary efficacy endpoint was clinical cure defined as normal physiological discharge, whiff test negative for amine odor, and <20% clue cells.

At the time of study conduct, the US Food and Drug Administration (FDA) required the assessment at study days 21-30 be the primary endpoint in accordance with its 1998 guidance on BV. In 2016, FDA re-issued its guidance on BV recommending the primary assessment of cure be at study days 7-14. This timing is consistent with study days 7-10 for assessment of treatment success proposed by a US National Institutes of Health workshop on BV clinical practice<sup>16</sup>, and with the timing of the key, pre-specified endpoint at day 9-12 used in the current studies.

For this reason, the original primary endpoint at day 21-30 was changed to day 9-12 and clinical cure at day 21-30 became a secondary endpoint.

Other secondary efficacy measures assessed at day 9-12 and the follow-up visit included Nugent cure ( $NS \leq 3$ ), and absence of vaginal discharge and vaginal odor reported by the patients.

Additional assessments included resolution of each individual Amsel criterion, NS and use of rescue medication.

Clinical cure was also assessed for population subgroups including baseline NS, condom use during the studies, number of previous episodes of BV in the past 12 months, use of vaginal products during the studies, menses occurring during the studies, and by geographic region (Study 2 only).

AEs were monitored throughout the studies.

### **Statistical Analyses**

Primary and secondary efficacy analyses using the Cochran-Mantel-Haenszel test controlling for study center were performed on the modified intent-to-treat (mITT) population, which was all patients randomized who had administered  $\geq 1$  dose of study product and had a NS  $\geq 4$  at the baseline visit. Missing data were imputed as failure.

The safety population was all patients randomized who received  $\geq 1$  dose of study product.

Sensitivity analyses (last-observation-carried-forward [LOCF] and “as observed”) were applied to participants who received rescue medication, with the last observation prior to rescue medication being carried forward. Absence of symptoms at day 9-12 and follow-up is reported using LOCF.

### **Sample Size Calculation**

Assuming clinical cure rates of 30% and 12% for Astodrimmer 1% Gel and placebo, respectively, a sample size of 212 evaluable participants provided 90% power to detect a treatment difference with a significance level of  $\alpha=.05$  (2-sided). Assuming a 12% attrition rate, 120 subjects per treatment arm and 240 subjects overall in each study were to be randomized.

## RESULTS:

### Disposition and Demographics

Between March and July 2012, a total of 250 women were randomized to Astodrimmer 1% Gel (astodrimmer) (N=127, 50.8%) or placebo (N=123, 49.2%) at 17 US sites in Study 1. In Study 2, 251 women were randomized to astodrimmer (N=128, 51.0%) or placebo (N=123, 49.0%) between April and October 2012 at 11 centers in the US, 3 in Belgium and 3 in Germany. The mITT population included 232 women in Study 1 and 237 women in Study 2. Treatment groups were well-balanced with respect to demographic and baseline characteristics, with the exception that the proportion of patients with Nugent score 7 to 10 at baseline was lower in the placebo group compared with astodrimmer in Study 2 (Table 1). The majority of women completed the study (Figure 1).

### Efficacy

Astodrimmer was superior to placebo for the primary outcome measure at day 9-12. In Study 1, 50.4% (59/117) of women given astodrimmer achieved clinical cure compared to 16.5% (19/115) for placebo ( $P<.001$ ); in Study 2, clinical cure rates were 56.7% (68/120) vs 21.4% (25/117), respectively ( $P<.001$ ) (Table 2).

The proportions of patients with resolution of individual Amsel criteria, including pH, were statistically significantly higher for astodrimmer patients vs placebo at day 9-12 in both Study 1 (data not shown) and Study 2 (Figure 2).

Resolution of BV symptoms at day 9-12 was also superior for women given astodrimmer compared with placebo (Table 2). A post-hoc analysis of study diary data showed that

more than 50% of women were odor-free within 1 day of the first astodrimer dose (Figure 3).

Nugent cure proportions at day 9-12 were 12.8% (15/117) vs 2.6% (3/115,  $P=.004$ ) (Study 1) and 13.3% (16/120) vs 5.1% (6/117,  $P=.030$ ) (Study 2) for astodrimer vs placebo. A majority of the participants in the astodrimer groups (61.1% [58/95] and 63.7% [72/113]) had a NS in the 0-6 range at day 9-12, compared with 7.5% (8/107) and 14.2% (15/106) for placebo ( $P<.001$ ).

Differences between groups narrowed at the follow-up visit but still favored astodrimer, and were in some cases statistically significant. Clinical cure proportions at the follow-up visit were 28.2% (31/117) and 30.8% (37/120) for astodrimer (Study 1 and 2, respectively) compared with 20.9% (24/115) and 28.2% (33/117) for placebo ( $P>.05$ ).

Vaginal discharge and vaginal odor were absent at follow-up (day 21-30) for a majority of women in the astodrimer group (Discharge: 61/117 [52.1%] and 72/120 [60.0%] in Study 1 and 2, respectively; Odor: 61/117 [52.1%] and 76/120 [63.3%]) compared with placebo (Discharge: 43/115 [37.4%],  $P=0.023$  and 59/117 [50.4%],  $P=0.131$ ; Odor: 51/115 [44.3%],  $P=0.222$  and 54/117 [37.4%],  $P=0.006$ ).

Slightly fewer women receiving astodrimer (53/117 [45.3%] and 58/120 women [48.3%] in Study 1 and 2, respectively) used rescue medication (typically metronidazole 0.75% vaginal gel) compared with placebo (59/115 [51.3%] and 67/117 [57.3%] women). Of these, most received the rescue medication at the follow-up visit.

When the primary efficacy analysis of clinical cure at day 9-12 was conducted in the

subgroup of patients with baseline NS  $\geq 7$ , astodrimer was also superior to placebo: 52.7% (58/110) vs 17.3% (19/110); and 57.5% (65/113) vs 14% (14/100) in Study 1 and 2, respectively; both  $P < .001$ . The treatment effect in this subgroup was greater than the effect in the subgroup of patients with baseline NS  $< 7$  in Study 2 ( $P < .002$ ). There was no difference in treatment effect in either study for any other subgroups assessed.

Based on diary data for both studies combined, a somewhat higher proportion of women reported penile-vaginal intercourse and unprotected sex in the astodrimer group (59.1% and 29.8%, respectively) than placebo (53.0% and 26.0%) between EOT and follow-up. Menstrual bleeding and tampon use were also more frequent in the astodrimer group (47.4% and 25.2%) compared to the placebo group (43.6% and 17.2%) between EOT and follow-up.

### **Safety/tolerability**

The overall incidence of AEs in the combined safety population was 41.4% (101/244) for placebo and 42.9% (108/252) for astodrimer (Table 3). AEs potentially related to treatment occurred in 9.4% (23/244) of placebo patients vs 14.7% (37/252) for astodrimer.

Vulvovaginal candidiasis, regardless of relationship to treatment, was reported in 15 (6.0%) and 9 (3.7%) women in the astodrimer and placebo groups, respectively.

Vulvovaginal candidiasis considered potentially related to study treatment was reported in 6/252 (2.4%) of patients using astodrimer vs 0/244 (0%) in placebo.

Most AEs were mild or moderate in intensity, and self-limiting. One patient using



astodrimmer discontinued treatment and the study due to a case of vaginal hemorrhage that was of moderate intensity and deemed unrelated to study treatment. One serious AE (pneumonia on day 27 requiring hospitalization) for a participant given astodrimmer was also considered unrelated to study treatment.

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**COMMENT:**

Astodrimer is a novel dendrimer administered vaginally and is not systemically absorbed.<sup>8,9</sup> Unpublished data show that it is able to inhibit formation of and disrupt biofilms, likely due to its ability to block bacterial adhesion. Therefore, astodrimer avoids issues typically associated with conventional antibiotics, such as systemic side effects and antibiotic resistance, and overgrowth of *Candida* species following treatment is minimal.

In these studies, clinical cure rates for astodrimer at day 9-12 (50-59%) were comparable to cure rates reported for conventional antibiotic products such as secnidazole using comparable cure criteria at a similar timeframe (58%).<sup>17</sup>

The absence of symptoms observed at day 9-12 and at follow-up is of particular importance for the routine clinical management of BV since patients will only return to the clinic if their symptoms persist or recur. Speed of resolution of BV symptoms is also important, because of the negative impact of BV symptoms on overall quality of life, relationships, and ability to work.<sup>2</sup> While >50% of women had absence of vaginal odor within 1 day of first astodrimer dose, a study of metronidazole 0.75% gel showed median time to resolution of vaginal odor of 3 days.<sup>18</sup>

Differences between astodrimer and placebo were in most cases no longer statistically significant at the follow-up visit, although women given astodrimer still showed a slightly better response than those given placebo across most efficacy endpoints.

As comparison, a recent study of metronidazole 0.75% gel showed that the clinical cure

rate at the follow-up timepoint was 28.8%<sup>17</sup>, which is similar to the cure rates observed at a similar time in our current studies. In that same study, the percentage of patients without relapse of symptoms at the day 21-30 study visit was approximately 22%, which is approximately half the percentage seen with astodrimmer.

BV shares some characteristics with STIs<sup>19</sup>, whereby re-exposure to triggers of BV, such as unprotected sex, douching or menses, may result in re-infection or relapse. In the current studies, there was a trend showing a somewhat higher proportion of women given astodrimmer compared with placebo engaged in unprotected sex or had menses between the day 9-12 and follow-up visits, potentially increasing the likelihood of BV recurrence in this treatment group. This finding, along with unexpectedly high and improving cure rates for placebo between EOT and follow-up, may have led to narrowing of the differences in response between astodrimmer and placebo, and the need for rescue medication at follow-up, which was similar between treatment groups.

Most episodes of candidiasis occurred during follow-up, which is expected after treatment of BV, but did not require treatment. The low incidence of candidiasis following treatment with astodrimmer contrasts favorably with the frequency for conventional antibiotic therapies, such as single dose oral secnidazole (13.6% vs 4.7% in placebo).<sup>16</sup>

Despite the narrowing of response and similar level of use of rescue therapy at follow-up in this study, the non-antibiotic mechanism and well-tolerated safety profile of Astodrimmer Gel means that the product may be better-suited than standard antibiotic therapies for repeat courses, and for longer-term maintenance or preventive therapy in

cases where that is required. Studies have shown continuing use of the product is able to prevent recurrence of BV.<sup>20</sup>

### **Strengths and limitations**

Strengths of the studies were that they were both well-controlled, double-blind, multicenter, placebo-controlled, and randomized Phase 3 studies. The studies were adequately powered to detect a difference in BV cure rates between astodrimmer and placebo.

A limitation is that the analysis of efficacy at day 9-12 was not the pre-specified primary endpoint of the studies. However, the risk of type I error in interpreting these results is minimized because assessment at day 9-12 was the sponsor's preferred primary endpoint when designing the studies and was a key, pre-specified secondary endpoint. In addition, the change in presentation was only made after the FDA published revised guidance on BV in 2016. In addition, the clinical response at day 9-12 was consistent across these two Phase 3 studies as well as the Phase 2 study<sup>10</sup>, with substantially homogenous relative risks of cure that consistently favored astodrimmer vs placebo (i.e., *P* values consistently <.001).

### **Conclusions**

Astodrimmer is a novel therapy, which acts locally, is not systemically absorbed and has a non-antibiotic mechanism of action related to effects on biofilms, thereby avoiding potential issues associated with conventional antibiotics.

These studies demonstrated that Astodrimmer 1% Gel, once daily for 7 days, was

effective and well-tolerated for the treatment of women with BV, including relief of symptoms. Astodrimmer has potential to fulfil areas of unmet clinical need in treatment of BV, such as women who fail to respond to or are intolerant of existing antibiotic therapies for BV, or who want an alternate treatment modality.

### **Declaration of interests**

Dr Chavoustie (Segal Institute, Miami, FL, USA) received research funding from Starpharma Pty Ltd for participating in this multicenter study.

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.

Dr Waldbaum (Downtown Women's Health Care, Denver, CO, USA) received research funding from Starpharma Pty Ltd for participating in this multicenter study and from Gage Development Company.

Prof Dr Donders (Femicare Clinical Research for Women, Tienen; Department of Obstetrics and Gynecology, The Regional Hospital Heilig Hart, Tienen; and University Hospital Antwerp, Antwerp, Belgium) received research funding from Starpharma Pty Ltd for participating in this multicenter study.

Dr Peters (Praxis Dr Peters, Hamburg, Germany) received research funding from Starpharma Pty Ltd for participating in this multicenter study.

Dr Schwebke is a paid consultant for Starpharma Pty Ltd, Talis One, Toltec, Lupin Pharmaceuticals, and Hologic.

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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TABLES:

**Table 1: Baseline Characteristics (modified intent-to-treat population), by treatment group**

	Study 1		Study 2	
	Astodrimer (N=117)	Placebo (N=115)	Astodrimer (N=120)	Placebo (N=117)
Age (yr)				
Mean (SD)	32.3 (10.0)	32.9 (9.7)	34.9 (9.9)	36.2 (12.3)
Range	18 to 57	18 to 57	18 to 59	19 to 88
Race, n (%)				
White	48 (41.0)	40 (34.8)	62 (51.7)	60 (51.3)
Black	62 (53.0)	68 (59.1)	54 (45.0)	51 (43.6)
All Others <sup>a</sup>	7 (6.0)	7 (6.1)	4 (3.3)	6 (5.1)
Nugent Score, n (%)				
4 to 6	7 (6.0)	5 (4.3)	7 (5.8)	17 (14.5)
7 to 10	110 (94.0)	110 (95.7)	113 (94.2)	100 (85.5)

N=number of patients; n=number of patients with observation; yr =years;  
SD=standard deviation

<sup>a</sup> All Others=Native American or Alaskan Native, Native Hawaiian or Other Pacific Islander, Middle Eastern, Multiple (i.e., White/African-American, White/African-American/American Indian, White/Hispanic, White/Mexican, Black/Haitian, Black/Dominican).

**Table 2: Efficacy outcomes at end of treatment (study days 9 to 12) (modified intent-to-treat population), by study and treatment group**

Endpoint	Astodrimet	Placebo	RR (95% CI)	P value
	n/N (%) [95% CI]	n/N (%) [95% CI]		
<b>Study 1</b>				
<b>Clinical Cure<sup>a</sup></b>	59/117 (50.4) [41.0, 59.8]	19/115 (16.5) [10.3, 24.6]	3.05 (1.95, 4.78)	<.001 <sup>b</sup>
<b>Clinical Cure<sup>c</sup></b>	59/105 (56.2) [46.2, 65.9]	19/108 (17.6) [10.9, 26.1]	3.19 (2.05, 4.97)	<.001 <sup>b</sup>
<b>Absence of Discharge<sup>c</sup></b>	67/106 (63.2) [53.3, 72.4]	49/110 (44.5) [35.1, 54.3]	1.42 (1.10, 1.83)	.010 <sup>b</sup>
<b>Absence of Odor<sup>c</sup></b>	83/106 (78.3) [69.2, 85.7]	51/110 (46.4) [36.8, 56.1]	1.69 (1.35, 2.11)	<.001 <sup>b</sup>
<b>Study 2</b>				
<b>Clinical Cure<sup>a</sup></b>	68/120 (56.7) [47.3, 65.7]	25/117 (21.4) [14.3, 29.9]	2.65 (1.81, 3.88)	<.001 <sup>b</sup>
<b>Clinical Cure<sup>c</sup></b>	68/116 (58.6) [49.1, 67.7]	25/111 (22.5) [15.1, 31.4]	2.60 (1.78, 3.80)	<.001 <sup>b</sup>
<b>Absence of Discharge<sup>c</sup></b>	88/117 (75.2) [66.4, 82.7]	51/109 (46.8) [37.2, 56.6]	1.61 (1.28, 2.01)	<.001 <sup>b</sup>
<b>Absence of Odor<sup>c</sup></b>	96/117 (82.1) [73.9, 88.5]	49/109 (45.0) [35.4, 54.8]	1.83 (1.46, 2.28)	<.001 <sup>b</sup>

N=number of patients; n=number of patients with observation; CI=confidence interval; RR=relative risk (of event)

<sup>a</sup> Missing values imputed as failures

<sup>b</sup> Indicates statistical significance

<sup>c</sup> As observed (no imputation of missing values)

**Table 3: Tolerability (safety population: Study 1 and 2 combined), by treatment group**

<b>Incidence of AEs</b>	<b>Astodrimer</b>	<b>Placebo</b>
<b>Parameter</b>	<b>N=252</b> <b>n (%)</b>	<b>N=244</b> <b>n (%)</b>
Patients with $\geq 1$ AE	108 (42.9)	101 (41.4)
Patients with $\geq 1$ AE considered by investigator to be related to study treatment	37 (14.7)	23 (9.4)
Patients with $\geq 1$ severe AE	1 (0.4)	5 (2.0)
Patients with $\geq 1$ serious AE	1 (0.4)	0
Patients who stopped treatment due to AE	1 (0.4)	0
AE of special interest		
Urinary Tract Infection	4 (1.6)	3 (1.2)
Vulvovaginal Candidiasis	15 (6.0)	9 (3.7)
AEs (incidence $\geq 5\%$ )		
Headache	19 (7.5)	17 (7.0)
Vulvovaginal Candidiasis	15 (6.0)	9 (3.7)
Vulvovaginal Pruritus	13 (5.2)	11 (4.5)
AEs considered by investigator to be related to study treatment (incidence $\geq 2\%$ )		
Vulvovaginal Pruritus	9 (3.6)	5 (2.1)
Vulvovaginal Burning Sensation	6 (2.4)	2 (0.8)
Vulvovaginal Candidiasis	6 (2.4)	0 (0)
Vulvovaginal Discomfort	1 (0.4)	6 (2.5)

AE=adverse event; N=number of patients; n=number of patients with observation

**FIGURE LEGENDS:**

Figure 1: CONSORT diagram

Figure 1 Description: Study 1 and Study 2 CONSORT diagrams

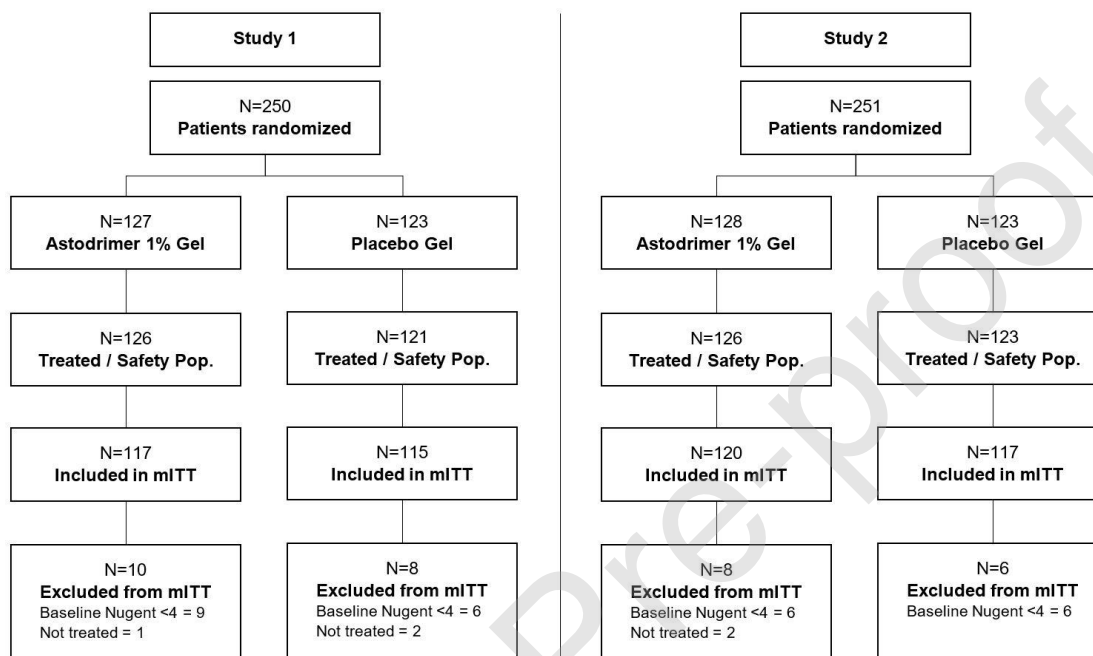


Figure 2: Proportion of patients with resolution of Amsel criteria at day 9-12 for Astodrimers 1% Gel or placebo – Study 2

Figure 2 Description: Proportion of patients with resolution of individual Amsel criteria at day 9-12 for Astodrimers 1% Gel or placebo, by treatment group in Study 2 (Astodrimers 1% Gel: N=120; Placebo: N=117)

Resolution of Amsel Criteria at EOT (mITT) - Study 2

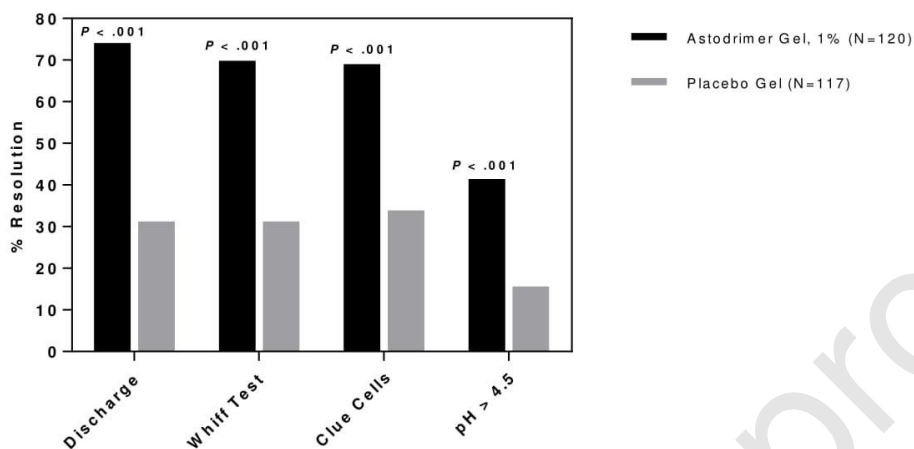


Figure 3: Proportion of patients odor-free by day after first dose of Astodimer 1% Gel or placebo

Figure 3 Description: Proportion of patients odor-free by day after first dose of

Astodrimmer 1% Gel or placebo, by treatment group (Study 1 Astodrimmer 1% Gel: N=116; Study 2 Astodrimmer 1% Gel: N=122; Study 1 Placebo: N=112; Study 2 Placebo: N=117)

