Astodrimer Gel for Treatment of Bacterial Vaginosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Bacterial vaginosis is a frequent source of vaginal infection among reproductive-aged women. Astodrimer gel is a novel drug which demonstrated favorable outcomes for treatment of patients with bacterial vaginosis. Aim: We attempted to conduct a systematic review and meta-analysis of all randomized controlled trials (RCTs) which examined the efficacy and safety of astodrimer gel in patients with bacterial vaginosis. Methods: We searched four databases from inception to August 15th, 2020 using relevant keywords. We identified all RCTs which surveyed the efficacy and safety of astodrimer gel in treating patients with bacterial vaginosis. We appraised the quality of the included RCTs using the Cochrane risk of bias assessment tool. We pooled dichotomous outcomes as numbers and totals and reported them as risk ratios (RR) with 95% confidence intervals (95% CI) under random- or fixed-effects meta-analysis models depending on heterogeneity. Results: Three eligible studies comprising four independent RCTs and 1165 patients were identified (614 and 551 patients received astodrimer gel and placebo, respectively). For efficacy outcomes (n=320 astodrimer gel versus n=260 placebo), astodrimer gel was significantly superior to placebo for all pooled efficacy outcomes, including clinical cure rate (at 9-12 and 21-30 days), microbiological Nugent cure rate (at 9-12 and 21-30 days), patient self-reported absence of vaginal odor/discharge (at 9-12 and 21-30 days), resolution of Amsel criteria (at 9-12 days) and percentage of patients who received rescue therapy (during study). With respect to safety outcomes (n=614 astodrimer gel versus n=551 placebo), astodrimer gel demonstrated equal tolerability to placebo for all pooled safety endpoints, expect unfavorably for vulvovaginal candidiasis and treatment-related vulvovaginal candidiasis. Conclusions: Astodrimer gel is effective in treating bacterial vaginosis and corroborated by clinical (Amsel criteria) and microbiological (Nugent score) measurements as well as patient-reported symptoms. Moreover, astodrimer gel is largely safe and associated with marginal rate of vulvovaginal candidiasis.

KEYWORDS

Astodrimer gel; SPL7013; bacterial vaginosis; Gardnerella vaginalis; meta-analysis

REVIEW CRITERIA

- We carried out a systematic review and meta-analysis of all RCTs which surveyed the efficacy and safety of astodrimer gel versus placebo in treating patients with bacterial vaginosis.

- We searched four (Cochrane Central, PubMed, Scopus, and Web of Science) databases from inception to August 15th using relevant keywords and specific inclusion/exclusion criteria.
- We pooled dichotomous outcomes as risk ratios with 95% confidence intervals, both under random- or fixed-effects meta-analysis models.

MESSAGE FOR THE CLINIC

- Astodrimer gel is safe and superior to placebo in treating patients with bacterial vaginosis.
- Unique features of astodrimer gel include satisfactory effectiveness, well-endured safety profile, negligible rate of vulvovaginal candidiasis, topical administration, reduced systemic exposure, anti-biofilm activity, non-antibiotic mechanism of action and absence of antibiotic resistance.
- Astodrimer gel may represent a promising alternative therapy to patients who fail to respond or intolerant to various conventional antibiotics.

1. INTRODUCTION

Globally, bacterial vaginosis is the most frequent source of vaginal infection among reproductive-aged women.[1] Its approximated worldwide prevalence is high ranging from 23% to 29%.[1] Clinically, it is correlated with amplified risks for adverse infectious and obstetric aftermaths, such as pelvic inflammatory disease, human immunodeficiency virus infection, sexually transmitted infections, abortion, preterm delivery, miscarriage and postoperative endometritis.[2-5]

The standard of care for bacterial vaginosis includes oral or vaginal antimicrobial therapies. Such therapies largely comprise clindamycin and 5-nitroimidazole derivatives (most commonly, metronidazole, tinidazole and secnidazole).[6] However, these available conventional antimicrobial therapies are unsatisfactory for various factors. Such factors include the unfavorable gastrointestinal adverse events, high frequencies of vulvovaginal candidiasis, medication interaction with alcohol, insufficient targeting of the pathogenic bacterial vaginosis biofilms and high recurrence rates post treatment.[7-15] Probiotics have been shown to be beneficial for bacterial vaginosis treatment when compared to placebo.[16] Nevertheless, no studies are available for head-to-head comparison between probiotics and conventional antimicrobial therapies to establish the tangible therapeutic impact of probiotics for treatment of bacterial vaginosis.[16] A recent report demonstrates no substantial benefit of combination metronidazole and probiotics versus monotherapy metronidazole for treatment of bacterial vaginosis.[17] All in all, there is a pressing requirement to conceive alternative treatments for bacterial vaginosis.

Astodrimer gel (also known as VivaGel® or SPL7013) is a novel muco-adhesive gel that belongs to a unique class of dendrimers—highly branched nanoparticles with microbicidal actions against bacteria and viruses.[18, 19] Astodrimer gel has been illustrated in healthy women to be well-endured without systemic absorption.[20, 21] Thus, astodrimer gel is advantageous over conventional antibiotics that give rise to drug-related systemic adverse events. Four randomized controlled trials (RCTs) have demonstrated favorable outcomes for astodrimer gel for treatment of patients with bacterial vaginosis.[22-24]Mechanistically, astodrimer gel has been depicted to suppress propagation of bacterial pathogens involved in bacterial vaginosis, including *Gardnerella vaginalis* .[22, 23] When compared to conventional antibiotics, the novel mechanism of action of astodrimer gel involves hindering bacterial attachment to vaginal epithelial cells as well as interrupting and thwarting formation of bacterial biofilms.[22, 23] Thus, the potential for development of therapy resistance or relapse is minimized with astodrimer gel when compared to conventional antibiotics.

The aim of this systematic review and meta-analysis is to pool the available evidence from RCTs that examined the efficacy and safety of astodrimer gel for the treatment of patients with bacterial vaginosis.

2. METHODS

We conducted this systematic review and meta-analysis in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[25]

2.1. Literature Search

We searched PubMed, Cochrane Library, Web of Science and Scopus databases using the following search strategy: (astodrimer OR SPL7013 OR "SPL 7013" OR SPL-7013 OR BRI7013 OR BRI-7013). We targeted all publications from inception to August 15th, 2020, that matched our eligibility criteria.

2.2. Inclusion and Exclusion Criteria

We selected all studies that met the following criteria for our PICOS evidence-based research question: 1) Patients: individuals with bacterial vaginosis, 2) Intervention: astodrimer gel, 3) Comparator: placebo, 4) Outcomes: efficacy endpoints during active status of bacterial vaginosis and safety endpoints, and 5) Study design: RCTs. We excluded abstracts, non-randomized trials, patients with conditions other than bacterial vaginosis, animal trials, and studies that did not report any of our outcomes.

2.3. Screening of Results

After retrieving the search results, the included articles were screened through two steps. The first step comprised title and abstract screening. Preliminary included articles from the first step entered step two which involved full-text screening. We obtained the full-text for all included studies and carefully examined them for final inclusion. Additionally, we screened the references of the included research studies. One screened abstract prompted us to identify a relevant RCT that was posted in a preprint server and we eventually included it in our analysis.[24]

2.4. Data Extraction

After completing the screening process, we commenced the data extraction step. Four investigators extracted data. Three main categories of data were extracted: 1) baseline characteristics of the included studies and clinico-demographic information of the research subjects, 2) efficacy endpoints, and 3) safety outcomes. Efficacy endpoints included clinical cure rate at 9-12 and 21-30 days, Nugent cure rate at 9-12 and 21-30 days, patient self-reported absence of vaginal odor at 9-12 and 21-30 days, patient self-reported absence of vaginal discharge at 9-12 and 21-30 days, resolution of Amsel criteria (pH, Whiff test, clue cells >20%, and vaginal discharge)[26] and administration of rescue therapy. Safety outcomes included patients with [?]1 adverse event (AE), patients with [?]1 treatment-related AE, patients with [?]1 severe AE, patients with [?]1 serious AE, urinary tract infection, vulvovaginal candidiasis, treatment-related vulvovaginal candidiasis and patients who stopped treatment due to an AE. Clinical cure was defined as absence of Amsel criteria. Nugent cure was defined was Nugent score [?]3 when a score of [?]7 was identified at baseline.

2.5. Quality Assessment

To assess the risk of bias among the included studies, we used the Cochrane's risk of bias tool.[27] This tool evaluates the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. Two investigators independently assessed the quality of the eligible studies and discrepancies were resolved by a third investigator, if applicable. The investigators' judgment comprised low, unclear, or high risk of bias for each evaluated domain.

2.6. Data Synthesis

One study used three different concentrations of astodrimer gel as following: 0.5%, 1%, and 3%.[23] We considered each dose as a separate study during statistical analysis. Another study reported the findings of two stand-alone clinical trials, both of which used the same dose of 1%.[22] Likewise, we considered each clinical trial as a separate study during statistical analysis. We analyzed dichotomous data using the Mantel-Hanszel method and reported outcomes as risk ratios (RR) with 95% confidence intervals (95% CI). The analysis of efficacy endpoints was conducted using the Review Manager Software version 5.3. The analysis of safety outcomes was conducted using the OpenMeta[Analyst] software. Two main tests were used to indicate inconsistency among studies, namely p-value of the Chi-square test and I-square test (I^2).[28] Values of $p<0.1$ and $I2>50\%$ were considered significant identifiers of heterogeneity. Homogeneous data were analyzed under

a fixed-effects model while heterogeneous data were analyzed under a random-effects model. A sensitivity analysis (leave-one-out) would be performed to resolve heterogeneity, if applicable. This would be achieved by excluding one study at a time and witnessing whether the heterogeneity would be resolved. Moreover, we performed a subgroup analysis at 9-12 and 21-30 days for selected efficacy outcomes. We could not assess publication bias of the included studies using Egger's funnel plots. This is because the number of included studies was less than the minimum required number, which is ten studies.[29]

3. RESULTS

3.1 Characteristics of included studies

Figure 1 shows the PRISMA flow chart for our literature search. The search process of four medical databases resulted in the retrieval of 156 unique records after removal of duplicates. After we performed the screening of titles and abstracts, 11 full-text studies were rigorously screened against the inclusion and exclusion criteria. Finally, we found three studies to be eligible for this systematic review and meta-analysis, reporting a total of four independent RCTs with 1165 patients with bacterial vaginosis (614 and 551 patients received astodrimer gel and placebo, respectively). **Table 1**depicts a summary of the baseline characteristics of included studies and the clinico-demographic information of research subjects.

3.2. Results of risk of bias assessment

The studies were of high quality and we found an overall low risk of bias among the included studies. **Figure 2** shows the risk of bias summary and graph.

3.3. Analysis of efficacy outcomes

3.3.1. Clinical cure rate

Three RCTs were meta-analyzed (**Figure 3**).[22, 23] The pooled RR significantly favored the astodrimer gel group over placebo group (RR=2.10 [1.76, 2.51], p<0.01). Subgroup analysis showed that clinical cure rates were significantly higher in the astodrimer gel group at 9-12 days (RR=2.86 [2.25, 3.64], p<0.01) and 21-30 days (RR=1.39 [1.06, 1.83], p=0.02) when compared to the placebo group. The pooled analyses were homogeneous (p=0.94 and p=0.2, respectively).

3.3.2. Nugent cure rate

Three RCTs were meta-analyzed (**Figure 4**).[22, 23] The pooled RR significantly favored the astodrimer gel group over placebo group (RR=4.41 [2.49, 7.81], p<0.01). Subgroup analysis showed that Nugent cure rates were significantly higher in the astodrimer gel group at 9-12 days (RR= 4.65 [2.44, 8.89], p<0.01) and 21-30 days (RR= 3.55 [1.03, 12.22], p=0.04) when compared to the placebo group. The pooled analysis were homogeneous (p=0.56 and p=0.91, respectively).

3.3.3. Percentage of patients with self-reported absence of vaginal odor

Three RCTs were meta-analyzed (**Figure 5**).[22, 23] The pooled RR significantly favored the astodrimer gel group over placebo group (RR=1.57 [1.40, 1.77], p<0.01). Subgroup analysis showed that the astodrimer group was significantly superior to placebo group with respect to the percentage of patients with absence of vaginal odor at 9-12 days (RR=1.83 [1.57, 2.14], p<0.01) and 21-30 days (RR= 1.33 [1.12, 1.58], p<0.01). The pooled analyses were homogeneous (p=0.3 and p=0.27, respectively).

3.3.4. Percentage of patients with self-reported absence of vaginal discharge

Three RCTs were meta-analyzed (**Figure 6**).[22, 23] The pooled RR significantly favored the astodrimer gel group over placebo group (RR=1.45 [1.29, 1.64], p<0.01). Subgroup analysis showed that the astodrimer group was significantly superior to placebo group with respect to the percentage of patients with absence of vaginal discharge at 9-12 days (RR=1.57 [1.33, 1.85], p<0.01) and 21-30 days (RR=1.34 [1.12, 1.60], p<0.01). The pooled analyses were homogeneous (p=0.42 and p=0.19, respectively).

3.3.5. Percentage of patients with resolution of Amsel criteria

Two RCTs were meta-analyzed (**Figure 7**).[22, 23]The overall RR significantly favored astodrimer gel group over placebo group with regard to resolution of pH (RR=2.85 [1.81, 4.48], p<0.01), resolution of Whiff test (RR=2.36 [1.79, 3.10], p<0.01), resolution of clue cells (RR=2.27 [1.74, 2.95], p<0.01) and resolution of vaginal discharge (RR=2.46 [1.89, 3.18], p<0.01) at 9-12 days. The pooled analyses were homogenous (p=0.46, p=0.58, p=0.17 and p=77, respectively).

3.3.6. Percentage of patients who received rescue therapy

Three RCTs were meta-analyzed (**Figure 8**).[22, 23] The pooled RR significantly favored the astodrimer gel group over placebo group (RR=0.70 [0.54, 0.90], p=0.005). The pooled analysis was heterogeneous (p=0.04). Heterogeneity was resolved by removing the results of Waldbaum 2020 (1%) and the overall RR still significantly favored astodrimer gel group over placebo group (RR=0.79 [0.67, 0.93], p=0.004; heterogeneity I^2=10%, p=0.34).

3.4. Analysis of Safety endpoints

Three studies comprising four RCTs were meta-analyzed for safety outcomes (**Supplementary File 1**).[22-24] When compared to placebo, astodrimer gel favorably reduced the incidence of severe AEs (RR=0.373, 95% CI [0.146, 0.950], p=0.039). Pooled analysis was homogenous (p=0.519). However, astodrimer gel significantly correlated with an increased incidence of vulvovaginal candidiasis (RR=1.427, 95% CI [1.025, 1.986], p=0.035) and treatment-related vulvovaginal candidiasis (RR=1.181, 95% CI [1.020, 3.239], p=0.043). Pooled analyses were homogenous (p=0.910 and p=0.566, respectively). On the hand, the overall RR presented no significant difference between astodrimer gel and placebo groups regarding patients with [?]1 AE (RR=1.056, 95% CI [0.947, 1.177], p=0.111), patients with [?]1 treatment-related AE (RR=1.252, 95% CI [0.950, 1.651], p=0.327), patients with [?]1 serious AE (RR=1.316, 95% CI [0.296, 5.854], p=0.718), patients who stopped treatment due to AE (RR=0.999, 95% CI [0.292, 3.417], p=0.999) and urinary tract infection (RR=1.740, 95% CI [0.948, 3.193], p=0.074). Pooled analyses were homogenous (p=0.492, p=0.780, p=0.549, p=0.444 and p=0.123).

4. DISCUSSION

4.1. Summary of findings

With regard to astodrimer gel versus placebo for treatment of bacterial vaginosis, we included three studies comprising four independent RCTs with a total of 1165 patients (614 and 551 patients received astodrimer gel and placebo, respectively). Results obtained from this systematic review and meta-analysis are clinically significant and all the included RCTs are of high quality and low risk of bias.

Astodrimer gel was significantly superior to placebo for all pooled efficacy outcomes, including clinical cure rate, Nugent cure rate, patient self-reported absence of vaginal odor/discharge, resolution of Amsel criteria and percentage of patients who received rescue therapy. These efficacy outcomes consistently favored, without heterogeneity, astodrimer gel over placebo at subgroup analyses at 9-12 and 21-30 days. In 2008, a workshop was conducted by bacterial vaginosis experts from United States National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and Department of Health and Human Services (DHHS).[30] The workshop recommended timeframes of 7-10 and 35-40 days (posttreatment commencement) for assessment of 'early' and 'late' treatment efficacy, respectively. For the included studies in this review, the timeframes 9-12 and 21-30 days are relatively close to the ones recommended by the workshop.[30] Nonetheless, long-term follow-up periods are needed to concretely conclude the efficacy of astodrimer gel in sustaining therapeutic cure and preventing relapse.

The pooled clinical cure rate for bacterial vaginosis at 9-12 days of 59% is relatively analogous to an experimental anti-infective drug TOL-463 (50%)[31] and standard of care antibiotics, such as metronidazole 1.3% gel (46%)[32] and 2-gram secnidazole (58%).[33] Interestingly, the pooled clinical cure rate at 21-30 days was reduced by almost half (30%), suggesting that recurrence of bacterial vaginosis took place. However, this proportion is largely equivalent to metronidazole 0.75% gel administered for five days (29%) in patients with bacterial vaginosis.[34]

Clinically, bacterial vaginosis is characterized by distressing thin white vaginal discharge and fish-like odor.[35] Both symptoms negatively impact infected women at multiple levels, including physically, sexually, emotionally and socially.[36]Thus, the qualitative and speed of resolution of these symptoms are critically important. Chavoustie et al.[22] and Waldbaum et al.[23] demonstrated that more than half the of patients who received astodrimer 1% gel had resolution of vaginal odor within as early as one day post-initiation of treatment. This finding contrasts satisfactorily when compared to the relatively longer median time to resolution of vaginal odor of two and three days for metronidazole 1.3% and 0.75% gel, respectively.[34]

Waldbaum et al.[23] used three different concentrations of astodrimer gel (0.5%, 1%, and 3%). Interestingly, the mid-dose 1% was associated with the best outcomes, in terms of efficacy and safety. This observation is in agreement with the postulation that treatment of bacterial vaginosis with astodrimer gel rectifies the dysbiotic vaginal environment and reestablishes equilibrium of the normal vaginal microbiota.[23] Thus, higher doses of astodrimer gel may negatively exhibit a suppressing impact on normal vaginal bacterial flora, namely lactobacilli. On the other hand, lower doses of astodrimer gel may be not adequate enough to exert an antimicrobial effect. This phenomenon is noted with rifaximin whereby a mid-range dose is associated with the maximum cure proportion in patients with bacterial vaginosis.[37] Based on the efficacy and safety of astodrimer 1% gel, one phase III[38] and two phase II clinical trials were carried out.[22] Due to the small number of included studies, we could not perform meta-regression for the different doses.

With respect to safety profile, astodrimer gel demonstrated equal tolerability to placebo for all pooled safety outcomes, expect for vulvovaginal candidiasis and treatment-related vulvovaginal candidiasis. The pooled proportion of drug-related vulvovaginal candidiasis was only 4.9% (n=31/639) and this proportion compares favorably when contrasted to oral 2-gram secnidazole (13.6%).[33] This overall safety of astodrimer gel can be ascribed to its favorable pharmacokinetics, in terms of topical application and decreased systemic absorption[20, 21] when compared to conventional antibiotics.

4.2. Clinical implications

The etiopathogenesis of BV is not completely delineated. Nonetheless, formation of a pathogenic biofilm—principally by *Gardnerella vaginalis* —is a prime event in bacterial vaginosis.[8, 39] This biofilm has an augmented propensity to attach to vaginal epithelial cells, consequently mediating the adherence and propagation of additional bacterial vaginosis-associated anaerobes, for instance,*Atopobium vaginae* and others. The end result in bacterial vaginosis is a substitution in vaginal microbiota composition from normal Gram-positive lactobacilli to pathogenic anaerobic bacteria, most prominently *Gardnerella vaginalis* .[8, 39] This biofilm barrier persists after therapy. Additionally, it contributes to treatment resistance and relapse by reducing the penetration capability of drugs targeting bacterial vaginosis [8, 40].

Astodrimer gel emerges as a novel therapy for treatment of bacterial vaginosis. When compared to conventional antibiotics, astodrimer gel holds several substantial advantages. Most importantly, astodrimer gel exhibits a unique non-antibiotic based activity against biofilms, in terms of dismantling and suppressing the formation of biofilms implicated in the pathogenesis of bacterial vaginosis. This anti-biofilm activity is principally related to the structural features of astodrimer. To elaborate, astodrimer is a large-sized molecule with negative charge, which favorably impedes the capacity of bacteria to attach to epithelial surfaces, thus eventually inhibiting and disrupting biofilms. This non-antibiotic mechanism of action is highly beneficial, particularly for patients who are intolerant of current antibiotic medications or those who desire a substitute management option. Also, astodrimer gel may be appealing to patients who fail to respond to various conventional antibiotics. Eventually, astodrimer gel evades the hurdle of antibiotic resistance. The satisfactory pharmacokinetic properties of astodrimer gel—particularly local drug application and lack of systemic absorption—further encourage its use in patients with bacterial vaginosis. With regard to safety, astodrimer gel is largely well endured and the rate of posttreatment candidiasis overgrowth is marginal. Overall, astodrimer gel carries the prospect to satisfy the gap of unmet clinical necessity for a more suitable treatment option for patients with bacterial vaginosis.

4.3. Future directions

The optimal dose range of astodrimer gel is yet to be determined, despite the available evidence suggest astodrimer 1% gel is associated with the best efficacy and safety outcomes. More large-sized, placebo-controlled, clinical trials are needed to solidly draw definitive conclusions about the efficacy and safety profiles of astodrimer gel for treatment of patients with bacterial vaginosis. Additionally, head-to-head comparative clinical trials challenging astodrimer gel against conventional antibiotics are warranted to establish therapeutic superiority. Moreover, whether astodrimer gel used as an adjunct to (or in combination with) conventional antibiotics will be beneficial is a question that merits an investigation.

Recurrence of bacterial vaginosis is a major management issue and it remains a plausible question as whether astodrimer gel is effective in preventing recurrence of bacterial vaginosis on the long-term. To that end, a phase 3, placebo-controlled study was completed (but not yet published in a peer-reviewed journal) to investigate the efficacy and safety of astodrimer gel in preventing recurrence of bacterial vaginosis up to four months post successful cure with oral metronidazole. In this trial, a total of 586 patients were cured with metronidazole and randomized to receive astodrimer 1% gel (n=294) or placebo (n=291) at a dose of 5 g vaginally every second day for four months. Overall, astodrimer 1% gel was superior to placebo for the primary and secondary endpoints. Specifically, administration of astodrimer 1% gel resulted in lower percentage of patients with recurrence (based on clinical cure and Amsel criteria), prolonged time to recurrence and decreased percentage of patients with self-reported recurring symptoms of vaginal odor/discharge. All in all, this study proved the superiority of astodrimer 1% gel in decreasing the probability of recurrence of bacterial vaginosis in women with a history of recurrent bacterial vaginosis. Nonetheless, while this study is strongly powered, additional comparative studies are needed to harden the efficacy and safety of monotherapy or combination astodrimer 1% gel in preventing long-term recurrence.

4.4. Study strengths and limitations

Our study has several strengths. Most significantly, this is the first systematic review and meta-analysis report that pooled the efficacy and safety outcomes of astodrimer gel for the treatment of patients with bacterial vaginosis. In addition, we pooled as many efficacy and safety outcomes as possible using meta-analysis as a high-quality study design. Moreover, we conducted subgroup analyses at 9-12 and 21-30 days for all the reported efficacy outcomes. Whenever heterogeneous findings existed, we performed a sensitivity analysis. Nonetheless, our study is not without limitations. Such limitations include the small number of included studies and their respective small sample size. Moreover, two independent clinical trials originated from a single study.[22] Lastly, one of the included studies was published in a preprint server and did not yet undergo peer-review.[24]

5. Conclusions

This systematic review and meta-analysis suggests that in patients with active bacterial vaginosis, astodrimer gel is superior to placebo for all efficacy outcomes, including clinical (Amsel criteria) microbiological (Nugent score) measures as well as patient-reported symptoms. Moreover, astodrimer gel is largely safe and associated with marginal rate of vulvovaginal candidiasis when compared to standard of care antibiotics. Unique features of astodrimer gel include satisfactory effectiveness, well-endured safety profile, negligible rate of vulvovaginal candidiasis, topical administration, reduced systemic exposure, anti-biofilm activity, non-antibiotic mechanism of action and absence of antibiotic resistance. Thus, astodrimer gel may represent a promising alternative therapy to patients who fail to respond or intolerant to various conventional antibiotics. Further placebo- and active comparator-controlled trials with longer follow-up periods are needed to solidify the therapeutic efficacy and safety of astodrimer gel in treatment of patients with bacterial vaginosis.

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Table and Figure legends

Table 1. A summary of the baseline characteristics of included studies and the clinico-demographic information of research subjects.

Figure 1. PRISMA flowchart.

Figure 2. Risk of bias summary and graph.

Figure 3. Forest plot showing the clinical cure rates between astodrimer gel versus placebo groups.

Figure 4. Forest plot showing the Nugent cure rates between astodrimer gel versus placebo groups.

Figure 5. Forest plot showing the percentage of patients with self-reported absence of vaginal odor among astodrimer gel versus placebo groups.

Figure 6. Forest plot showing the percentage of patients with self-reported absence of vaginal discharge among astodrimer gel versus placebo groups.

Figure 7. Forest plot showing the percentage of patients with resolution of individual Amsel criteria among astodrimer gel versus placebo groups.

Figure 8. Forest plot showing the percentage of patients who received rescue therapy during study among astodrimer gel versus placebo groups.

Supplementary File 1

Supplementary Figure 1. Patients with [?]1 adverse event.

Supplementary Figure 2. Patients with [?]1 treatment-related adverse event.

Supplementary Figure 3. Patients with [?]1 severe adverse event.

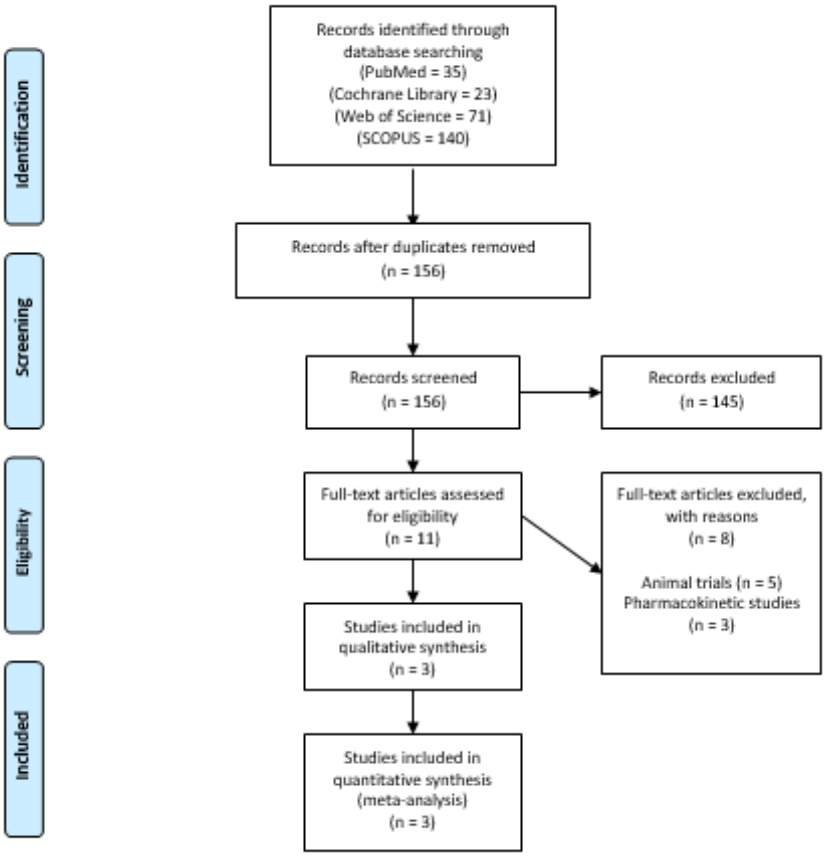
Supplementary Figure 4. Patients with [?]1 serious adverse event.

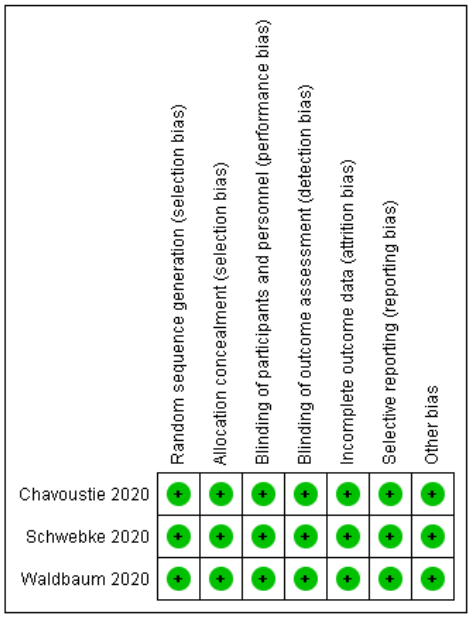
Supplementary Figure 5. Patients who stopped treatment due to adverse event.

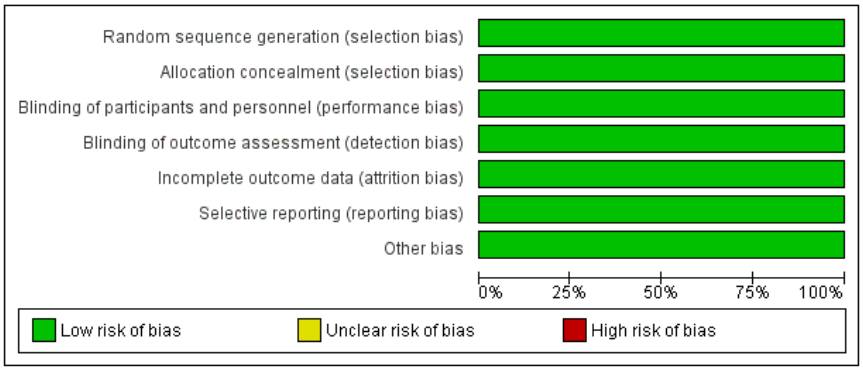
Supplementary Figure 6. Patients with urinary tract infection.

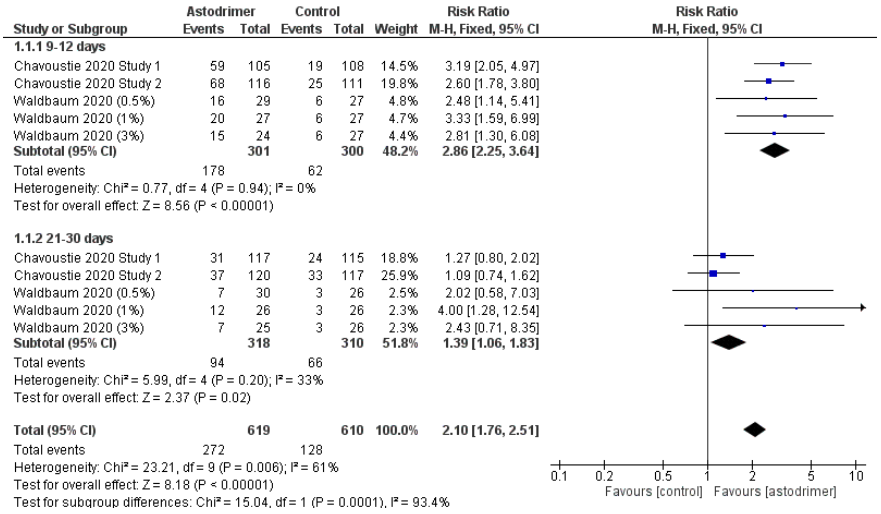
Supplementary Figure 7. Patients with vulvovaginal candidiasis.

Supplementary Figure 8. Patients with treatment-related vulvovaginal candidiasis.

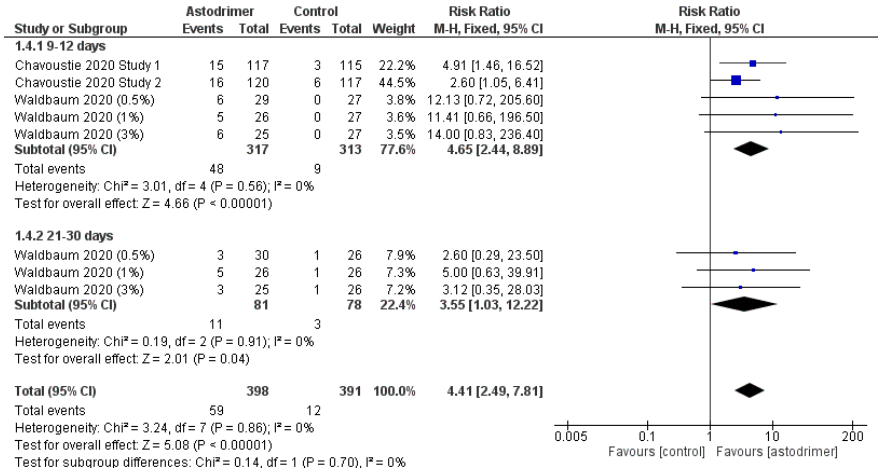


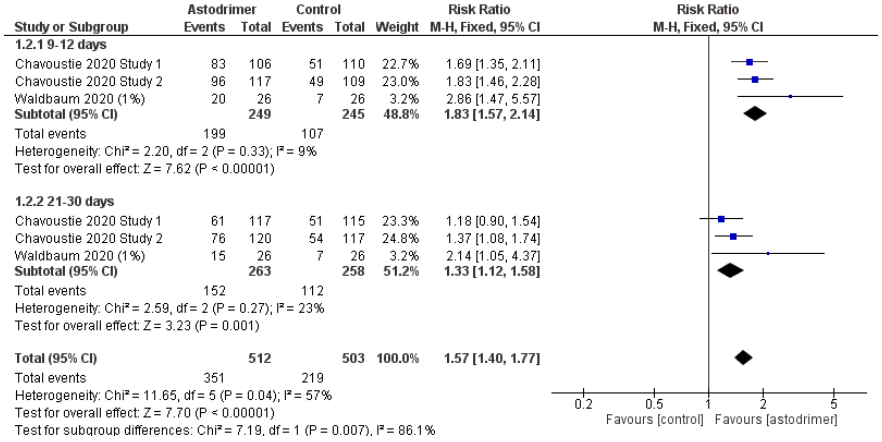


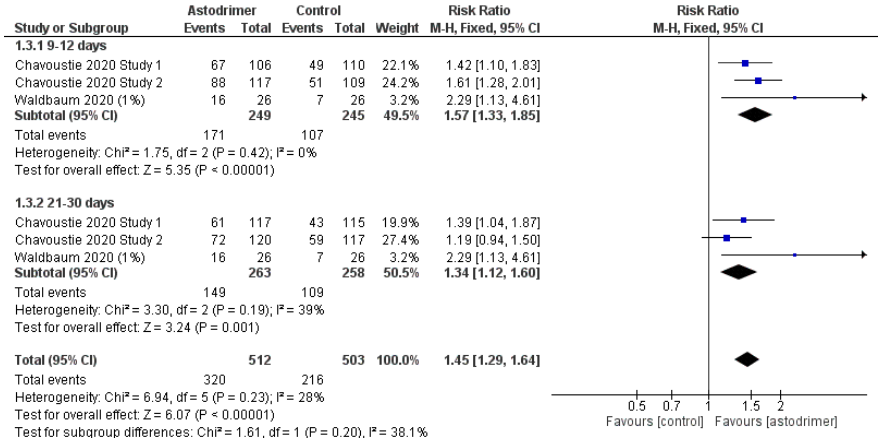


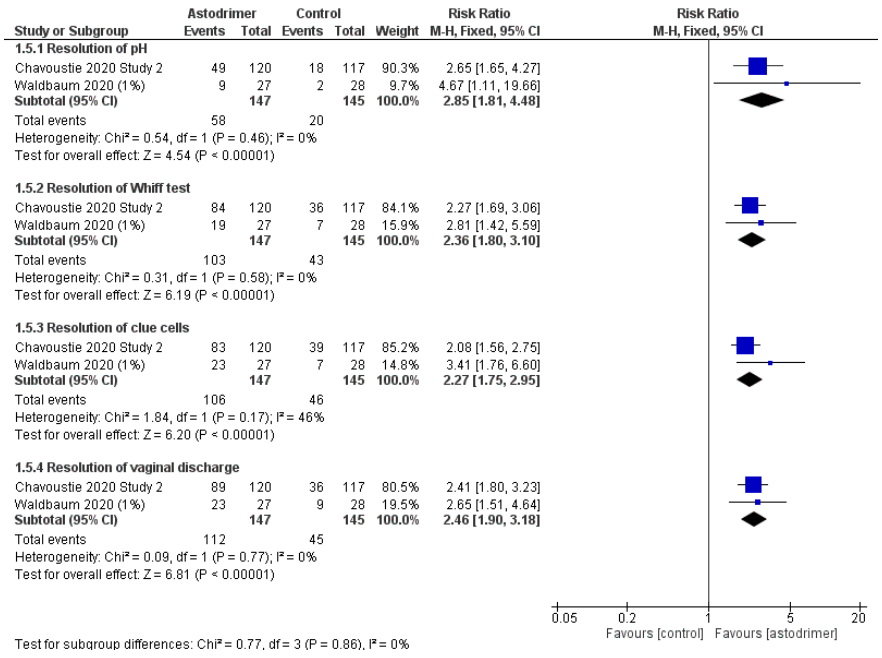


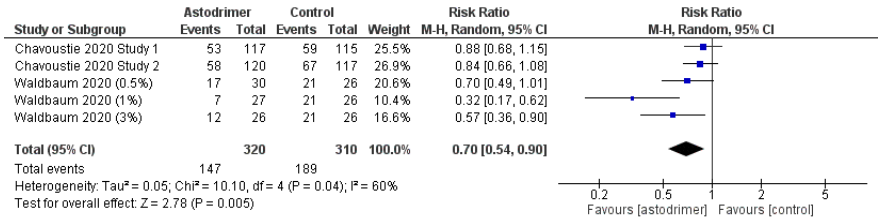
Study or Subgroup	Astodrimer Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 9-12 days						
Chavoustie 2020 Study 1	59	105	19	108	14.5%	3.19 [2.05, 4.97]
Chavoustie 2020 Study 2	68	116	25	111	19.8%	2.60 [1.78, 3.80]
Waldbaum 2020 (0.5%)	16	29	6	27	4.8%	2.48 [1.14, 5.41]
Waldbaum 2020 (1%)	20	27	6	27	4.7%	3.33 [1.59, 6.99]
Waldbaum 2020 (3%)	15	24	6	27	4.4%	2.81 [1.30, 6.08]
Subtotal (95% CI)		**301**		**300**	**48.2%**	**2.86 [2.25, 3.64]**
Total events	178		62			
Heterogeneity: Chi² = 0.77, df = 4 (P = 0.94); I² = 0%						
Test for overall effect: Z = 8.56 (P < 0.00001)						
1.1.2 21-30 days						
Chavoustie 2020 Study 1	31	117	24	115	18.8%	1.27 [0.80, 2.02]
Chavoustie 2020 Study 2	37	120	33	117	25.9%	1.09 [0.74, 1.62]
Waldbaum 2020 (0.5%)	7	30	3	26	2.5%	2.02 [0.58, 7.03]
Waldbaum 2020 (1%)	12	26	3	26	2.3%	4.00 [1.28, 12.54]
Waldbaum 2020 (3%)	7	25	3	26	2.3%	2.43 [0.71, 8.35]
Subtotal (95% CI)		**318**		**310**	**51.8%**	**1.39 [1.06, 1.83]**
Total events	94		66			
Heterogeneity: Chi² = 5.99, df = 4 (P = 0.20); I² = 33%						
Test for overall effect: Z = 2.37 (P = 0.02)						
Total (95% CI)		**619**		**610**	**100.0%**	**2.10 [1.76, 2.51]**
Total events	272		128			
Heterogeneity: Chi² = 23.21, df = 9 (P = 0.006); I² = 61%						
Test for overall effect: Z = 8.18 (P < 0.00001)						
Test for subgroup differences: Chi² = 15.04, df = 1 (P = 0.0001), I² = 93.4%						











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