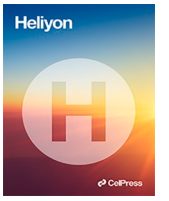
Heliyon 10 (2024) e28776

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Efficacy and safety of ibrexafungerp in the treatment of vulvovaginal candidiasis: A meta-analysis of randomized controlled trials

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ARTICLE INFO

Keywords:
Ibrexafungerp
Vulvovaginal candidiasis
Candida albicans
Meta-analysis

ABSTRACT

Background: This study aims to evaluate the efficacy and safety associated with ibrexafungerp in the treatment of vulvovaginal candidiasis infection patients.
Methods: We conducted a comprehensive search of the PubMed, Embase, Cochrane Library, and Clinical Trials databases up to December 25, 2022. The primary outcomes were clinical cure rate and mycological eradication rate, whereas the secondary outcomes were the risk of an adverse events.
Results: In total of four studies encompassing 880 patients diagnosed with vulvovaginal candidiasis (VVC) were included in the analysis. The findings demonstrated that ibrexafungerp exhibited superior clinical cure ratio (RR = 1.33 [1.07, 1.66]), mycological eradication rate (RR = 1.72 [1.00, 2.95]), and overall success ratio (RR = 1.64 [0.92, 2.92]) when compared to the fluconazole/placebo in the treatment of VVC. Furthermore, patients treated with ibrexafungerp demonstrated significantly higher clinical cure rates, mycological eradication, and overall success ratio compared to those receiving other treatments for vulvovaginal candidiasis caused by *C. albicans*. When ibrexafungerp was compared to fluconazole/placebo, the duration of any treatment-related treatment-emergent adverse events (TEAE), nausea, and diarrhea during therapy was significantly longer.
Conclusion: In summary, the use of ibrexafungerp was linked to superior clinical cure ratio, and mycological eradication when compared to fluconazole/placebo.

1. Introduction

Vulvovaginal candidiasis (VVC), commonly known as vaginal yeast infections caused by *Candida*, is the second most prevalent vaginal disorder, with *Candida albicans* being the primary organism [1–3]. Clinical manifestations of VVC include pruritus, vaginal soreness, abnormal vaginal discharge, painful urination, and dyspareunia, all of which can significantly impact the quality of life [3]. VVC is a highly prevalent condition, estimated to affect 70%–75% of women worldwide at least once in their lifetime. Additionally,

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https://doi.org/10.1016/j.heliyon.2024.e28776
Received 16 November 2023; Received in revised form 24 March 2024; Accepted 25 March 2024
Available online 5 April 2024

studies suggest that 40%–50% of women with VVC experience recurrent infections [3]. Despite affecting a significant portion of women during their lifetime, VVC treatment options remain limited. Standard treatment options for VVC consist of various topical azole antifungal medications (clotrimazole, miconazole, etc.), but some oral antifungal medications are also therapeutic options (fluconazole, itraconazole, oteseconazole, etc.). It is administered orally; there is no topical version [4,5]. Fluconazole, itraconazole, oteseconazole are oral antifungal drugs approved for the treatment of vaginal *Candida* infections by the U.S. Food and Drug Administration (FDA) and account for more than 90% of annual prescriptions for *Candida* infections. Since 1990, the FDA has approved two new therapies in 2021 and 2022: ibrexafungerp and oteseconazole, respectively oteseconazole [4–6].

Fluconazole and topical agents may not adequately meet the requirements of patients with moderate-to-severe VVC, recurrent VVC, VVC caused by fluconazole-resistant *Candida*, and VVC in women of reproductive age [4,7,8]. Additionally, in April 2022, the FDA approved oteseconazole for RVVC. The oteseconazole has a different chem-structure for fluconazole, with a target affinity similar to fluconazole and being sensitive to the *Candida* spp. clinical isolates exhibiting reduced susceptibility to fluconazole [9]. But, like fluconazole, oteseconazole also includes a warning about potential harm to the fetus, so patients need innovative antifungal therapies that are safer and more effective, and there is an urgent clinical medical need [10,11]. Especially for patients who have developed resistance to the existing drug fluconazole, they are urgently need of new therapies to treat this disease.

Ibrexafungerp is the first non-azole oral antifungal drug in over 20 years, serving as a glucan synthase inhibitor with a novel triterpenoid structure and a new mechanism of action [12–14]. In vitro studies have revealed that Ibrexafungerp has broad-spectrum antifungal activity against infections caused by multi-drug resistant azole and echinocandin strains [15,16]. Ibrexafungerp, marketed under the trade name BREXAFEMME®, received FDA approval in June 2021 for the treatment of vaginal yeast infections in adult and postmenarchal pediatric females [14,17]. Ibrexafungerp is currently in the advanced stages of clinical development for various indications, including hospital-acquired infections caused by fungi such as *Candida* (including *Candida auris*) and *Aspergillus* [18].

Furthermore, while some studies have reported good clinical activity and a low incidence of adverse events (AEs) associated with ibrexafungerp [19,20], except for the fetotoxicity, there is still a need for a comprehensive evaluation of its clinical efficacy and safety in the treatment of VVC. Therefore, in this meta-analysis study, we selected ibrexafungerp as the focus of our investigation to conducted systematic review of studies that assessed efficacy and safety in the treatment of VVC.

2. Methods

2.1. Protocol

A Population, Intervention, Comparison, and Outcome (PICO) model was utilized to extract pertinent information from each study. The Population consisted of patients diagnosed with VVC; the Intervention was Ibrexafungerp; the Comparison involved other antifungal drugs or a placebo; and the Outcome focused on efficacy and safety. The aim of our search was to identify clinical trials investigating the impact of ibrexafungerp on VVC patients. Thus, the inclusion criteria for this study encompassed patients with a diagnosis of VVC, intervention with ibrexafungerp, comparison with another antifungal drug or placebo, and assessment of efficacy and safety outcomes, including clinical response, microbiological response, and AEs. The primary outcome measure focused on achieving clinical cure, which involved the complete resolution of baseline signs and symptoms as observed in each study. In accordance with the PICO model, the exclusion criteria encompassed in vitro studies, animal model studies, and pharmacokinetic and pharmacodynamic (PK/PD) studies, in that respective order.

2.2. Search strategy

The design and process of this study adhered to the PRISMA checklist [21]. A systematic search was conducted on the PubMed, Embase, and Cochrane Library databases from inception to December 25, 2022, with the inclusion of only English language studies. Unpublished data were accessed from Clinical Trials (https://clinicaltrials.gov/), the International Clinical Trials Registry Platform (ICTRP, https://www.who.int/clinical-trials-registry-platform), and the European Union Clinical Trials Register (EUCTR, https://www.clinicaltrialsregister.eu/). The search terms utilized were “ibrexafungerp” and “SCY-078”. Endnote X8 software (Thomson Research, USA) was used for effective management of all research records.

2.3. Data collection

Duplicate records were eliminated using software. Following that, two researchers performed initial screening by reviewing the titles and abstracts of the research records. Any literature that potentially met the inclusion criteria underwent a full-text review. In the event of disagreements, resolution was achieved through discussion or with the assistance of a third reviewer. Following this, data from the included studies were independently extracted by two investigators. The extracted data encompassed authorship, year of publication, study design, study population, intervention measures, clinical and microbiological outcomes, and the risk of AEs.

2.4. Risk of bias assessment

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool was used to assess the overall quality of the evidence [22]. Furthermore, two reviewers utilized the Cochrane Collaboration’s bias assessment tool to subjectively assess the risk of bias in the included studies [23]. The risk of bias assessment was classified as “high risk”, “low risk”, or “unclear” based on the

tool's criteria.

2.5. Statistical analysis

The meta-analysis was performed using Review Manager version 5.4. Risk ratios (RRs) and 95% confidence intervals (CIs) were employed as measures of association between the outcomes and the use of ibrexafungerp. Heterogeneity was evaluated using the chi-squared-based Cochran's Q statistic and I^2. A significance level was set at $P < 0.10$ or when I^2 exceeded 50% to indicate significant heterogeneity. The fixed-effect model was employed when the data were homogeneous, while the random-effect model was utilized in the presence of substantial heterogeneity. Assessment of publication bias is considered no risk when $P > 0.05$.

3. Results

3.1. PRISMA summary of results

Fig. 1 depicts the PRISMA results illustrating the database search, revealing a total of 380 papers retrieved from six different databases. The distribution of papers is as follows: PubMed (n = 106), Embase (n = 212), Cochrane Library (n = 27), Clinical Trials (n = 14), EUCTR (n = 5), and ICTRP (n = 16). 257 papers were then obtained after excluding 123 duplications. In the end, a total of 4 studies involving 880 patients were ultimately included in this study [24–27]. Three articles were published in 2022, while one study

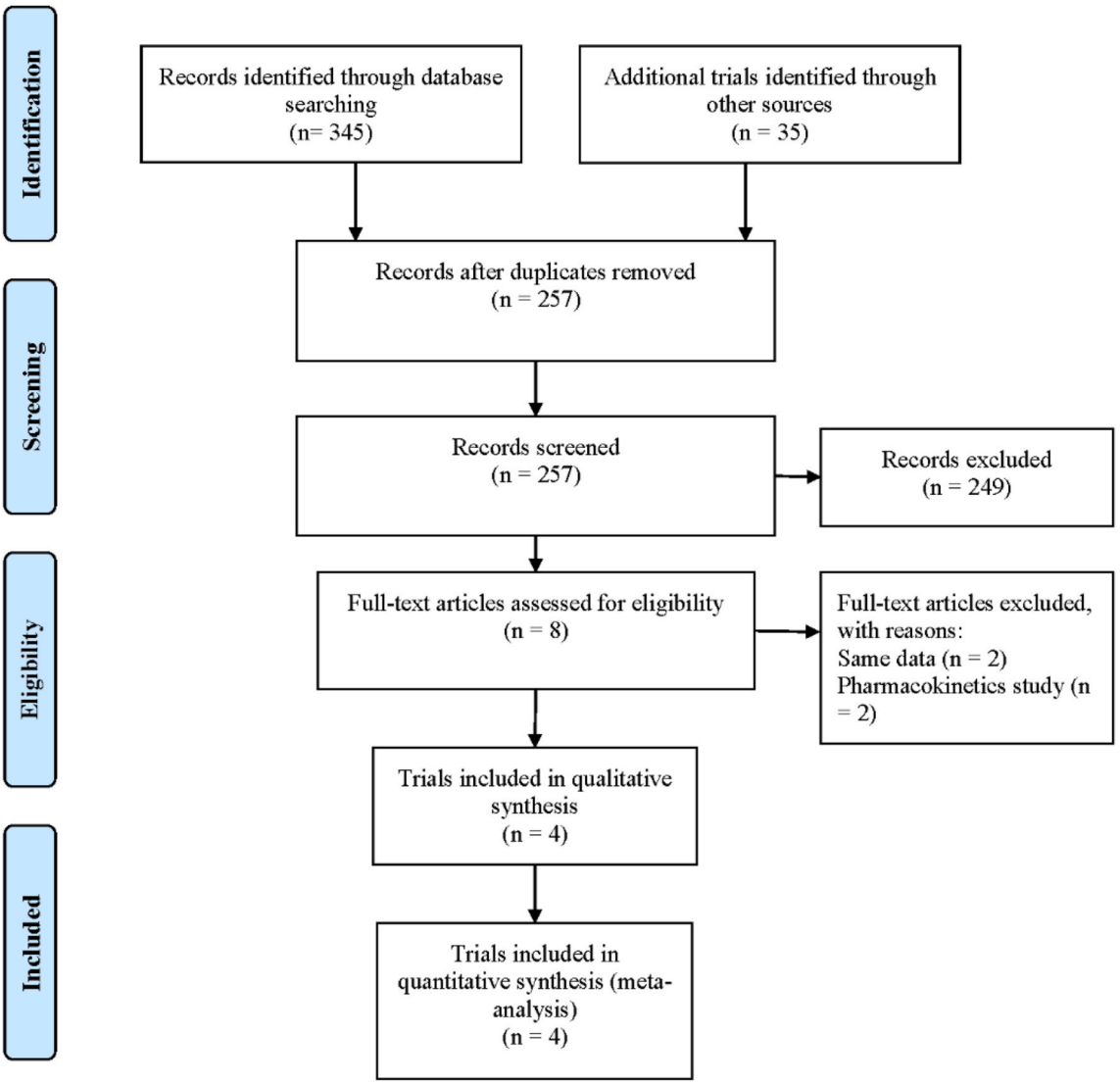

Fig. 1. The Ibrexafungerp flow diagram.

has not been published (NCT04029116, Table 1). One study compared ibrexafungerp to fluconazole, and two studies compared ibrexafungerp to a placebo. For the purpose of this meta-analysis study, the chosen dosage of ibrexafungerp was 300 mg twice daily for a duration of one day, as determined by the patient efficacy and safety data in the study.

3.2. Quality assessment

Fig. 2 presents the risk of bias for the included studies. One study is classified as Phase 2, while the other two studies are classified as Phase 3. All studies included in the analysis were randomized and double-blind. Randomization was conducted using an interactive response system. The quality assessment using GRADE criteria revealed high-quality evidence for all analyses, attributed to the substantial number of participants and blinding in the majority of studies (Table S1).

3.3. Clinical and microbiological response

In this study, the vulvovaginal signs and symptoms (VSS) were scored as 0, indicating the absence of symptoms. Clinical cure was defined as the complete resolution of signs and symptoms. In this study, the clinical cure ratio of ibrexafungerp was higher than that of fluconazole/placebo in the treatment of VVC (RR = 1.33 [1.07, 1.66], I^2 = 52%, Fig. 3A) in the combined analysis of 4 studies. Furthermore, the combined analysis of three studies revealed that ibrexafungerp had a high mycological eradication rate (documented and presumed) compared to that of fluconazole/placebo in the treatment of VVC (RR = 1.72 [1.00, 2.95], I^2 = 82%, Fig. 3B). In the sensitivity analysis, the heterogeneity of the mycological eradication rate decreased from 82% to 0% after removing the DOVE [26] study. Furthermore, when the VANISH 303 [25] study was removed, the heterogeneity of clinical cure decreased from 52% to 31%. Patients who had both a clinical cure and mycological eradication were considered successful overall. In the pooled analysis of three studies, the overall success ratio of ibrexafungerp was higher than that of fluconazole/placebo in the treatment of vulvovaginal candidiasis (RR = 1.64 [0.92, 2.92], I^2 = 71%, Fig. 3C). In addition, when compared with placebo, ibrexafungerp had a high clinical cure ratio (RR = 1.41 [1.16, 1.73], I^2 = 42%), mycological eradication rate (RR = 2.18 [1.66, 2.86], I^2 = 0%), and overall success (RR = 2.07 [1.19, 3.60], I^2 = 63%) in the treatment of VVC.

Patients treated with ibrexafungerp exhibited a significantly higher clinical cure rate at the test-of-cure (TOC) visit for *C. albicans* infection compared to those receiving fluconazole/placebo in the treatment of VVC (RR = 1.40 [1.02, 1.93], I^2 = 55%, Fig. 4A). And the mycological eradication at the TOC visit for patients with *C. albicans* infection on ibrexafungerp was higher than fluconazole/placebo in the treatment of vulvovaginal candidiasis (RR = 1.79 [0.96, 3.33], I^2 = 86%, Fig. 4B). In the sensitivity analysis, with the removal of the DOVE [26] study, the heterogeneity of the clinical cure rate at the TOC visit for patients with *C. albicans* infection and mycological eradication of *C. albicans* decreased from 55% to 25% and 86% to 0%, respectively.

In the pooled analysis, the overall success ratio at the TOC visit for patients with *C. albicans* infection (RR = 2.15 [1.22, 3.79], I^2 = 62%, Fig. 4C) with ibrexafungerp was higher than fluconazole/placebo in the treatment of vulvovaginal candidiasis. Furthermore, ibrexafungerp improved both symptom resolution (RR = 1.37 [1.16, 1.60], I^2 = 0%) and clinical improvement (RR = 1.34 [1.00, 1.80], I^2 = 70%) [24–26].

3.4. Safety

The therapy with ibrexafungerp resulted in a higher risk of any treatment related treatment-emergent adverse events (TEAE, RR = 1.96 [1.07, 3.59], I^2 = 85%, Fig. 5A) during the therapy duration compared to fluconazole/placebo. The most common adverse events were gastrointestinal in nature, with the risks of nausea (RR = 2.41 [1.36, 4.30], I^2 = 0%, Fig. 5C) and diarrhea (RR = 4.40 [2.03, 9.51], I^2 = 27%, Fig. 5B) being higher in ibrexafungerp than fluconazole/placebo, but the risk of abdominal pain (RR = 1.69 [0.49, 5.78], I^2 = 23%, Fig. 5E) being not statistically different. Headache is one of the most common nervous system disorders, and the risk of headache (RR = 1.49 [0.94, 2.37], I^2 = 4%, Fig. 5D) was similar between ibrexafungerp and fluconazole/placebo. In sensitivity

Table 1
Baseline demographic characteristics of the study.

Study, year published	Intervention	Study population	Study design
Nyirjesy P, 2022 DOVE [26]	Ibrexafungerp 300 mg BID (n = 30) Fluconazole 150 mg (n = 32)	≥18 years of age with a diagnosis of symptomatic moderate-to-severe acute VVC.	Phase 2
Schwebke JR, 2022 VANISH 303 [25]	Ibrexafungerp 300 mg BID (n = 188) Placebo (n = 98)	≥12 years of age with acute VVC.	Phase 3
Sobel R, 2022 VANISH 306 [24]	Ibrexafungerp 300 mg BID (n = 188) Placebo (n = 84)	≥12 years with moderate to severe VVC.	phase 3
NCT04029116	Ibrexafungerp 300 mg BID (n = 130) Placebo (n = 130)	12 years and older with RVVC.	Phase 3

Vulvovaginal signs and symptoms: VSS; test-of-cure: TOC.

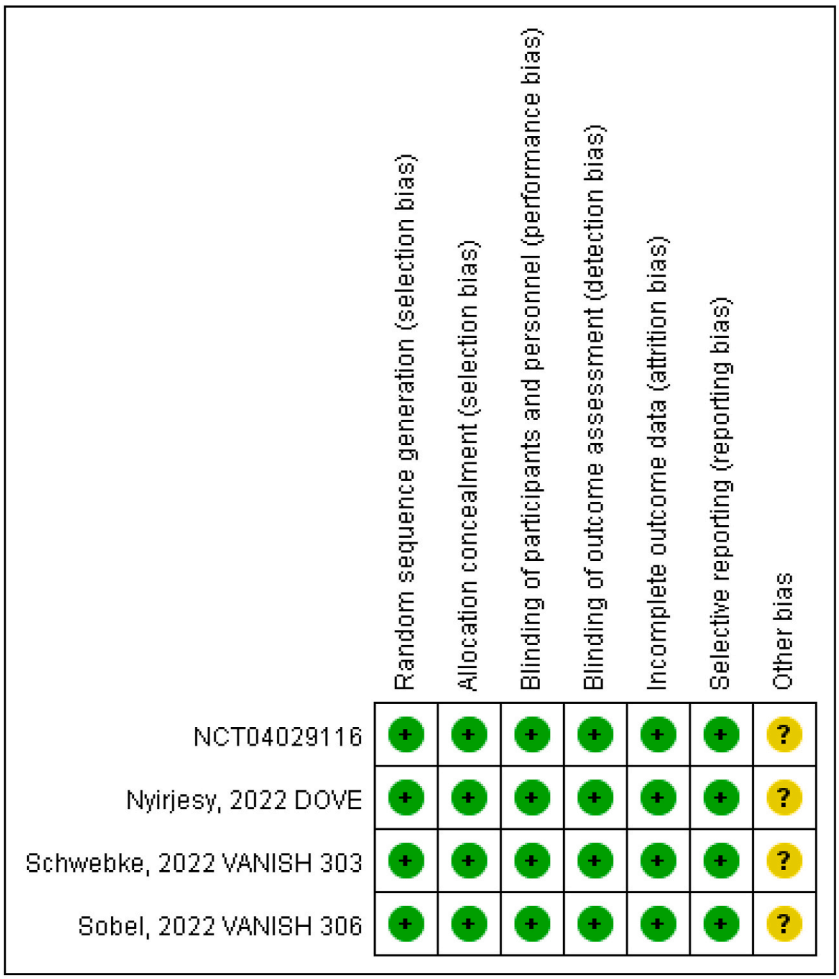

Fig. 2. Risk of bias summary.

analysis, after removing the NCT04029116 study, the heterogeneity of any treatment-related TEAE decreased from 85% to 0%.

4. Discussion

Four reports have been conducted to assess the efficacy and safety of ibrexafungerp [24–27]. Furthermore, ongoing trials are evaluating ibrexafungerp for the treatment of oral and esophageal candidiasis, as well as for *Candida*-related bone and joint infections [28,29]. Each of these studies has been conducted as a single study, thus lacking a comprehensive synthesis of the available evidence. Therefore, this systematic review and meta-analysis aims to present the initial assessment of the efficacy and safety of ibrexafungerp, utilizing the available evidence.

The analysis of patient efficacy and safety data in this study reveals promising results. Specific parameters, including a high clinical cure ratio, improved and sustained VSS scores, and mycological eradication, demonstrate more favorable outcomes with ibrexafungerp compared to fluconazole/placebo at the TOC visit. Firstly, the clinical cure ratio, which represents the clinical cure rate at the TOC visit for patients with *C. albicans* infection, and the overall success ratio for these patients were higher in those treated with ibrexafungerp compared to the comparators in the pooled populations of the four randomized controlled trials (RCTs) examined. These results align with findings from Sobel's study [24], but contradict the outcomes reported in Nyirjesy's study [26]. The study by Nyirjesy indicated that ibrexafungerp had similar efficacy to fluconazole in the clinical cure of VVC (51.9% vs. 58.3%) [26]. In addition, the results of the study by Spec [28] indicated that 86% favorable response rates were reported in the ibrexafungerp 750 mg group and 71% in the ibrexafungerp 500 mg group. Moreover, the results of two phase 3 clinical trials showed that ibrexafungerp was statistically superior to a placebo for clinical cure in moderate-to-severe VVC [20]. Second, in the treatment of VVC, ibrexafungerp had a higher mycological eradication rate and mycological eradication at the TOC visit for patients with a *C. albicans* infection than fluconazole/placebo. Our results were supported by the in vitro susceptibility testing of *C. albicans*, which showed that the MIC_{90} of ibrexafungerp and fluconazole were 0.12 μg/mL and <2 μg/mL, respectively [20]. Thus, ibrexafungerp can be a choice for VVC patients and an alternative to fluconazole.

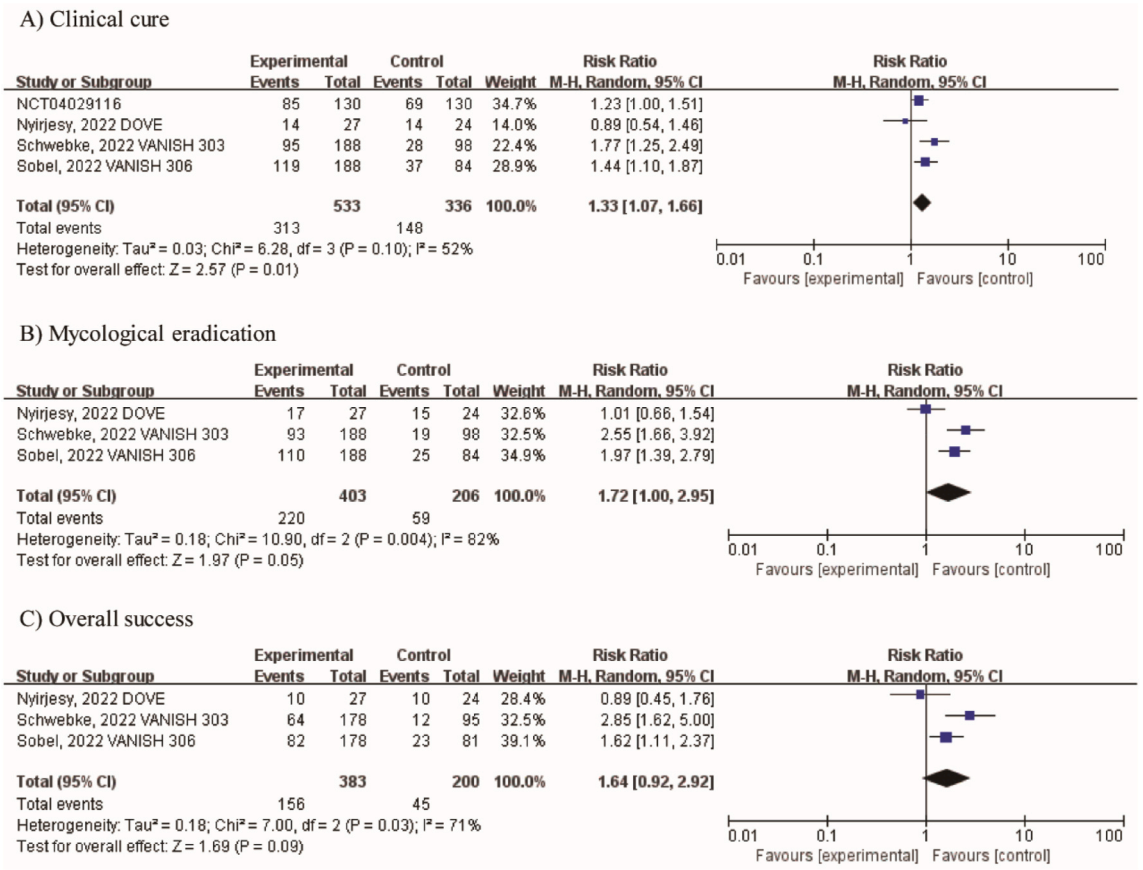

Fig. 3. The (A) clinical cure rates, (B) mycological eradication rates, (C) overall success of ibrexafungerp and comparators in the treatment of VVC.

In terms of safety, it is crucial to assess the potential adverse events (AEs) linked to the administration of ibrexafungerp for VVC treatment. In all the studies included in this analysis, AEs were reported following the administration of both ibrexafungerp and fluconazole/placebo, albeit to varying extents. In this study, the pooled risks of any treatment-related TEAE were higher in ibrexafungerp than fluconazole/placebo. Moreover, the risk of headache was similar between ibrexafungerp and fluconazole/placebo. The findings are consistent with those of Schwebke's [25] and Nyirjesy's [26] studies. The results of the meta-analysis showed that ibrexafungerp had a high incidence of gastrointestinal disorders, such as nausea and diarrhea. But the results of three clinical trials indicated that gastrointestinal disorders were mild in severity [24–26].

In addition, some AEs have been reported, including abdominal discomfort, dizziness, upper abdominal pain, flatulence, somnolence, fatigue, and toothache [20,24–26]. The product labels for ibrexafungerp list certain adverse events (AEs) based on clinical experience and safety data from clinical trials, such as vomiting and urinary tract infections (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214900s002lbl.pdf). Moreover, no study has shown adverse effects on liver and kidney function.

Ibrexafungerp was initially utilized for the treatment of VVC; however, as per the FDA label, it is also indicated for reducing the frequency of RVVC. Currently, ibrexafungerp is undergoing evaluation in two clinical trials for the treatment of recurrent and RVVC (ClinicalTrials.gov Identifiers: NCT02679456 and NCT05399641). Additionally, other ongoing trials are assessing the efficacy of ibrexafungerp against various fungal infections [28–30]. FURI represents a phase 3 study aimed at evaluating ibrexafungerp effectiveness in patients with fungal diseases resistant to or intolerant of standard antifungal therapy (ClinicalTrials.gov Identifier: NCT03059992). SCYNERGIA is a phase 2 study investigating the safety and efficacy of ibrexafungerp when co-administered with voriconazole in patients with invasive pulmonary aspergillosis (IPA) (ClinicalTrials.gov Identifier: NCT03672292). MARIO, a Phase 3 trial, is assessing ibrexafungerp in patients with invasive Candidiasis who have received IV echinocandin followed by either oral ibrexafungerp or oral fluconazole (ClinicalTrials.gov Identifier: NCT05178862). Further, CARES is a phase 3 study evaluating the safety and efficacy of oral ibrexafungerp in patients with Candidiasis caused by *Candida Auris* (ClinicalTrials.gov Identifier: NCT03363841). Lastly, a phase 2 study is examining the safety and efficacy of oral ibrexafungerp versus standard-of-care following IV echinocandin for treating invasive Candidiasis (ClinicalTrials.gov Identifier: NCT02244606).

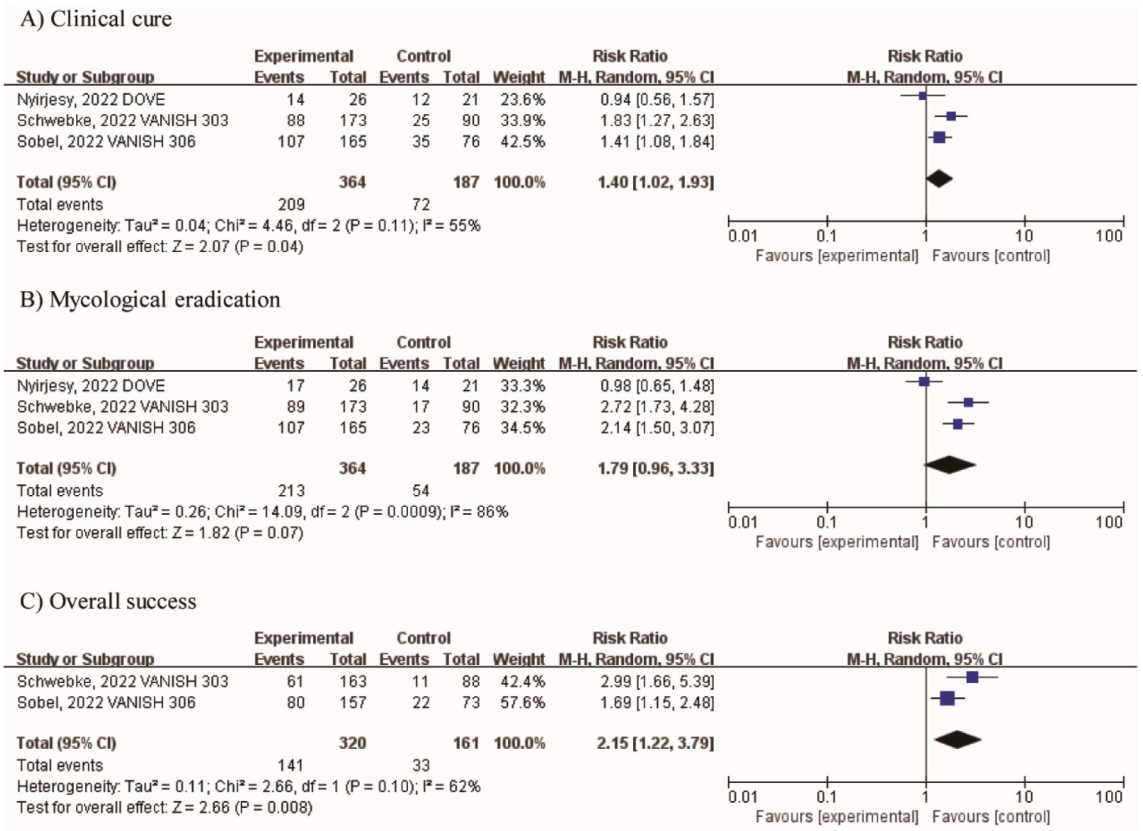

Fig. 4. The (A) clinical cure rates, (B) mycological eradication rates, (C) overall success rates at the TOC visit for patients with *C. albicans* infection of ibrexafungerp and comparators in the treatment of VVC.

5. Conclusion

In conclusion, ibrexafungerp is associated with a higher clinical cure ratio, and mycological eradication compared to fluconazole/placebo. In addition, ibrexafungerp is well-tolerated and could be a choice for VVC patients.

Ethics declarations

This study did not require ethics committee review and approval as it solely consists of a literature review and does not involve ethical issues related to animal, cellular, or human experimentation.

Financial support

All authors did not receive any financial support.

Data availability

The original contributions to the study are detailed in the article and supplementary material.

CRediT authorship contribution statement

Rong He: Writing – original draft, Investigation, Data curation, Conceptualization. **Fei Lin:** Writing – review & editing, Software, Methodology. **Bin Yu:** Software, Methodology. **Ling Huang:** Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

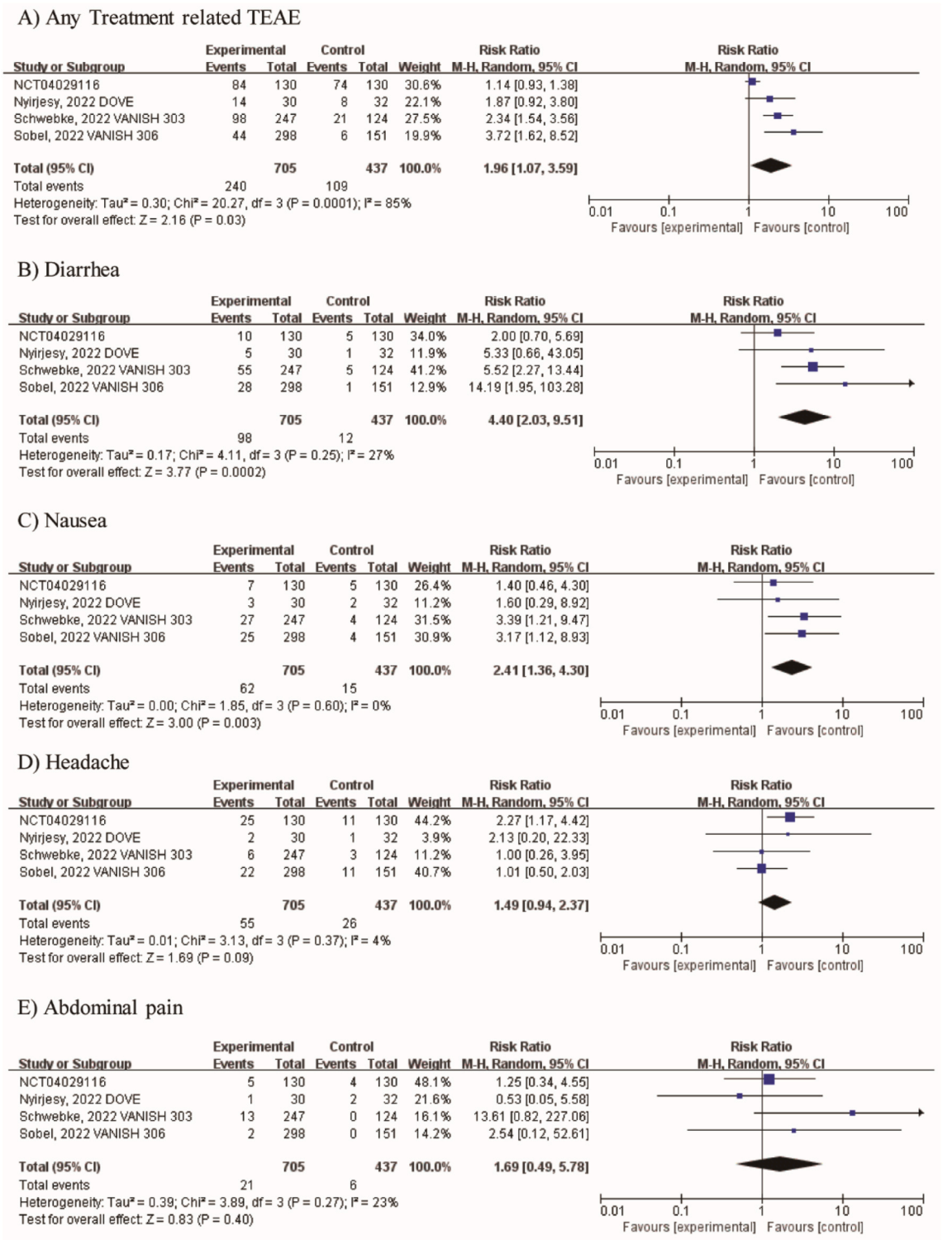

Fig. 5. The risk of (A) Any Treatment related TEAE, (B) diarrhea, (C) nausea, (D) headache, and (E) abdominal pain between ibrexafungerp and comparators in the treatment of VVC.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:mmcdoino

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