

F-755

Novel Echinocandin CD101 Gel Formulation is Highly Effective in Eradicating *Candida albicans* in a Rat Model of Vulvovaginal Candidiasis

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Abstract

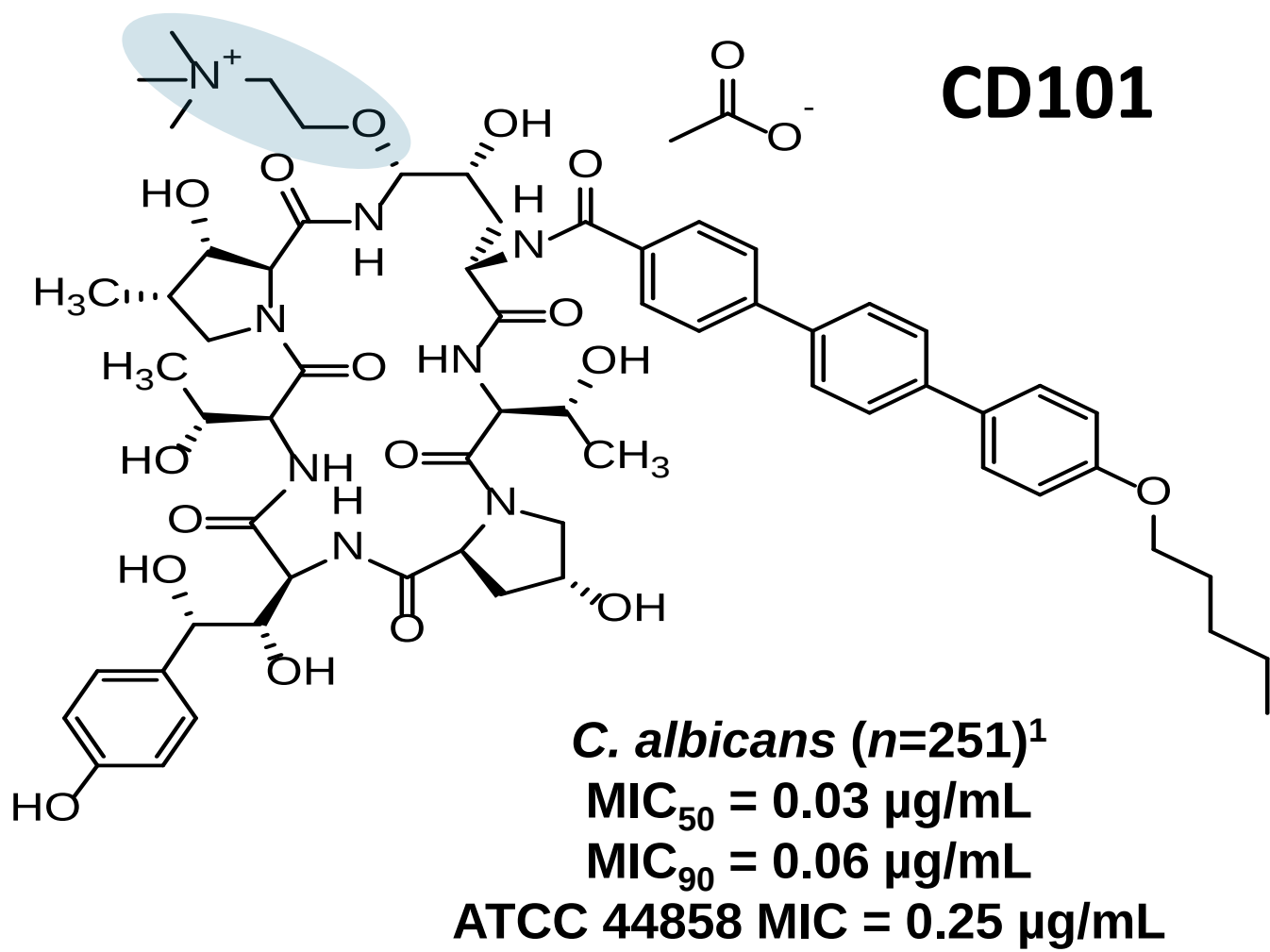
Background: Efficacy of vaginal administration of CD101, a novel long-acting and highly stable echinocandin, formulated in a gel, was compared to marketed 2% miconazole cream in an immunosuppressed rat model of vulvovaginal candidiasis (VVC). Currently marketed echinocandins lack chemical stability to be effectively formulated for topical administration.

Methods: Groups of five oophorohysterectomized female Wistar rats were used. Estradiol (ED) was administered at 10 mg/kg subcutaneously 3 days before *C. albicans* (ATCC 44858) challenge then maintained with 4 mg/kg weekly injections throughout the study. Animals were immunosuppressed with dexamethasone applied in drinking water (2 mg/L) 3 days before challenge and throughout the study. To establish vaginal infection, anesthetized rats were inoculated intravaginally with *C. albicans* (10⁷ CFU) in PBS. All treatments began 48 hour after challenge. CD101 gels, 3% and 10%, and miconazole 2%, were administered intravaginally at 0.1 mL/rat twice daily for 3 days. Rats were sacrificed at time points (1, 3, 5, and 8 days) after treatment cessation followed by vaginal lavage. *C. albicans* counts (CFU/mL) were measured in lavage fluid. Unpaired Student's t test was performed to determine the significance of treatment effects relative to the vehicle control groups.

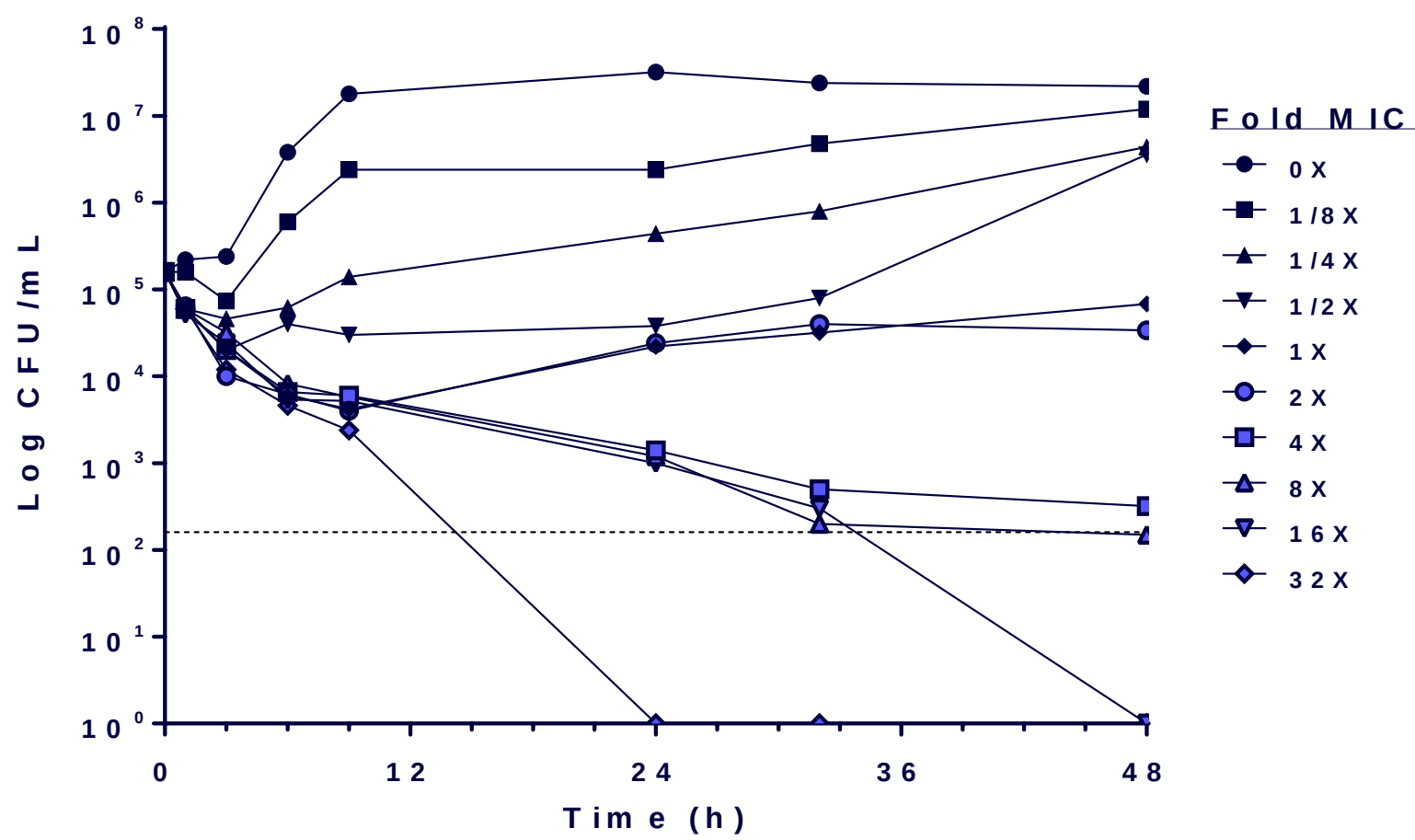
Results: All test articles resulted in significant reductions in fungal counts relative to the vehicle controls (*p < 0.05). However, results suggested that CD101 appears more effective than miconazole in preventing recurrence of vaginal candidiasis, since vaginal CFUs were below the limit of detection and significantly lower than vehicle-treated controls from 1 day after the end of treatment and remaining undetected thereafter.

Conclusion: CD101 was shown to be highly effective in eradicating *C. albicans* when administered intravaginally as a gel in a rat vulvovaginal candidiasis model.

- Echinocandins have potent fungicidal activity against *Candida* species and are used for invasive or systemic infection.
- However, all marketed echinocandins are chemically unstable and not suitable for topical application.
- CD101 is a novel echinocandin with excellent stability and long-acting pharmacokinetics with fungicidal properties against *C. albicans* (3, 4).
- The objective of this study was to evaluate the efficacy of topical CD101 formulations in a rat model of recurrent VVC.



Fungicidal properties of CD101 *C. albicans* ATCC 44858



Methods

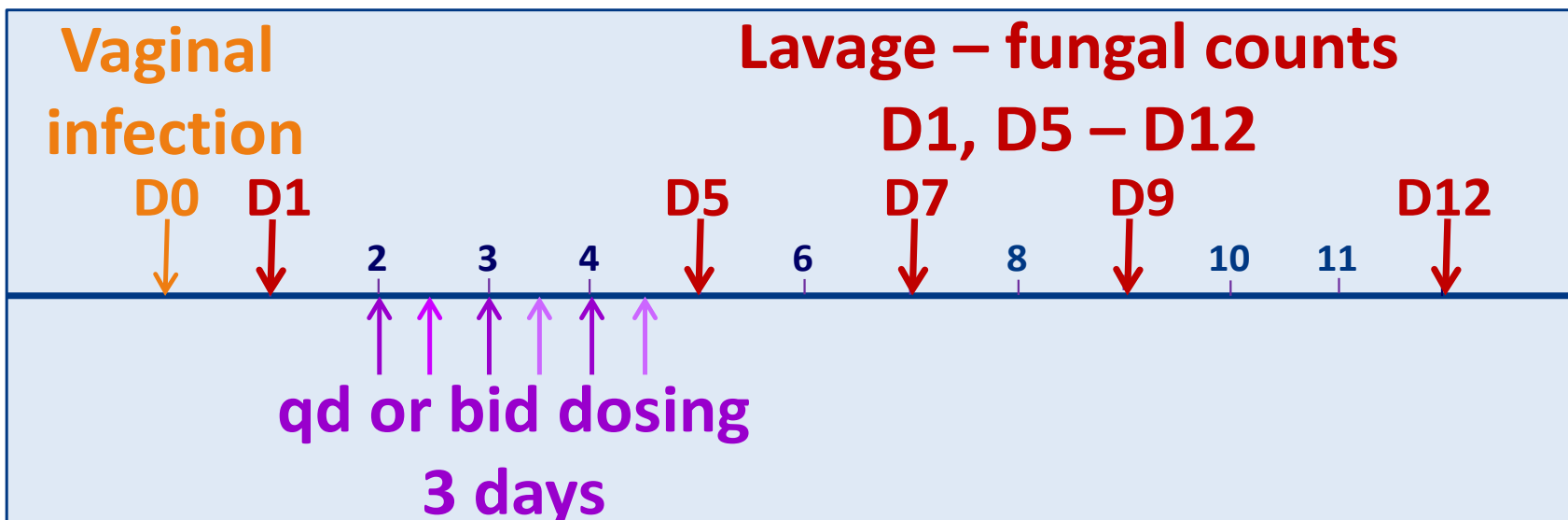
Rat VVC model

Animals Female Wistar rats weighing 150 ± 10 g were used. Animals were oophorohysterectomized and allowed 7 days recovery from surgery. Estrogen supplementation was supplied by subcutaneous administration of 17β-estradiol at 10 mg/kg 3 days before infection and subsequently maintained by subcutaneous administration at 4 mg/kg weekly throughout the experiment. Animals were immunosuppressed with dexamethasone added to drinking water at a final concentration of 2 mg/L. Immunosuppressive treatment was started 3 days before infection and maintained throughout the experiment.

Infection Rats were anesthetized with pentobarbital (40 mg/kg, IP) and inoculated intravaginally with a *C. albicans* (ATCC 44858) suspension in 0.1 mL saline, 1 x 10⁷ CFU/rat on Day 0 (D0). Infected animals were then randomly distributed into groups of 5 each. The initial vaginal *C. albicans* burden was evaluated in one animal group, one day after infection (24 hr before treatment start).

Test articles Topical CD101 gel and cream/ointment formulations, and positive controls agents miconazole (Mycoderin Pharmacy topical cream formulation), and oral fluconazole were used.

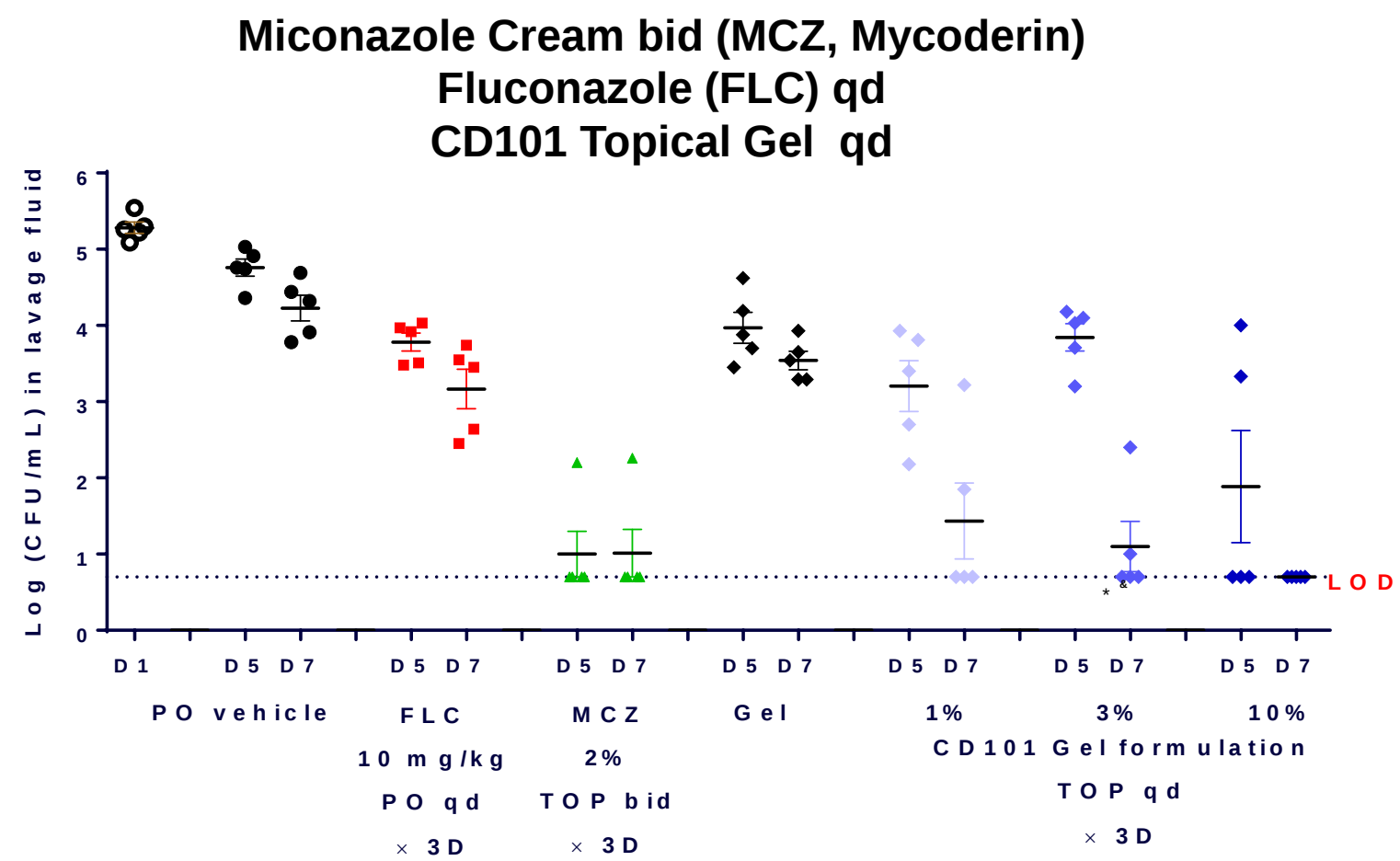
Treatment Antifungal therapy was started 48 hours after infection (D2). Groups of 5 rats each were treated intravaginally with vehicle and test articles, once (qd) or twice daily (bid) for 3 consecutive days. Rats were humanely euthanized by CO₂ asphyxiation at time points starting 12 hr after the last dose (D5 to D12 after infection). Vaginal lavage was performed and the fungal counts in the lavage fluid was determined.



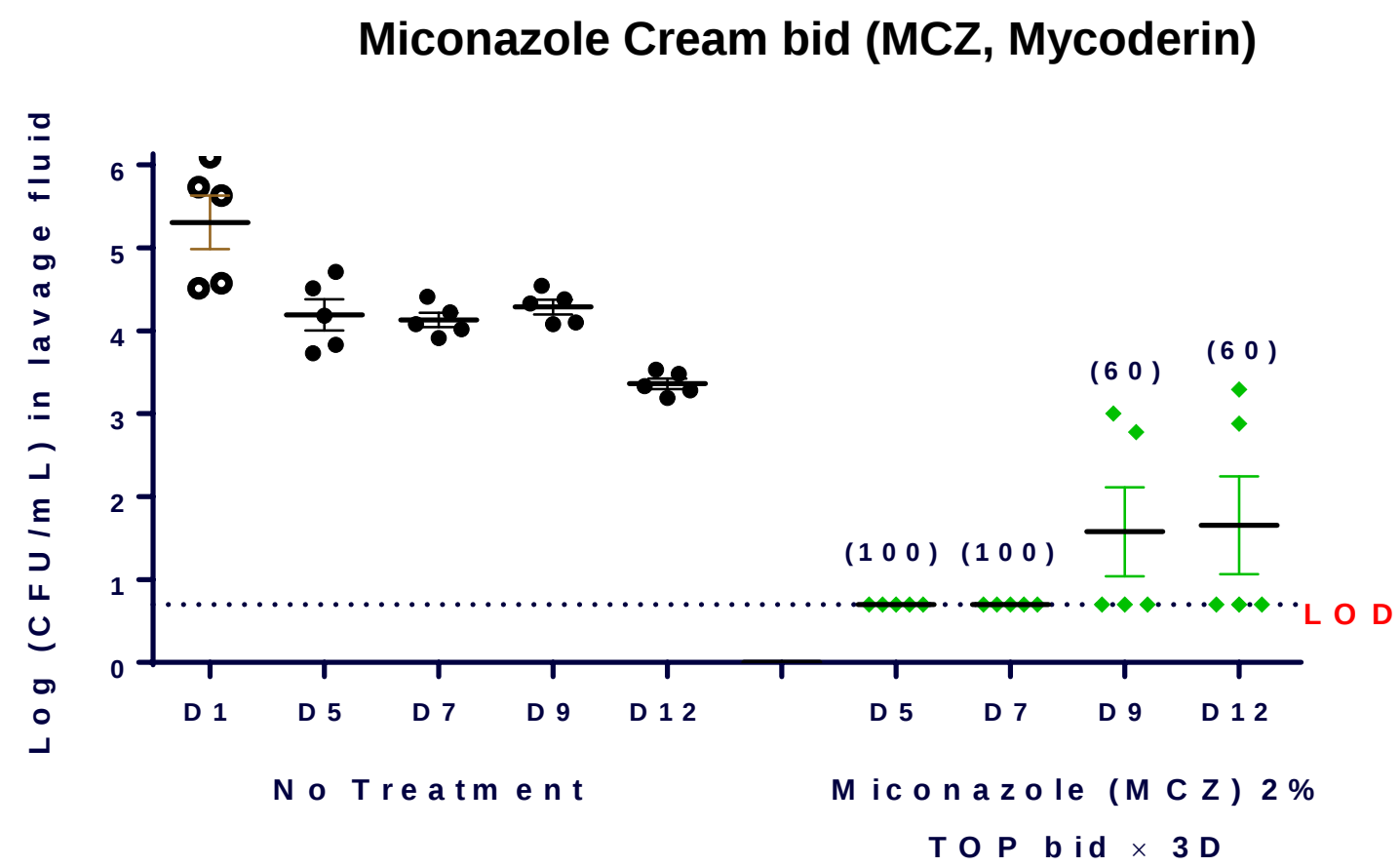
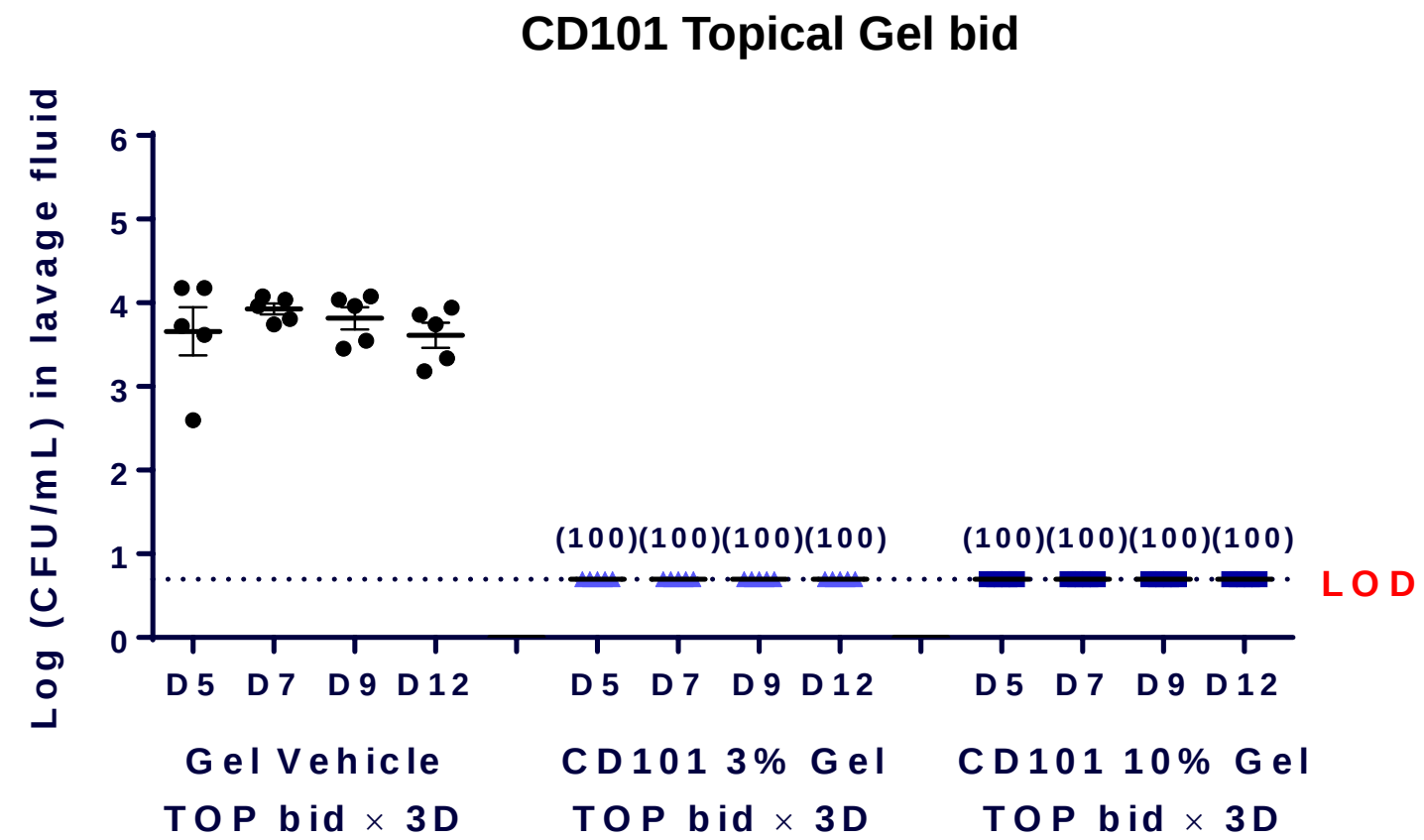
All aspects of this work including housing, experimentation, and animal disposal was performed in general accordance with the Guide for the Care and Use of laboratory animals (National Academy Press, Washington, DC, 2011). The experiment was performed under ABSL2 conditions in the Eurofins Panlabs' AAALAC-accredited vivarium with the oversight of veterinarians to assure compliance with the Eurofins Panlabs IACUC regulations and the humane treatment of laboratory animals.

Results

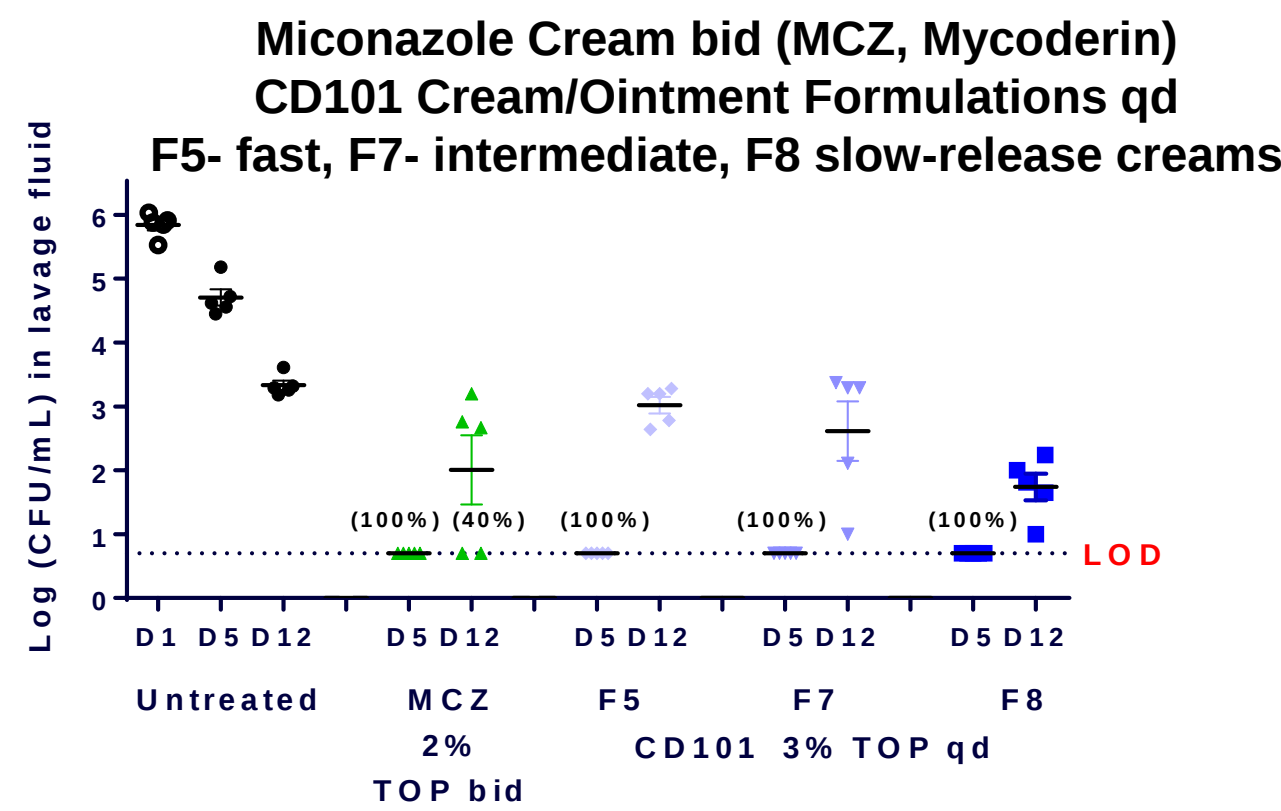
(A) Once daily (qd) application of CD101 topical gel significantly reduced vaginal fungal counts



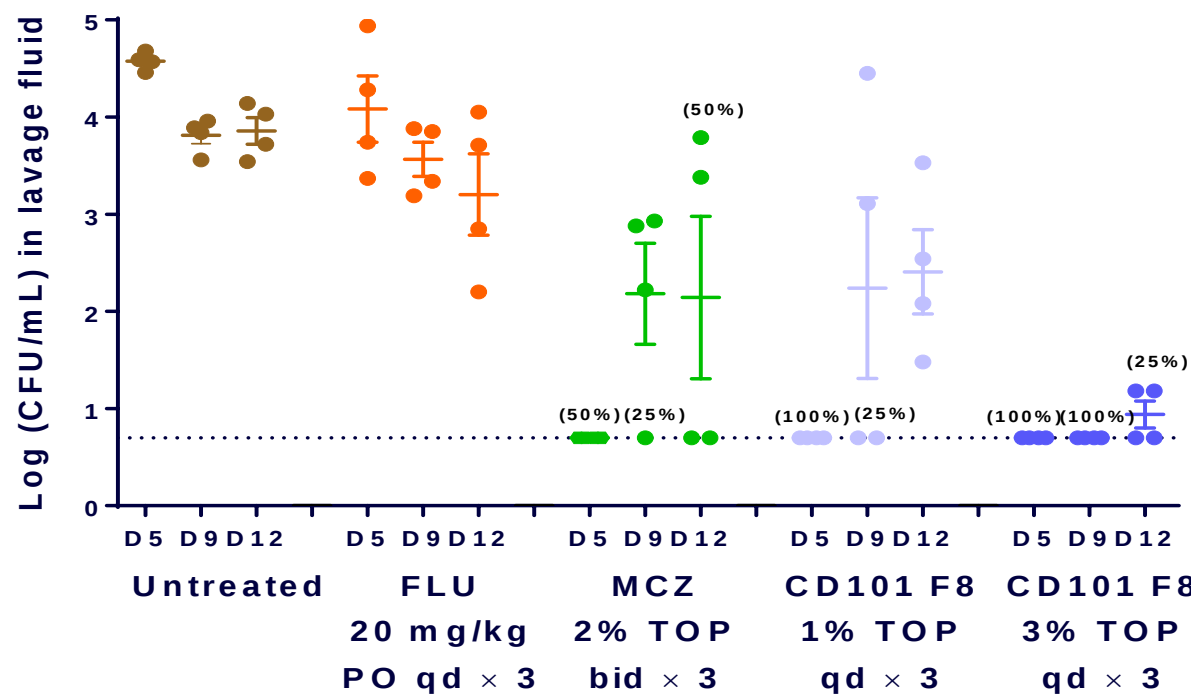
(B) Twice daily (bid) application of CD101 topical gel eliminated detectable fungal counts (<LOD)



(C) Slower-release cream/ointment formulations of CD101 showed prolonged efficacy after qd dosing



Topical CD101 F8 Ointment Formulation qd, Miconazole Cream bid (MCZ, Mycoderin), and Oral Fluconazole 20 mg/kg qd



Conclusion

- CD101 gel and cream/ointment formulations are highly effective at reducing *C. albicans* burden in the rat VVC model.
- Once daily application of 3% CD101 in a slow release ointment (F8) significantly reduced the fungal burden, one week after treatment cessation.
- The efficacy of the 3% CD101 slow release ointment exceeded that of 2% miconazole (topical) and 20 mg/kg oral fluconazole.
- CD101 may offer a promising alternative for the treatment of recurrent VVC in humans.

Reference

- ICAAC (2015) Poster M-849.

Acknowledgement

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