Efficacy and Safety of Oral VT-1161, a Novel Inhibitor of Fungal CYP51, in a Randomized Phase 2 Study in Patients with Acute Vulvovaginal Candidiasis

Stephen Brand[1], Thorsten Degenhardt[1], Paul Nyirjesy[2], Michael Augenbraun[3], Robert Schotzinger[1]

[1]Viamet Pharmaceuticals, Inc., Durham, NC, USA; [2]U Drexel University College of Medicine, Philadelphia, PA, USA; [3]SUNY Downstate Medical Center, Brooklyn, NY,USA.

Introduction and Objective

- VT-1161 is a novel, selective inhibitor of fungal CYP51[1,2], under development for the treatment of patients with invasive, mucosal, or superficial fungal infections
- VT-1161 is highly active against candida and non-candida yeasts (or species) in murine models of systemic infection and is generally superior to currently-available azoles
- VT-1161 was safe and well tolerated in Phase 1 studies
- A Phase 2a proof-of-concept study was conducted to evaluate the safety, tolerability, efficacy and PK of VT-1161 in subjects with moderate-to-severe acute vulvovaginal candidiasis (VVC)

Materials & Methods

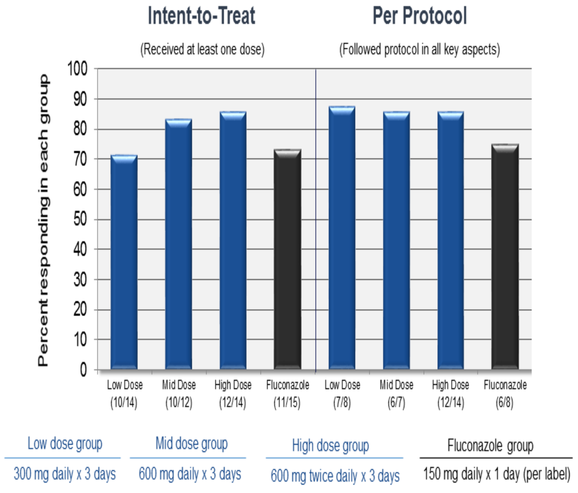
This was a Phase 2, randomized, double-blind study to evaluate the efficacy and safety of 3 dosing regimens of oral VT-1161 compared to fluconazole in the treatment of patients with moderate-to-severe acute VVC (Identifier: NCT01891331).

At baseline, patients were required to have a positive fungal KOH test and a score of 6 or greater on a symptoms and signs scale (maximum score of 18).

Fifty-five patients were randomly assigned to one of the following arms: 1) VT-1161 300 mg daily for 3 days; 2) VT-1161 600 mg daily for 3 days; 3) VT-1161 600 mg twice daily for 3 days or 4) fluconazole 150 mg administered as a single dose (per the US package insert) followed by placebo. Effective therapeutic cure, defined as a symptoms and signs score of 0 or 1 and a negative Candida culture, was assessed on Day 28. To assess mycologic and clinical recurrence, patients were followed for additional 5 months while off study drugs.

Patient demographics were similar across all groups. Approximately 76% of patients had a positive culture for Candida spp. at baseline.

Results



Efficacy was evaluated at the Day 28 Test-of-Cure (TOC) visit in the Intent-to-Treat population (defined as all randomized patients receiving at least one dose of study drug) and the Per Protocol population (defined as subjects that were compliant with all key aspects of the protocol). Patients in the intent to treat population and randomized into the low, mid, high-dose VT-1161 groups or fluconazole control group achieved an effective clinical cure rate (defined as having a total severity score of 0 or 1 and a negative culture) of 71%, 83%, 86% and 73% respectively.

Patients in the per protocol population achieved effective therapeutic cure at a rate of approximately 87%, 86%, 86% and 75%, respectively, in the low-dose, mid-dose, or high-dose VT-1161 or fluconazole groups at the Day 28 TOC visit

Efficacy at Day 28 Test-of-Cure Visit (ITT Population)

Group	Effective Clinical Cure**	Mycologic Cure***
Low-Dose VT-1161 Arm (N=14)[#]	71%	100%
Mid-Dose VT-1161 Arm (N=12)[##]	92%	92%
High-Dose VT-1161 Arm (N=14)[###]	93%	93%
Fluconazole Arm (N=15)[####]	93%	73%

* Requires both Effective Clinical Cure and Mycologic Cure, ** Total acute VVC severity score of 0 or 1, *** Negative culture for Candida species. [#] 300 mg QD x3d, [##] 600 mg QD x3d, [###] 600 mg BID x 3d [####] 150 mg single dose

Safety at Day 28 Test-of-Cure Visit (ITT Population

No subjects discontinued due to an adverse event. In general, the reported adverse events were mild in severity and considered unrelated to study drug by the investigator.
There were no clinically significant changes in vital signs, physical findings, ECGs or laboratory parameters.

	VT-1161 Low-Dose Arm (N=14)	VT-1161 Medium-Dose Arm (N=14)	VT-1161 High Dose Arm (N=14)	Fluconazole Arm (N=15)
Patient Discontinued Due to AE	0%	0%	0%	0%
Patient Reported Any AE Through Day 28	71%	42%	14%	47%
Patient Reported Any Severe AE	0%	0%	0%	13%
Patient Had Grade 3 or Greater LFT Increase	0%	0%	0%	0%
Patient Required Additional Antifungal Therapy	14%	0%	0%	47%

Following 5 months of follow-up, none of the patients in the VT-1161 arms experienced a positive Candida culture and fungal KOH prep compared to 46% of patients in the fluconazole arm. Additionally, there were few clinical recurrences.

Conclusions

- VT-1161 was determined to be safe and well tolerated at all dose levels through Day 28
- Day 28 cure rates in patients receiving VT-1161 were similar to those in the fluconazole arm.
- During follow-up, fluconazole patients frequently experienced disease reoccurrence compared to no patients receiving VT-1161
- VT-1161 may be uniquely qualified to treat recurrent VVC (RVVC), a condition for which there is no approved therapy, and warrants further study for the treatment of both acute VVC and RVVC.

Note: A Phase 2b randomized study in subjects with RVVC has begun in the United States .

References

1. Hoekstra WJ, Garvey EP, Moore WR, Rafferty SW, Yates CM, Schotzinger RJ. 2014. Design and optimization of highly-selective fungal CYP51 inhibitors. Bioorg. Med. Chem. Lett. **24:**3455-3458.
2. Warrilow, AGS, Martel, CM, Parker, JE, Garvey, EP, Hoekstra, WJ, Moore, WR, Schotzinger, RJ, Kelly, DE, Kelly, SL. 2014. The Clinical Candidate VT-1161 is a Highly Potent Inhibitor of *Candida albicans* CYP51 but Fails to Bind the Human Enzyme. Antimicrob. Agents Chemother. **58:**7121-7127.