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Investigational CYP51 Inhibitors VT-1161 and VT-1129 Show Strong *In Vitro* Activity Against *Candida glabrata Isolates Clinically Resistant to Azole and Echinocandin Compounds*

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Introduction and Objectives

- Antifungal resistance is increasing and appears to be co-emerging, particularly in *C. glabrata.*
- VT-1161 & VT-1129 are highly selective fungal CYP51 inhibitors with potent *in vitro* activity against *Candida* spp.
- In Phase 1 and 2 clinical trials, VT-1161 has achieved plasma concentrations of up to 10 µg/mL with an excellent safety profile. Preclinical data for VT-1129 predict similar safety and PK profiles.
- This study was conducted to determine in vitro activity of VT-1161 and VT-1129 against *C. glabrata isolates* clinically resistant to azole and echinocandin compounds. *In vitro* activities of VT-1129, VT-1161, fluconazole, voriconazole, anidulafungin, caspofungin, and micafungin were concurrently determined for 34 *C. glabrata* patient isolates known to be either clinically refractory, *in vitro* resistant or both, to one or more standard antifungal drugs.

Materials and Methods

- Viamet Pharmaceuticals, Inc. provided VT-1161, VT-1129, fluconazole, voriconazole, and caspofungin as powders of ≥97% purity. Caspofungin and anidulafungin microtiter plates were purchased from Trek Diagnostic Systems.
- Broth microdilution testing was performed via the Clinical and Laboratory Standards Institute M27-A3/S4 method. Stock solutions of VT-1161 and VT-1129 were prepared in DMSO; endpoints were recorded at 24 and 48 hours and were defined as 50% growth inhibition compared to drug-free controls.
- Isolates were screened for FKS mutations as previously described [1].

Results

Table 1. *Candida glabrata* (N=34) MIC (µg/mL) values at 24 hour timepoints*

	VT-1129	VT-1161	Fluconazole	Voriconazole	Anidulafungin	Caspofungin	Micafungin
Range	0.03-2	≤0.01-1	1-128	≤0.01-4	0.06-8	0.5-16	≤0.01-16
Geometric mean	0.24	0.16	6.01	0.25	0.92	1.57	0.44
Median	0.185	0.12	3	0.12	1.50	1	0.5
MIC_{50}	0.12	0.12	2	0.12	1	1	0.5
MIC_{90}	1	1	64	2	8	4	8

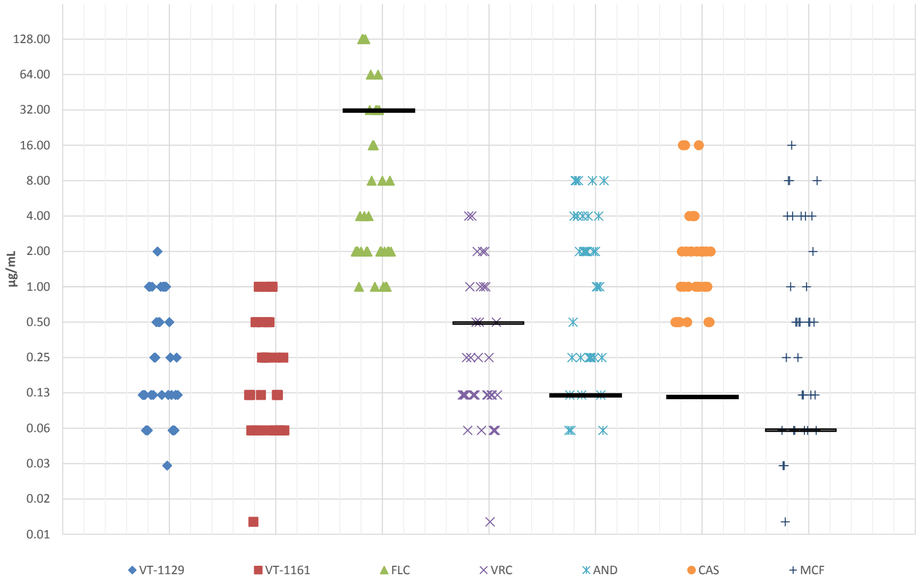
*Two isolates required 48 hours incubation

Table 2. *Candida glabrata* MIC (µg/mL, range) values at 24 hour time points*, by mutation type

Mutation	Number tested N=34	VT-1129	VT-1161	Fluconazole	Voriconazole	Anidulafungin	Caspofungin	Micafungin
None	7	0.06-0.25	0.06-0.12	1-8	≤0.01-0.5	0.06-4	0.05-2	0.06-4
I634V	4	0.06-0.12	0.06-0.12	1-2	0.12	0.06-0.25	0.05-0.5	0.01-0.06
2-S663P	4*	0.06-1	≤0.01-1	2-128	0.06-4	0.5-8	0.05-16	0.25-8
S663P	3	0.12-1	0.06-1	2-128	0.12-4	2-8	1-16	1-16
I1376V	2	0.25	0.12-0.25	2-4	0.12	0.12-0.25	0.5-1	0.06
D632E	2*	0.5-2	0.5-1	32-64	0.5-2	2-4	2-4	0.5
F659V	2	0.5	0.25	8-16	0.25-0.5	2	2-4	0.25-0.5
F625S	2	0.5-1	0.25-0.5	8-16	0.25-1	2	2-4	0.5
delF658	1	0.12	0.06	1	0.06	4	4	4
R631G	1	1	0.5	32	2	0.25	1	0.12
R665G	1	1	1	32	1	0.25	2	0.12
R665S	1	1	1	64	2	0.25	1	0.06
1-S629P	1	1	1	32	1	8	16	4
2-S663F	1	0.03	0.06	2	0.12	2	1	1
P667T	1	1	0.5	32	2	0.25	1	0.12
Not Tested	1	0.12	0.06	2	0.12	8	2	8

*One isolate required 48 hours incubation

Figure 1. VT-1129 & VT-1161 MIC data for 34 drug-resistant *Candida glabrata* isolates



Bars indicate CLSI interpretive breakpoints for *C. glabrata*. The breakpoint is not yet estabilished for *C. glabrata* and voriconazole; thus, an epidemiological cutoff value (≤0.5µg/mL) is used for the purpose of this graph.

Conclusions

- VT-1161 and VT-1129 MICs for clinically and/or *in vitro* resistant *C. glabrata* isolates were at least 10-fold below achievable human plasma levels for VT-1161 (10 µg/ml).
- VT-1161 and VT-1129 show compelling promise for the treatment of resistant *C. glabrata* infections.

References

1. Garcia-Effron G, Lee S, Park S, Cleary J, Perlin DS. Antimicrob Agents Chemother 2009;53:3690-9.

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