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Investigational CYP51 Inhibitors VT-1161 and VT-1129 Show Strong Activity In Vitro Against *Candida krusei*

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Introduction and Objectives

- *Candida krusei* is the fifth most common *Candida* species recovered from clinical specimens in the U.S. and worldwide.
- *C. krusei* is intrinsically resistant to fluconazole, and the emergence of voriconazole resistance following exposure to fluconazole is a pressing concern.
- VT-1161 & VT-1129 are highly selective fungal CYP51 inhibitors with potent *in vitro* activity against *Candida* species.
- 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, VT-1129, fluconazole, voriconazole, anidulafungin, caspofungin, and micafungin against 50 *C. krusei* blood isolates

Methods

- Broth microdilution testing was performed using the Clinical and Laboratory Standards Institute M27-A3/S4 method.
- VT-1161-M and VT-1129-G (powders >99% pure) were provided by Viamet Pharmaceuticals, Inc. (Durham, NC) and stock solutions were prepared at a concentration of 1,600 µg/mL in pure DMSO.
- Anidulafungin, micafungin, caspofungin and voriconazole were purchased in the form of frozen microtiter plates (Trek Diagnostics, Inc., Independence, OH).
- Fluconazole was purchased as powder (Alfa Aesar, Inc., Ward Hill, MA, 99% pure).
- Drugs were tested in concentrations ranging from 0.015 µg/ml to 16 µg/mL, except for fluconazole (0.12 µg/ml to 128 µg/ml).
- Endpoints recorded at 24 and 48 hours were defined as ≥50% growth inhibition compared to drug-free controls.
- Inoculum concentrations were verified by quantitative culture, and *C. parapsilosis* ATCC 22019 was used as the quality control strain.

Results

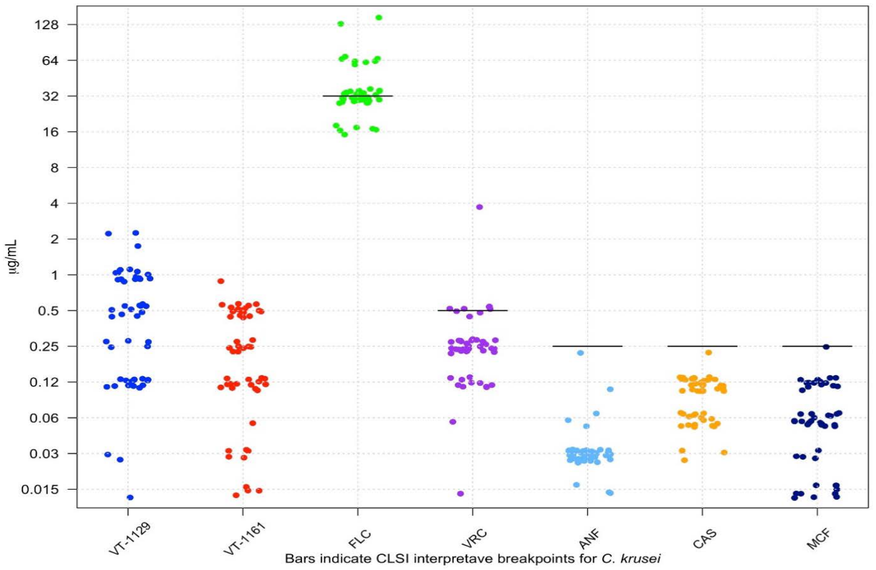
- At 24 hours, all 50 isolates were inhibited by VT-1129 and VT-1161 at concentrations of ≤2 µg/mL.
- MICs at which 90% of isolates were inhibited were 1 and 0.5 µg/mL, respectively.

Table 1. *Candida krusei* (N=50) MIC (µg/mL) values at 24 hour timepoints

	VT-1129	VT-1161	Fluconazole	Voriconazole	Anidulafungin	Caspofungin	Micafungin
Range	≤0.015-2	≤0.015-1	16-128	≤0.015-4	≤0.015-0.12	0.03-0.25	≤0.015-0.25
Geometric mean	0.344	0.164	34.297	0.234	0.032	0.090	0.055
Median	0.5	0.25	32	0.25	0.03	0.12	0.06
Mode	1	0.5	32	0.25	0.03	0.12	0.06
MIC_{50}	0.5	0.25	32	0.25	0.03	0.12	0.06
MIC_{90}	1	0.5	64	0.5	0.03	0.12	0.12

MIC_{50} and MIC_{90}, minimum concentrations that inhibited 50% and 90% of isolates, respectively.

Figure 1. VT-1129 & VT-1161 MIC data for 50 *Candida krusei* isolates



Anidulafungin (ANF), caspofungin (CAS), fluconazole (FLC), micafungin (MCF), voriconazole (VRC)

Bars indicate CLSI "susceptible" MIC breakpoints for C. krusei. C. krusei is assumed to be intrinsically resistant to fluconazole and a breakpoint has not been established; a proposed epidemiological cutoff value (32µg/mL) is used for the purpose of this graph.

Conclusions

- VT-1161 and VT-1129 MICs for clinically and/or in vitro resistant *C. krusei* isolates were at least 5-fold below achievable human plasma levels for VT-1161.
- VT-1161 and VT-1129 show significant promise for the treatment of *C. krusei* infections.

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