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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

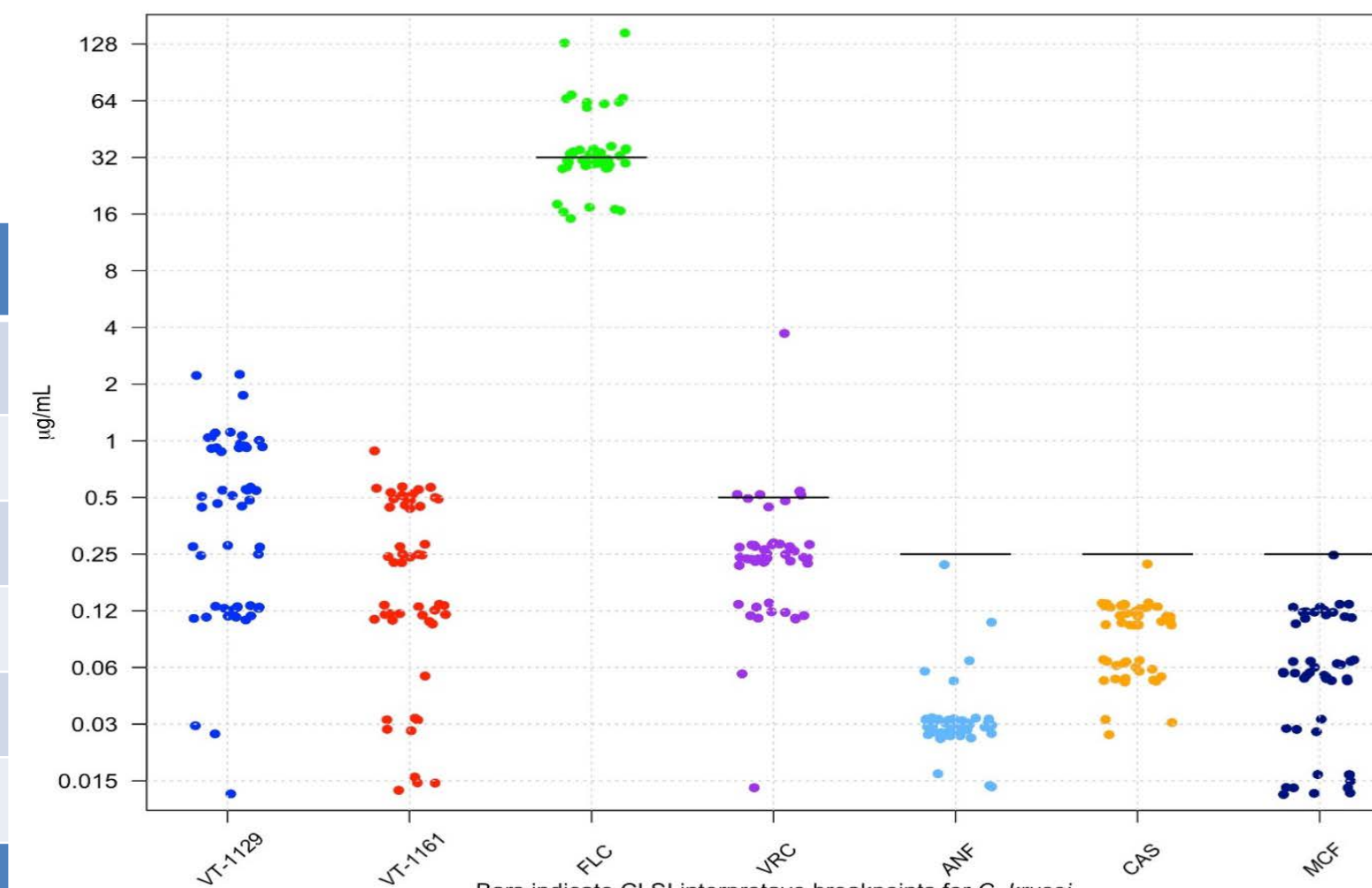
	VT-1129	VT-1161	Fluconazole	Voriconazole	Anidulafungin	Caspofungin	Micafungin
Range	≤0.015-2	≤0.015-1	16-128	≤0.015-4	≤0.015-0.12	0.03-0.25	≤0.015-0.25
Geometric mean	0.344	0.164	34.297	0.234	0.032	0.090	0.055
Median	0.5	0.25	32	0.25	0.03	0.12	0.06
Mode	1	0.5	32	0.25	0.03	0.12	0.06
MIC ₅₀	0.5	0.25	32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

MIC₅₀ and MIC₉₀, minimum concentrations that inhibited 50% and 90% of isolates, respectively.

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.

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



Bars indicate CLSI interpretative breakpoints for *C. krusei*
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.

Acknowledgements and Disclosure

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