High *In Vitro* Potency of the Clinical Investigational Agent VT-1161 against Clinical Isolates of *Candida* spp.

Lisa Long,[1] Nancy Isham,[1] Mahmoud A. Ghannoum,[1] Edward P. Garvey,[2] Stephen R. Brand,[2] Thorsten P. Degenhardt,[2] William J. Hoekstra,[2] Robert J. Schotzinger,[2] Annette W. Fothergill,[3] Nathan P. Wiederhold[3]

[1]Case Western Reserve Univ. (CWRU) and Univ. Hospitals Case Medical Ctr., Cleveland, Ohio, USA; [2]Viamet Pharmaceuticals, Inc., Durham, North Carolina, USA; [3]Univ. Of Texas Health Science Center San Antonio (UTHSCSA), San Antonio, Texas, USA

Intro and Objective

VT-1161 is a potent and highly selective inhibitor of fungal CYP51 [1,2] and is currently in Phase 2 clinical trials for superficial and mucosal fungal infections. Previous *in vitro* MIC studies have not determined its full potency (i.e., MIC values less than or equal to the lowest concentration tested). The objective of this study was to measure the *in vitro* potency of VT-1161 against *C. albicans* (CA) clinical isolates and probe for consistency when testing isolates at two different laboratories.

Materials & Methods

***In Vitro* Susceptibility –** The minimum inhibitory concentration (MIC) of antifungal agent against each isolate was determined according to the CLSI M27-A3 standard [3]. Briefly, RPMI-1640 was the medium, inoculum size was 0.5-2.5 x 10^3 CFU/ml, and incubation was at 35º C for 24 or 48 hours. The MIC endpoints of VT-1161, fluconazole, or caspofungin were recorded at 50% or 100% inhibition as compared to the growth control. VT-1161-M was supplied by Viamet Pharmaceuticals, Inc. Fluconazole and caspofungin was purchased from the respective manufacturers.

Clinical Isolates – The 60 isolates tested by the Center for Medical Mycology (CWRU, Cleveland, OH) were collected from patients with acute vulvovaginal candidiasis in the Phase 2a study of VT-1161 treatment conducted by Viamet (NCT01891331), with the species as follows: *C. albicans* (41), *C. parapsilosis* (12), *C. glabrata* (3), *C. lusitaniae* (3), and *C. tropicalis* (1). The 50 clinical isolates tested by the Fungus Testing Laboratory (UTHSCSA, San Antonio, TX) were fresh samples of *C. albicans* recently submitted to the FTL and from various tissue sources (e.g., bloodstream, CSF, mouth, vagina, etc.).

P1274

Table 1: MICs of 60 *Candida* spp. Isolates at CWRU – at 50% Growth Inhibition at 24 hr

***C. albicans* (41 isolates) MICs (μg/ml)**

Antifungal	Range	MIC_{50}	MIC_{90}	GeoMean
VT-1161	≤0.001 – 0.06	0.002	0.002	0.0017
Fluconazole	≤0.12 – 4	0.25	0.5	0.22

***C. parapsilosis* (12 isolates) MICs (μg/ml)**

Antifungal	Range	MIC_{50}	MIC_{90}	GeoMean
VT-1161	≤0.001 – 0.12	0.002	0.004	0.0033
Fluconazole	0.25 – 2	0.5	1	0.44

***C. glabrata, lusitaniae, tropicalis* (7 isolates) MICs (μg/ml)**

Antifungal	Range	MIC_{50}	MIC_{90}	GeoMean
VT-1161	0.002 – 1	N.A.	N.A.	0.013
Fluconazole	0.25 – 64	N.A.	N.A.	1.1

Table 2. MICs of 50 CA isolates at UTHSCSA

***C. albicans* MICs (μg/ml) at 50% Growth Inhibition at 24 hr**

Antifungal	Range	MIC_{50}	MIC_{90}	GeoMean
VT-1161	0.00012 – 0.12	0.001	0.004	0.00097
Fluconazole	≤0.12 – 4	≤0.12	≤0.12	0.16
Caspofungin	0.06 – 0.5	0.12	0.12	0.13

VT-1161 MICs at 24 and 48 hr (at 50% inhibition)

MIC time point	Range	MIC_{50}	MIC_{90}	GeoMean
24 hr	0.00012 – 0.12	0.001	0.004	0.00097
48 hr	0.0005 – 0.25	0.001	0.008	0.0018

VT-1161 MICs at 50 and 100% inhibition (at 24 hr)

Inhibition Endpoint	Range	MIC_{50}	MIC_{90}	GeoMean
50%	0.00012 – 0.12	0.001	0.004	0.00097
100%*	0.0005 – >16	~0.015	>0.015	N.D.

*100% inhibition read using the same concentration range as 50% inhibition. 22 isolates had defined MIC values ≤0.015 μg/ml (range 0.0005 – 0.015 μg/ml), and 27 isolates were determined to be >0.015 μg/ml. One isolate was tested up to 16 μg/ml VT-1161.

Conclusions

- VT-1161 was a very potent inhibitor of *C. albicans* with a geometric mean MIC of ~0.001 μg/ml.
- In these studies, VT-1161 was ~100-fold more potent than the positive comparator fluconazole.
- VT-1161 MICs against *C. albicans* isolates were consistent between two antifungal testing labs.
- VT-1161 potency against *C. albicans* was largely maintained against clinical isolates of *C. parapsilosis, C. glabrata, C. lusitaniae,* and *C. tropicalis*.

References

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Disclosure

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