Ibrexafungerp (formerly SCY-078) Displays Potent *In Vitro* Activity Against *C. Glabrata* Isolates with Mutations in *fks* Genes

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BACKGROUND

Candida glabrata is the second-most common fungal species isolated from blood in the United States and one of the most common fungal pathogens worldwide. Resistance to the Echinocandin (ECH) class of antifungal drugs is increasing, particularly among *C. glabrata* strains. Resistance to ECH is usually caused by point mutations in the hot spot (HS) regions of the *fks1* and *fks2* genes encoding 1,3-β-D-glucan synthase (GS). Ibrexafungerp (formerly SCY-078) is a first-in-class, intravenous and oral, triterpenoid antifungal, a novel class of glucan synthase inhibitors. While ibrexafungerp (IBX) shares the same mechanism of action as the ECH, it has the potential for unique activity profiles due to its novel structure. Here we report the *in vitro* activity of IBX against *C. glabrata* strains with *fks* mutations.

METHODS

In vitro MIC data (50% inhibition at 24 hrs) for IBX against *C. glabrata* isolates with *fks* mutations were compiled across 5 independent studies. The combined studies included 79 isolates with *fks* mutations (30 *fks1* and 49 *fks2*) and 142 wild-type (WT) *C. glabrata* isolates as controls. *In vitro* susceptibility was determined by broth micro-dilution using CLSI methods (M27-A3). Isolates with MIC values for IBX that were greater than two 2-fold dilutions in comparison to the respective WT MIC_{50} values within each study were considered to be non-WT, potentially indicating resistance. Comparator compounds varied by study and included caspofungin (CAS) and micafungin (MFG). Resistance to CAS and MFG was defined as MIC values ≥0.5 and ≥0.25 μg/mL respectively (CLSI M27-S4).

RESULTS

MIC (μg/mL) Distribution of *C. glabrata* WT and *fks* Mutants by Study

Study 1 (MIC μg/mL)			**Study 2 (MIC μg/mL)**			**Study 3 (MIC μg/mL)**			**Study 4 (MIC μg/mL)**				**Study 5 (MIC μg/mL)**			
WT (N=29)	**IBX**	**CAS**	WT (N=9)	**IBX**	**CAS**	WT (N=31)	**IBX**	**MFG**	WT (N=39)	IBX	CAS	MFG	WT (N=34)	IBX	CAS	MFG
Range	0.5 - 2	0.03 - 16	Range	0.125 – 0.5	0.06 - 1	Range	0.015 – 2	0.007 – 0.5	Range	0.25 - 1	0.03 – 0.25	0.008–0.03	Range	0.25 - 1	0.015–0.25	0.015–0.125
Mode	0.5	0.06	Mode	0.25	0.06	Mode	0.125/ 0.5	0.007	Mode	0.5	0.06	0.015	Mode	0.25	0.015	0.015
MIC_{50}	0.5	0.125	MIC_{50}	NA	NA	MIC_{50}	0.125	0.007	MIC_{50}	0.5	0.06	0.015	MIC_{50}	0.5	0.015	0.015
Fks (N=12)			Fks (N=11)			Fks (N=5)			Fks (N=25)				Fks (N=26)			
Range	0.5 - 2	0.125-16	Range	0.25 - 4	2 - 16	Range	0.125 - 2	0.03 – 0.5	Range	0.125 - 16	0.03 - 16	0.008 – 4	Range	0.25 - 4	0.015 - 16	0.015 - 4
Mode	0.5	0.125/16	Mode	0.5	2/16	Mode	None	0.125	Mode	1	0.5	0.03/1/2	Mode	0.5	0.015/1	0.015
MIC_{50}	1	1	MIC_{50}	1	4	MIC_{50}	NA*	NA	MIC_{50}	1	0.5	0.25	MIC_{50}	0.5	0.5	0.125

*NA – Not applicable (N<10), MIC values for IBX were 0.125, 0.25, 0.5, 1, and 2 μg/mL

Activity of IBX and Comparators Against *fks1* Mutant Strains[a]

Mutation (N)	**IBX[c]**	**CAS[d]**	**MFG[d]**
WT[b]	0.125 – 0.5	0.015 – 0.125	0.007 – 0.015
F625S (5)	1, 2, 4, 4, 4	0.06, 1, 1, 1, 2	0.03, 0.25, 0.5
F625Y (2)	0.5, 0.5	0.06, 0.125	0.03
S629P (7)	0.5, 0.5,1,1,1,1,1	0.5,8,8,8,16,16,16	0.06, 2,2,2
L630I (2)	0.5, 0.5	0.125, 0.125	0.008
R631G (1)	0.5	0.03	0.06
D632E (2)	1, 2	0.5, 1	0.125, 0.25
D632G (3)	1, 1, 4	2, 2, 16	
D632V (1)	0.5	0.25	0.03
D632Y (2)	0.5, 4	0.25, 1	0.125
I634V (4)	0.5, 0.5, 0.5, 0.5	0.015, 0.015, 0.015, 0.015	0.015, 0.015, 0.015, 0.015
S645P (1)	1	2	1

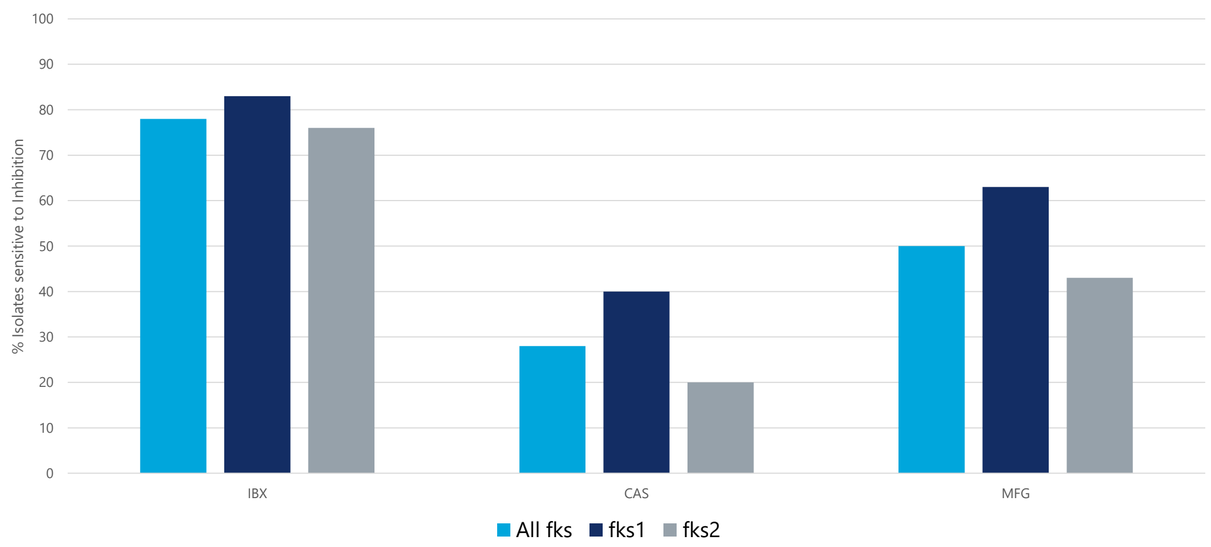
[a]MIC values in μg/mL, [b]Represent ranges of MIC_{50} values across studies. [c]Values in red font indicate non-WT MIC, [d]Values in red font indicate resistance

Activity of IBX and Comparators Against *fks2* Mutant Strains[a]

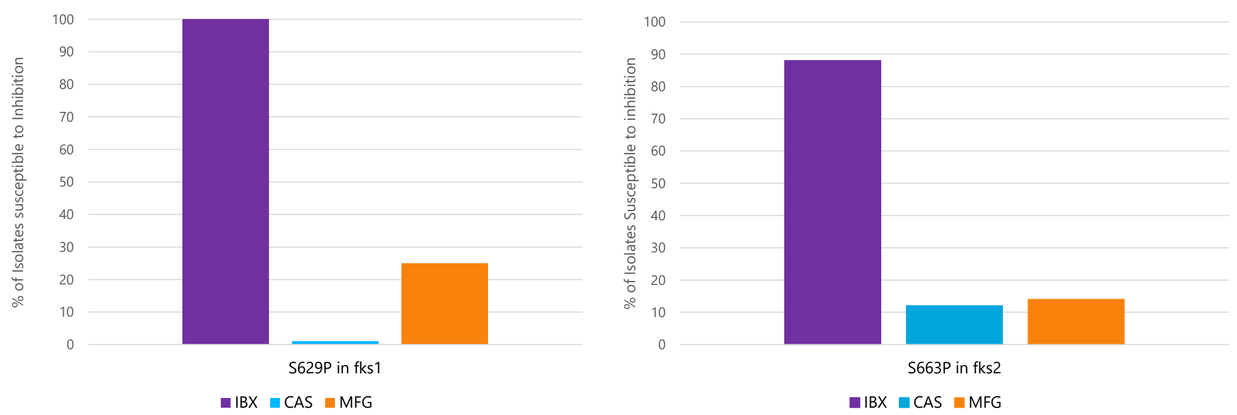
Mutation (N)	**IBX[c]**	**CAS[d]**	**MFG[d]**
WT[a]	0.125 – 0.5	0.015 – 0.125	0.007 – 0.015
D648E (2)	0.5, 1	0.125, 0.25	
F649del (1)	0.25		0.03
F659del (5)	1, 2, 2, 4, 16	2, 16, 16	0.125,0.125, 1, 2
F659S (2)	0.5, 4	16, 2	0.25
F659V (5)	2 ,2, 2, 4, 4	0.5,1, 1, 2, 4	0.03, 0.06, 0.125
F659Y (1)	1	2	0.25
L662W (1)	4	2	1
S663F (4)	0.25, 0.25, 0.5, 0.5,	0.25, 0.5, 0.5, 0.5	0.125, 0.25, 0.5
S663P (17)	0.125,0.25,0.5,0.5,0.5,0.5, 0.5,1,1,1,1,1,2,2,2,4,4	0.125,0.25, 0.5,0.5,0.5,1,2,4,4,8,8,16, 16,16,16,16	0.03,0.125, 0.25,0.5, 1,1,1,1,2,2,2,2,4,4
S663Y (1)	0.5		0.5
L664R (1)	1	2	
R665G (1)	0.5	0.5	0.25
R665S (1)	0.25	0.25	0.125
D666E (1)	0.25	2	
P667T (2)	0.25, 0.5	0.5, 2	0.06
K753Q (1)	0.25	0.5	0.06
P1371S (1)	0.125	0.03	0.03
I1376V (2)	0.5, 1	0.015, 0.03	0.015, 0.015

[a]MIC values in μg/mL, [b]Represent ranges of MIC_{50} values across studies. [c]Values in red font indicate non-WT MIC, [d]Values in red font indicate resistance

Ibrexafungerp Demonstrated Superior Activity Compared to ECH Against Isolates with *fks* Mutations



Ibrexafungerp Demonstrated Superior Activity Against the Most Common ECH-Resistance Associated Mutations in *C. glabrata*



Ibrexafungerp demonstrated activity against 78% of *C. glabrata* isolates with *fks* mutations, including those isolates with the most commonly observed S629P (*fks1*) and S663P (*fks2*) mutation. Resistance to ibrexafungerp in these studies was primarily associated with deletions at position F659 in *fks2* confirming previous findings of resistance development *in vitro*.[¥]

CONCLUSION

Ibrexafungerp demonstrated superior *in vitro* activity as compared to caspofungin and micafungin against *C. glabrata* isolates with *fks* mutations. These results suggest that ibrexafungerp may be a suitable option for the treatment of infections caused by ECH resistant *C. glabrata*.

[¥]Jimenez-Ortigosa et al., AAC 2017