# The new triterpenoid antifungal SCY-247 retained activity against most echinocandin and fluconazole-resistant *Candida* spp isolates: reduced susceptibility against *C. glabrata* isolates showing substitutions at the first amino acid in hotspot 1 *FKS2* gene

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## Background

- IV/oral SCY-247 is a second-generation fungerp antifungal, a new family of beta-d-glucan synthase inhibitors
- Its *in vitro* activity against *Candida* resistant isolates is mostly unknown

**The aim of this study was to assess *in vitro* antifungal activity profile of SCY-247 against a collection of Spanish antifungal-resistant *Candida* spp isolates**

## Materials and Methods

- We studied 161 clinical isolates collected from 16 centres from Madrid (Spain) showing different antifungal resistance profiles as follows:

| | |
|---|---|
| **Fluconazole-resistant (n=97)** | • ***C. parapsilosis*** showing *ERG11* gene mutations |
| **Fluconazole-susceptible and echinocandin-resistant (n=41)** | • ***C. glabrata*** (n=35): $FKS1^{P633T}$ (n=1); $FKS2^{\Delta F659}$ (n=10), $FKS2^{S663}$ (n=10), $FKS2^{F659S}$ (n=4), $FKS2^{D666}$ (n=3), $FKS2^{R1378S}$ (n=2), $FKS2^{L662W}$ (n=1), $FKS2^{L664R}$ (n=1), $FKS2^{W715L}$ (n=1), and *FKS1* and *FKS2* genes wild-type (n=2)<br>• ***C. albicans*** (n=5): $FKS1^{S645P}$ (n=4), $FKS1^{R1361H}$ (n=1)<br>• ***C. tropicalis*** $FKS1^{S654F/P}$ (n=4)<br>• ***C. parapsilosis*** (n=1) |
| **Fluconazole and echinocandin-resistant (n=23)** | • ***C. albicans*** (n=3): $FKS1^{R647G}$ (n=2) and $FKS1^{R1361L}$ (n=1)<br>• ***C. glabrata*** (n=15): $FKS1^{F629F}$ (n=1); $FKS2^{S663P}$ (n=7), $FKS2^{F708S}$ (n=2), $FKS2^{D666Y}$ (n=2), $FKS2^{F659S}$ (n=1), $FKS2^{\Delta F659}$ (n=1), $FKS2^{E655A}$ (n=1)<br>• ***C. krusei*** $FKS1^{D662Y}$ (n=1) |

- SCY-247 activity was studied by the EUCAST E.Def 7.4 procedure
- Minimum inhibitory concentration (MIC) was defined as the lowest concentration reaching 50% of fungal growth inhibition compared to the drug-free control

## Results

- SCY-247 MIC values against most *Candida* spp isolates spanned concentrations between 0.004 mg/L and 4 mg/L (Table)
- With the exception of *C. glabrata*, almost all resistant isolates had MIC values similar to those obtained against echinocandin-susceptible isolates (Poster P2966)
- The presence of fluconazole resistance did not affect the SCY-247 *in vitro* activity
- The single echinocandin-resistant *C. krusei* isolate ($FKS1^{D662Y}$) showed a SCY-247 MIC = 1 mg/L
- All echinocandin-resistant and FKS1-mutant *C. albicans* isolates showed SCY-247 MIC values ranging from ≤0.004 mg/L to 0.25 mg/L (Table and Figure)
- Four *C. tropicalis* isolates were echinocandin-resistant and FKS1-mutant and showed SCY-247 MIC values ranging from 0.25 mg/L to 4 mg/L (Table and Figure):

**Table**. Isolates tested and SCY-247 MIC distributions

| Species (no. of isolates) | MIC (in mg/L) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤0.004 | 0.008 | 0.016 | 0.03 | 0.06 | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | ≥16 |
| ***C. albicans* (n=8)** | 2 | 0 | 0 | 1 | 2 | 1 | 2 | 0 | **0** | **0** | **0** | **0** | - |
| ***C. glabrata* (n=50)** | 0 | 0 | 0 | 3 | 2 | 10 | 15 | 1 | **3** | **8** | **8** | 0 | - |
| ***C. parapsilosis* complex (n=98)** | 0 | 0 | 0 | 1 | 0 | 2 | 8 | 74 | 9 | **4** | **0** | **0** | - |
| ***C. tropicalis* (n=4)** | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | **0** | **1** | **0** | - |
| ***C. krusei* (n=1)** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | **0** | **0** | **0** | - |

**Cells with the "-" symbol indicate non-tested antifungal concentrations; MIC values above the highest MIC values found against echinocandin-susceptible isolates are depicted in bold (Poster P2966)**

- Echinocandin-susceptible *C. glabrata* isolates showed SCY-247 MIC values ≤ 0.5 mg/L (Table)
- As to the echinocandin-resistant ***C. glabrata*** isolates (Figure):
  - Two isolates had *FKS1* and *FKS2* genes wild type sequences and SCY-247 MIC values between 0.06 mg/L and 0.125 mg/L, respectively
  - Two isolates had only *FKS1* gene substitutions ($FKS1^{S629F}$ and $FKS1^{P633T}$) and SCY-247 MIC values = 0.25 mg/L
- The remaining isolates had *FKS2* gene substitutions, and SCY-247 MIC values were impacted by the position of the amino acid substitution (Figure):
  - Substitutions at $FKS2^{E655A}$, $FKS2^{W715L}$ and the first position of the HS1 ($FKS2^{F659S}$ and $FKS2^{\Delta F659}$) correlated with SCY-247 MIC values > 0.5 mg/L
  - Substitutions at $FKS2^{D666}$, $FKS2^{L662W}$, $FKS2^{L664R}$, $FKS2^{R1378S}$ and $FKS2^{S663P}$ led mostly to SCY-247 MIC values ≤ 0.5 mg/L

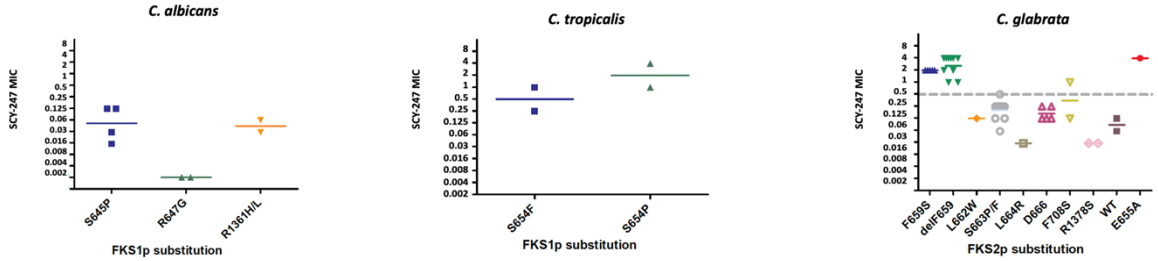


**Figure 1.** SCY-247 MIC distribution break down to *FKS* gene mutation

## Conclusions

- SCY-247 retained *in vitro* activity against antifungal-resistant *Candida* spp. isolates, including echinocandin-resistant isolates
- However, SCY-247 showed MIC values > 0.5 mg/L against *C. glabrata* isolates harbouring amino acid substitutions at the first amino acid of the *FKS2* gene Hot Spot 1

The study was supported by grant PI22/00005 and Scynexis Ltd. The study was co-funded by the European Regional Development Fund (FEDER) 'A way of making Europe'