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Research grants

Cidara, F2G, Gilead, MSD, Mundipharma, Pfizer, Scynexis

Consulting fees or expert testimony

Basilea, Cidara, Gilead, GlaxoSmithKline, Matinas, Mundipharma, Pfizer, Scynexis

Participation on a DRC, DSMB or Scientific Advisory Board

Cidara, Janssen, Pulmocide, Shionogi

Speaker and lecture honoraria

Al-Jazeera/Hikma, Gilead, GlaxoSmithKline, Biotoscana/United Medical/Knight, MSD, Mundipharma, Pfizer, Sandoz, Shionogi





Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

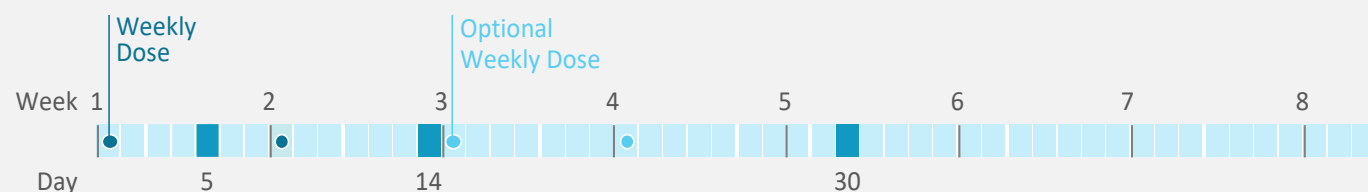
George R Thompson III, Alex Soriano, Oliver A Cornely, Bart Jan Kullberg, Marin Kollef, Jose Vazquez, Patrick M Honore, Matteo Bassetti, John Pullman, Methee Chayakulkeeree, Ivan Poromanski, Cecilia Dignani, Anita F Das, Taylor Sandison, Peter G Pappas, on behalf of the ReSTORE trial investigators

Integrated Analysis of Phase 2 and Phase 3 Data of Rezafungin for the Treatment of Candidemia and/or IC

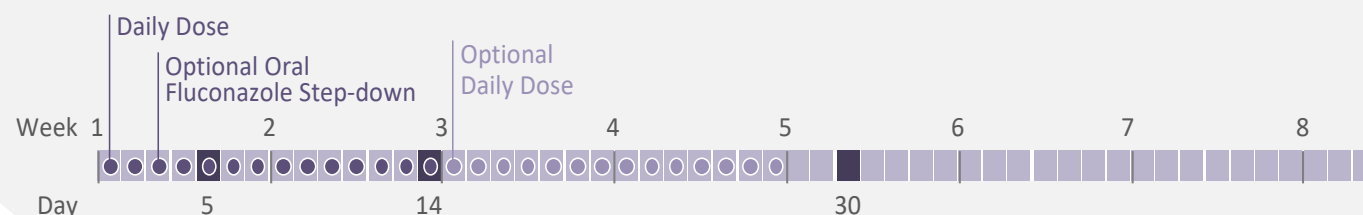
STRIVE and ReSTORE were Similarly Designed

Aligned Phase 2 and 3 Dosing and Design

REZAFUNGIN 400 mg/200 mg^a once weekly (QWk). (N=139 combined)^b



CASPOFUNGIN 70 mg/50 mg once daily (QD). (N=155 combined)^b
with optional oral step-down^a to fluconazole 6 mg/kg to nearest 200 mg QD



Pooled endpoints

- Primary^c: All-cause mortality at Day 30
- Adverse events
- Secondary/exploratory
 - Mycological response at Day 5
 - Time to first negative blood culture

IC=invasive candidiasis; mITT=modified intent to treat.

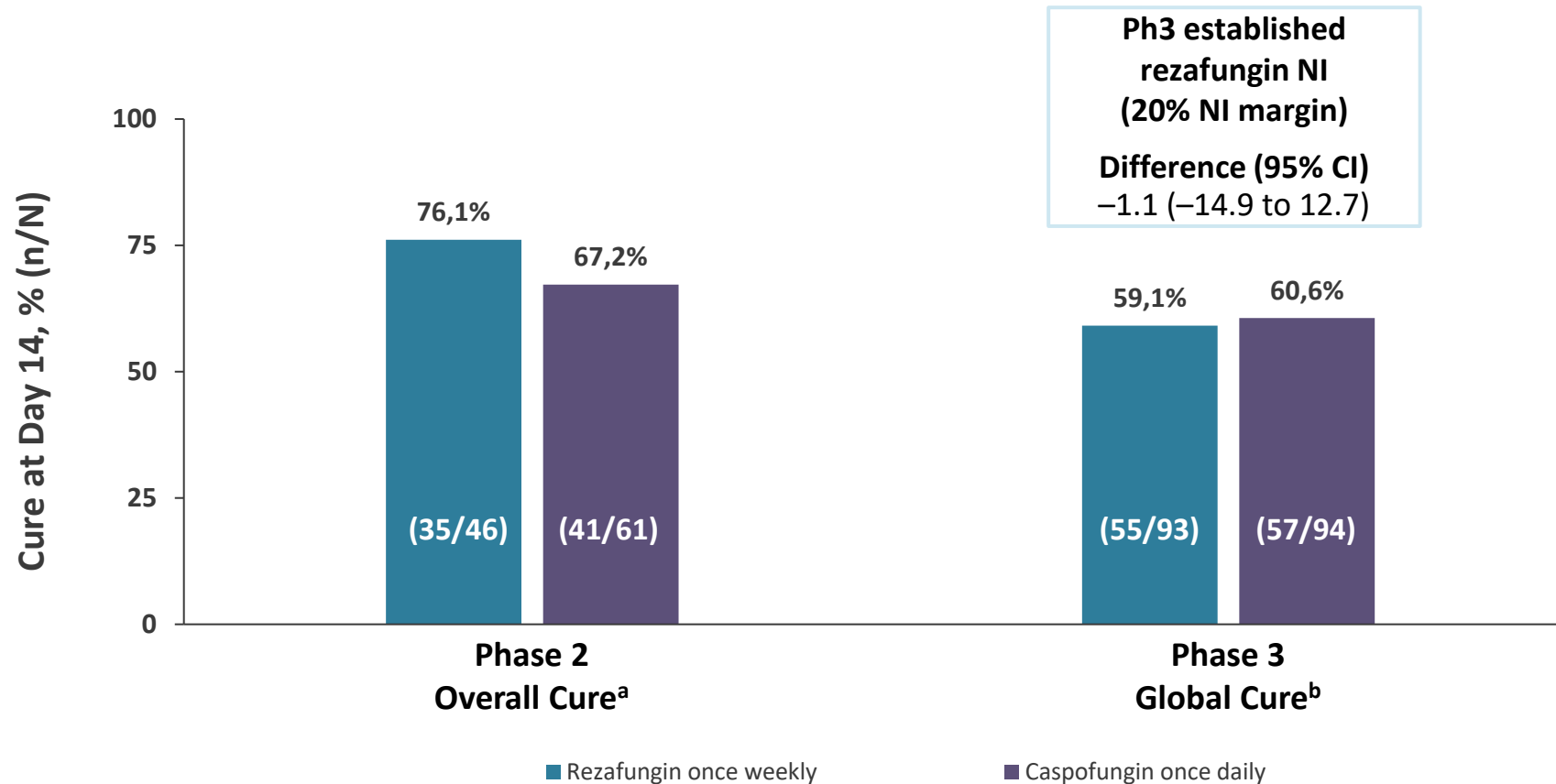
^aThe rezafungin arm included optional oral step-down to placebo, to maintain the study blind.

^bmITT population: all subjects (Ph2+Ph3) who received ≥ 1 dose of study drug and had documented *Candida* infection (candidemia and/or IC based on systemic signs and mycological confirmation).

^cPrimary endpoints not pooled were Overall Response (Phase 2) and Global Response (Phase 3).

Primary endpoint: Cure Rates at Day 14

mITT Population – Phase 2, Phase 3



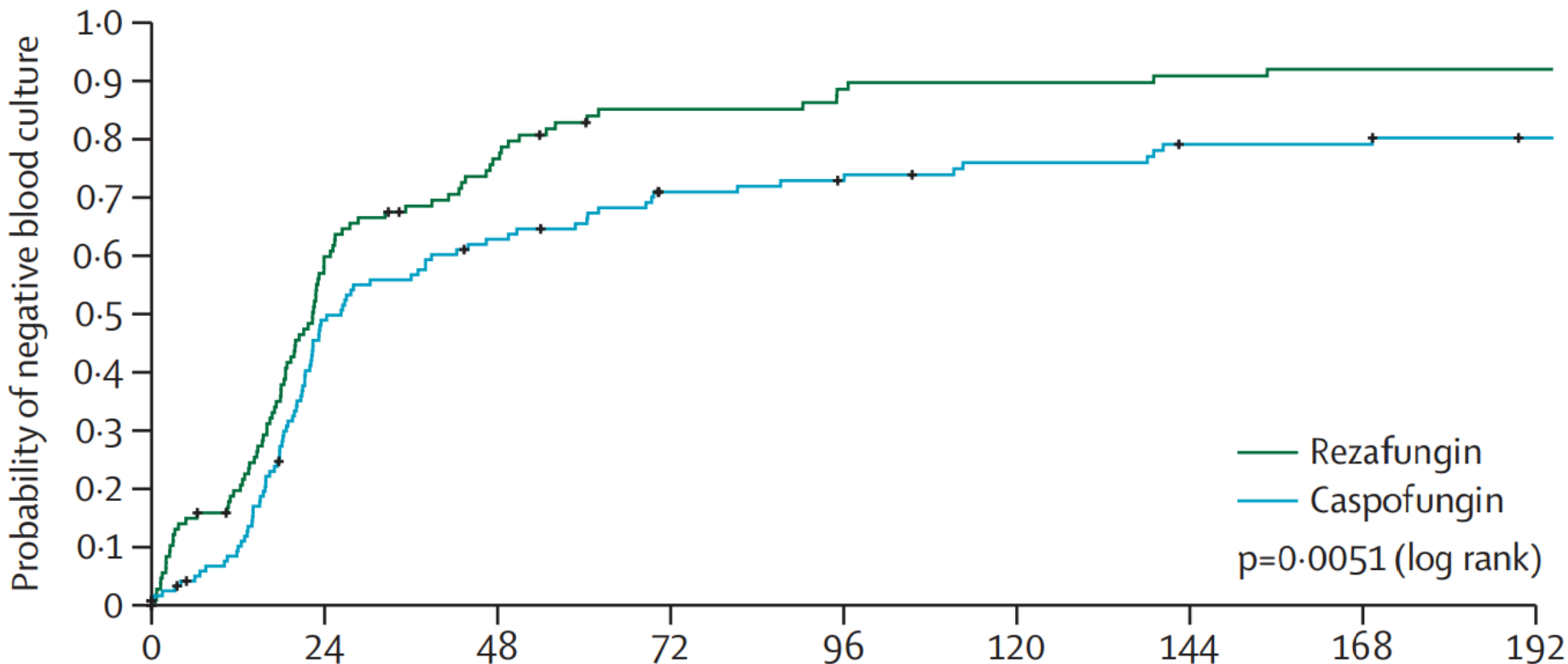
NI=non-inferiority.

^aOverall Cure (Phase 2): resolution of systemic signs attributable to candidemia or invasive candidiasis AND mycological eradication as demonstrated by a single tissue/fluid culture or 2 negative blood cultures at least 12 hours apart.

^bGlobal Cure (Phase 3): investigator assessment of clinical cure AND mycological eradication as demonstrated by a single negative blood or tissue/fluid culture AND (if pertinent) improvement or resolution of evidence of invasive candidiasis on radiographic imaging.



Time to First Negative Blood Culture

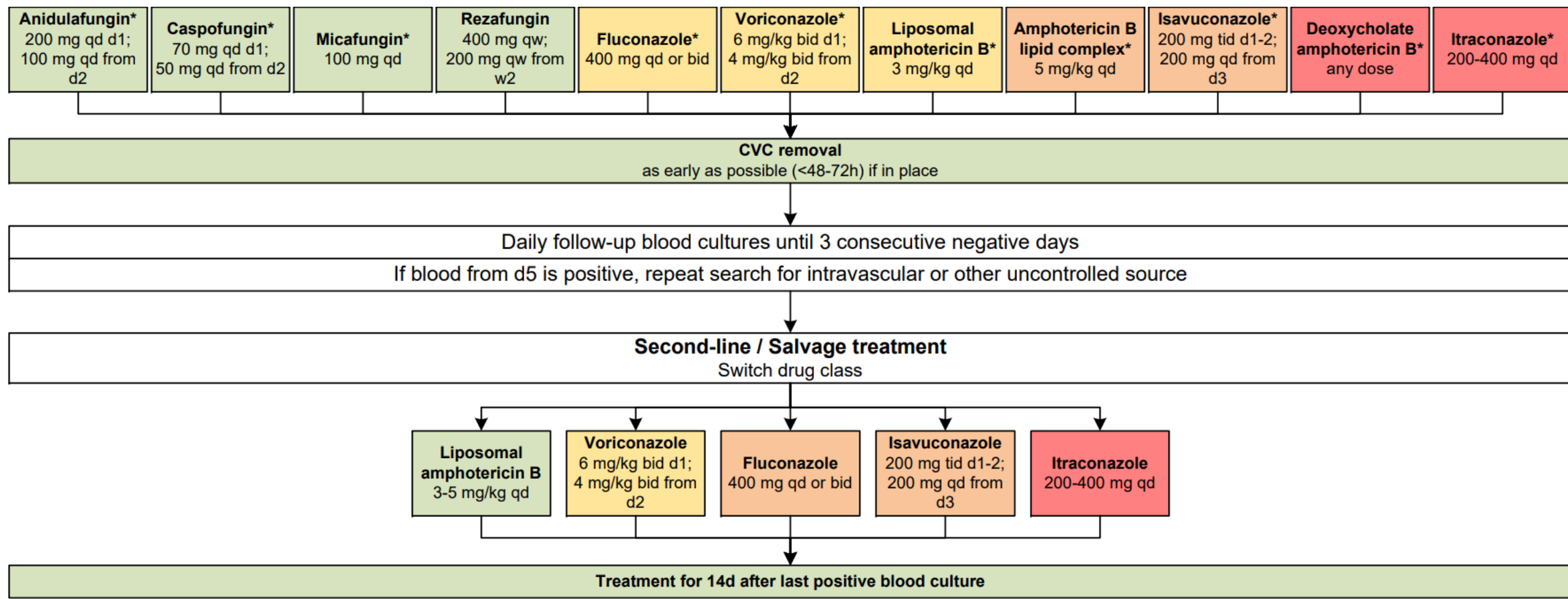


Number at risk
(number censored)

Rezafungin	109 (0)	42 (2)	23 (4)	13 (6)	10 (6)	9 (6)	8 (6)	7 (6)	7 (6)
Caspofungin	122 (0)	59 (3)	42 (4)	30 (7)	27 (8)	23 (9)	19 (10)	19 (10)	16 (12)



Candidemia Management





- **Fosmanogepix (APX001)**
- Ibrexafungerp (SCY078)
- Olorofim (F901318)
- Opelconazole (PC945)
- Oteseconazole (VT-1161)



- **Inhibits fungal glycosylphosphatidylinositol (GPI)-anchored wall transfer protein 1 (“Gwt1 inhibitor”)**
- **Broad-spectrum activity against yeasts and moulds**
 - **Candida**
 - **Aspergillus**
 - **Fusarium**
 - **Mucorales (TBD)**
- **IV and PO formulations**
- **Prodrug of manogepix**



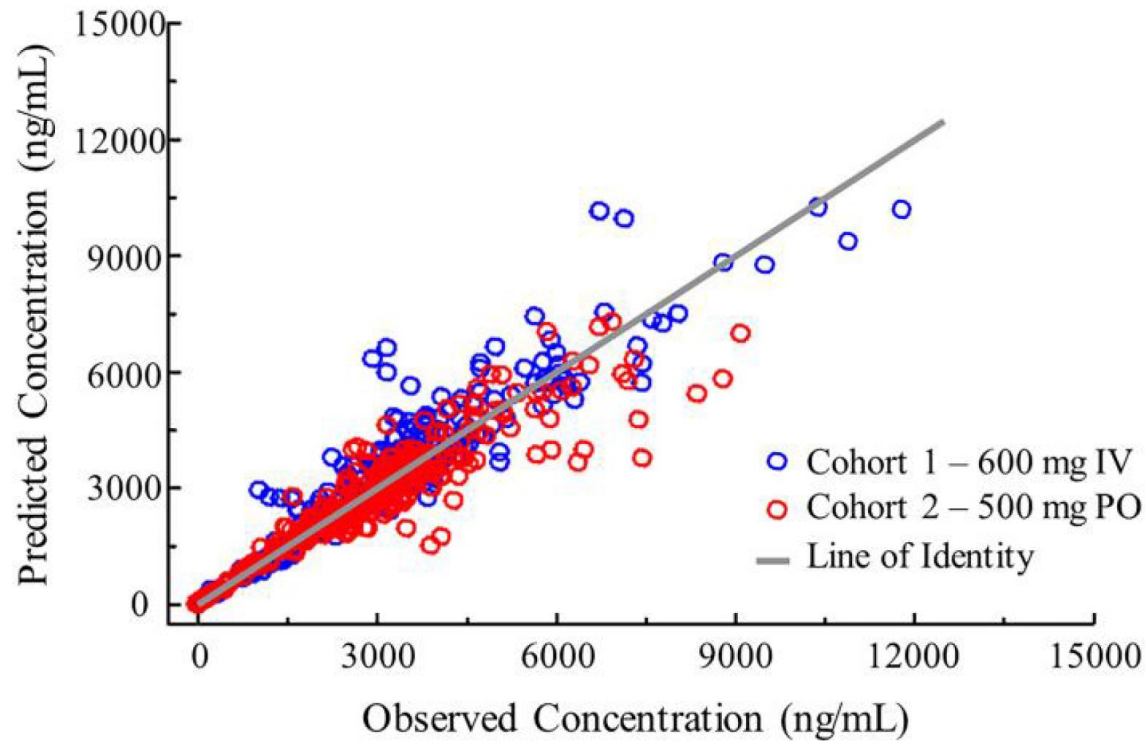
- **Open-label, single-arm study**
- **≥ 18 years**
- **Posaconazole prophylaxis during neutropenia**
- **Concomitant fosmanogepix**
 - **Dose 600 mg IV QD (d1-d14), N=10, (3-hour infusion)**
 - **Dose 500 mg PO QD (d1-d14), N=11**



- **26 fosmanogepix-related AE**
 - **IV 14 in 5 (50%) patients**
 - **PO 12 in 4 (36.4%) patients**
- **No SAE**
- **None leading discontinuation**
- **Related AEs**
 - **Grade 1/2 nausea (4 in 3 patients)**
 - **Vomiting**
 - **ALT increase (2 patients)**
 - **Delirium (2 patients)**
 - **Grade 3 hypertension**



- Dose-corrected geometric mean ratio of AUC (PO-to-IV) was 95%
- ~2 days elimination half-lives consistent with healthy volunteers





<u>Antifungal</u>	<u>MIC (micrograms/milliliter)</u>
Amphotericin B	2
Anidulafungin	>8
Caspofungin	>8
Micafungin	>8
Rezafungin	8
Ibrexafungerp	>8
Itraconazole	>16
Posaconazole	>16
Voriconazole	8
Isavuconazole	>16
Olorofim	>4
Terbinafine	>2
Manogepix	≤0.008



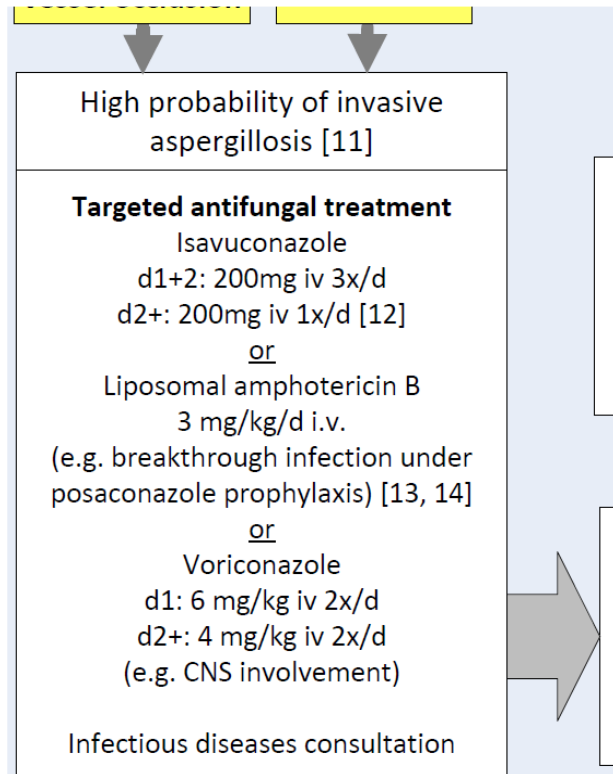
- Fosmanogepix (APX001)
- Ibrexafungerp (SCY078)
- **Olorofim (F901318)**
- Opelconazole (PC945)
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- **MOA**
 - **Selective inhibitor of fungal DHODH (Dihydroorotate dehydrogenase) involved in pyrimidine biosynthesis**
 - **2000-fold IC50 difference between human and fungal enzymes**
- **Pyrimidine inhibition**
 - **DNA synthesis and cell cycle regulation**
 - **RNA synthesis and protein production**
 - **Cell wall synthesis**
 - **Phospholipid synthesis**



- **Outcomes in ... invasive Scopulariopsis infections**
S. Hammond
- **Outcomes of ... Lomentospora prolificans infections**
M. Slavin
- **... treatment of azole-resistant ... aspergillosis**
A. Warris
- **Olorofim ... for resistant Microascus sp**
E. Faure



Olorofim?

Fosmanogepix?

BAL2062?

Rezafungin?



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