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Research grants

Amplifyx, Basilea, BMBF, Cidara, DZIF, EU DG Research and Innovation, F2G, Gilead, Matinas, MedPace, Merck/MSD, Mundipharma, Octapharma, Pfizer, Scynexis

Consulting fees or expert testimony

Abbvie, Amplifyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, Matinas, MedPace, Menarini, Molecular Partners, MSG-ERC, Noxxon, Octapharma, Pardes, PSI, Scynexis, Seres

Participation on DRC, DSMB or Scientific Advisory Board

Actelion, Allegra Therapeutics, Cidara, Entasis, IQVIA, Janssen, MedPace, Paratek, PSI, Pulmocide, Shionogi

Speaker honoraria

Abbott, Al-Jazeera Pharmaceuticals, Astellas, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Pfizer

Other Interests

DGHO, DGI, ECMM, ISHAM, MSG-ERC, Wiley





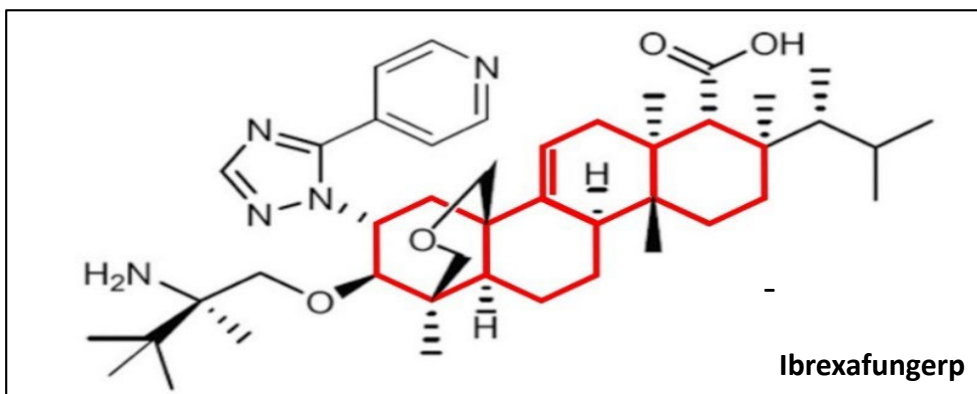
- 2012 Candida Diseases**
- 2018 Aspergillus Diseases**
- 2019 Mucormycosis**
- 2020 COVID-19 Associated Pulmonary Aspergillosis (CAPA)**
- 2021 Rare Moulds**
- 2021 Rare Yeasts**
- 2021 Endemic Mycoses**



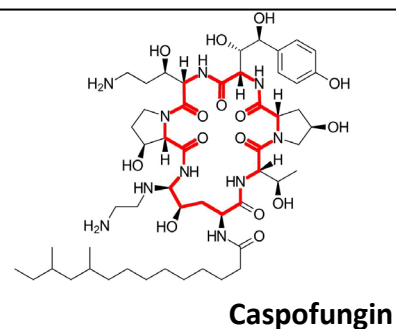
- Fosmanogepix (APX001)
- **Ibrexafungerp (SCY078)**
- Olorofim (F901318)
- Opelconazole (PC945)
- Oteseconazole (VT-1161)
- Rezafungin (CD101)

Oral Ibrexafungerp: A Novel Triterpenoid Glucan Synthase Inhibitor

Shared Fungicidal MOA with Echinocandins



Structurally distinct
from other GSIs
(echinocandins)



- Different enzyme-drug interaction → lower impact of common FKS mutations
- Oral bioavailability

Key Attributes

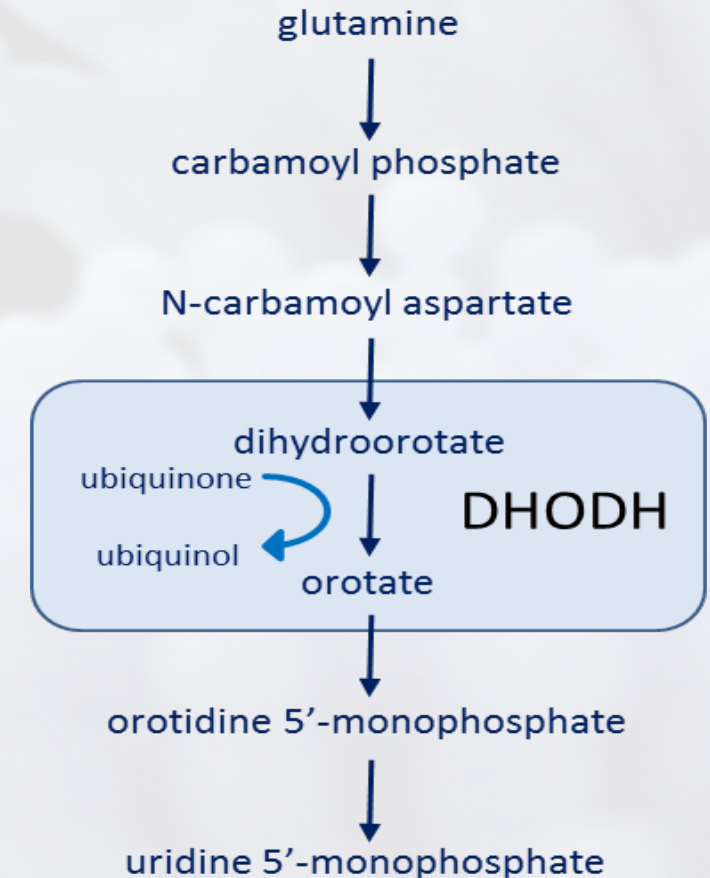
- Activity against:
 - *Candida* spp., including *Candida auris*
 - *Aspergillus* spp.
 - *Pneumocystis* spp.
 - Dimorphic fungi
 - Other emerging fungi
- Active against azole- and most echinocandin-resistant strains
- IV currently in Phase 1 development
- Favorable safety profile > 1500 exposed
- Low risk of drug-drug interactions
- Extensive tissue distribution- ($V_{dss} > 8$ L/kg)
- Half-life ~20 hours
- Antifungal activity not impacted by pH
- **Now approved by FDA for vulvovaginal candidiasis**



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Orotomide Mechanism of Action

- Olorofim is a potent selective inhibitor of fungal DHODH
 - DHODH (Dihydroorotate dehydrogenase) is a key enzyme involved in pyrimidine biosynthesis
- Humans also have this enzyme
 - But, > 2000-fold difference in IC_{50} between human and fungal enzymes
- Pyrimidine inhibition has profound effects as it interferes with
 - DNA synthesis and cell cycle regulation
 - RNA synthesis and protein production
 - Cell wall synthesis
 - Phospholipid synthesis





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About Rezafungin

- Next-generation, once-weekly IV echinocandin
- Analog of anidulafungin, designed for increased stability and improved PK

Properties

- Long-acting PK enables once-weekly dosing and front-loaded plasma exposure
- Broad-spectrum activity → in vivo efficacy against *Candida*, *Aspergillus*, and *Pneumocystis* spp.
- Absence of toxic degradation products → lack of hepatotoxicity
- No DDIs → No dosage adjustments needed with commonly administered medications



DDI, drug-drug interaction; PK, pharmacokinetics.

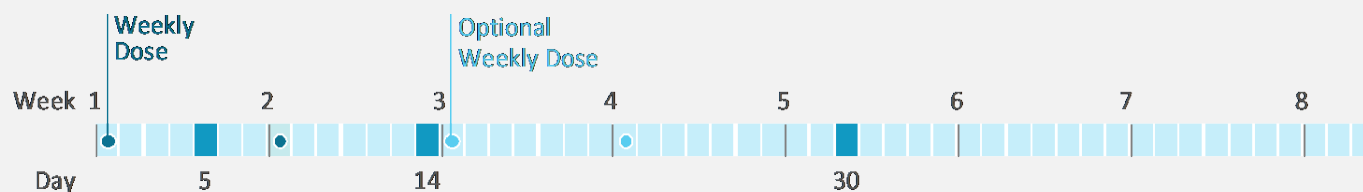
1. Thompson, et al. CID Sept 2020. 2. James et al. *Antimicrob Agents Chemother* 2017;61:e01541-16. 3. Krishnan, et al. *J Antibiot* (Tokyo). 2017;70:130-135. 4. Lakota, et al. *Antimicrob Agents Chemother*. 2017;61:e00758-17. 5. Zhao, et al. AAC October 2017. 6. Weiderhold, et al. *Antimicrob Agents Chemother*. 2019;63:e01165-19. 7. Flanagan, et al. ECCMID. April 2019:O0271. 8. Ong, et al. AAC November 2016. 9. Ong, et al. EBMT. March 2019.

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

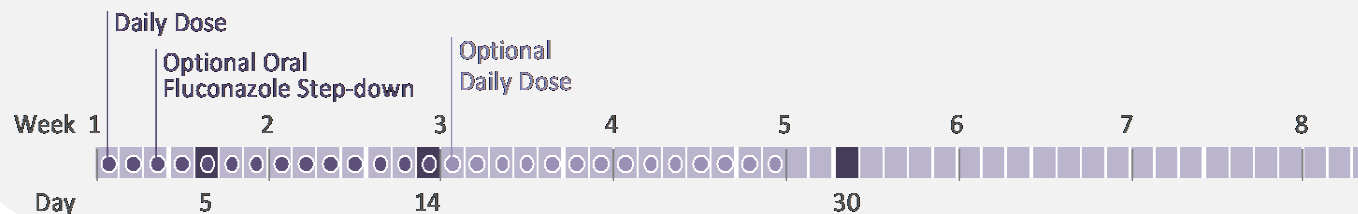
STRIVE and ReSTORE were Similarly Designed

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

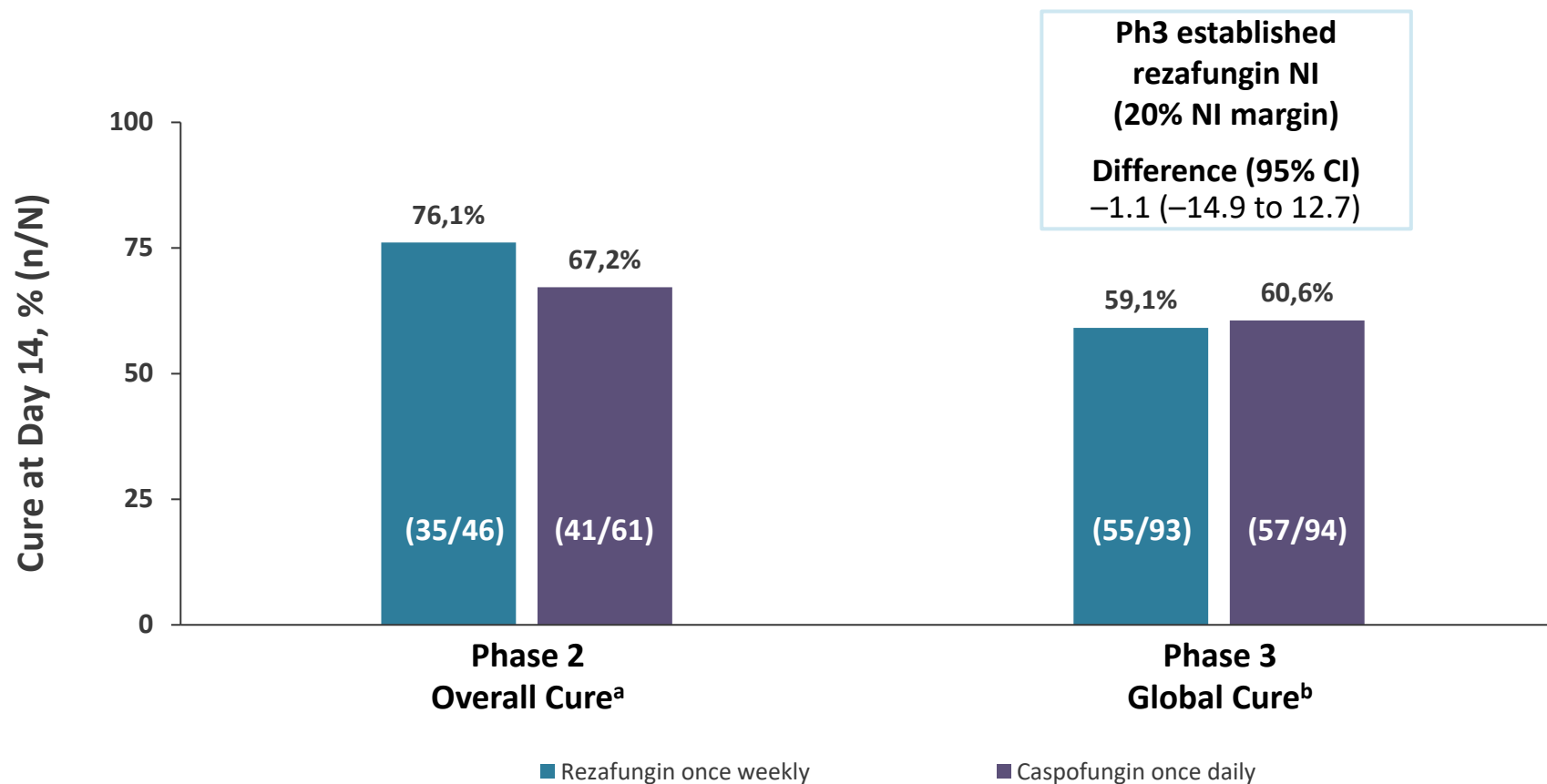
IC=invasive candidiasis; mITT=modified intent to treat.

^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).

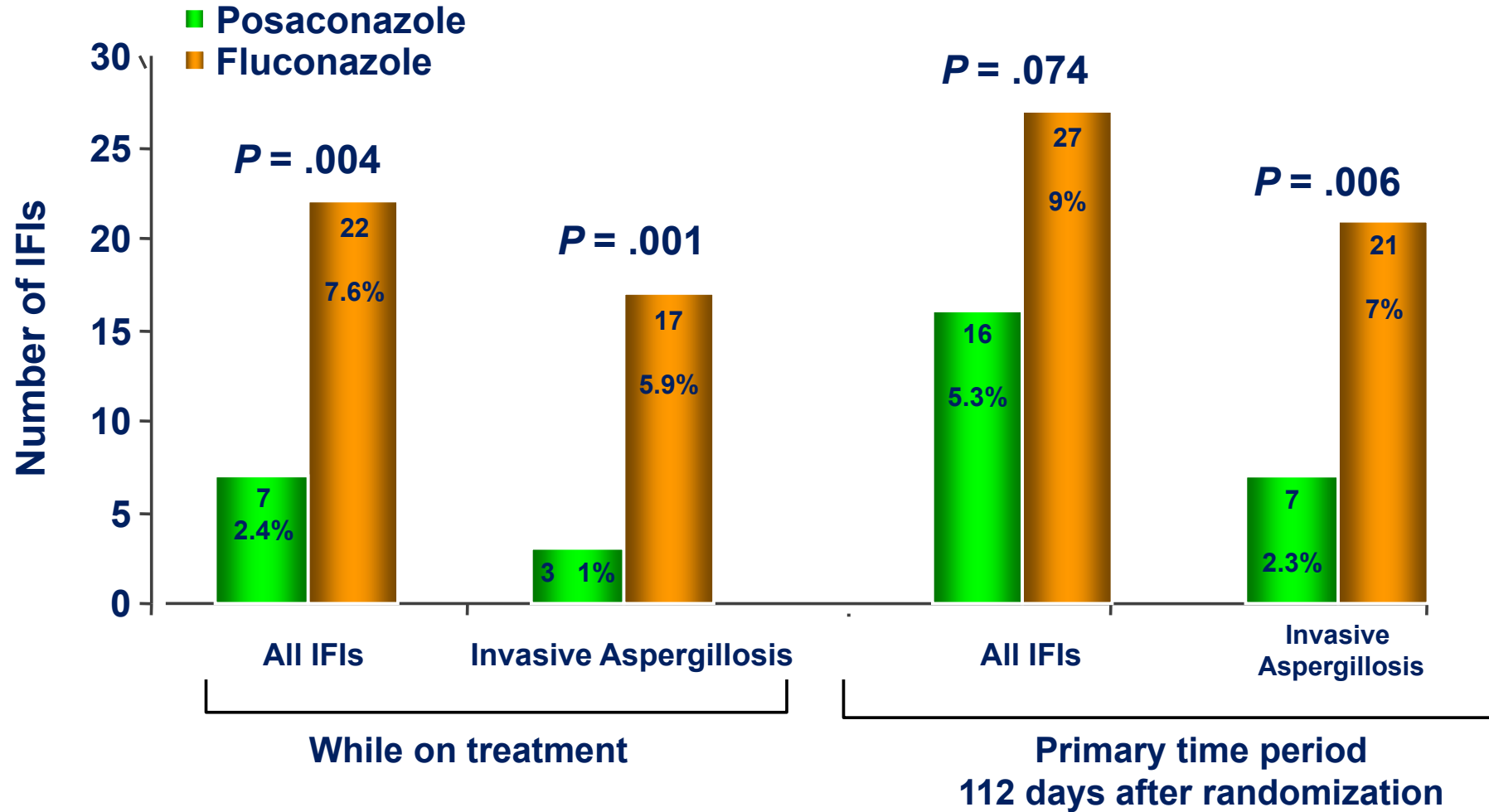
Primary endpoint: Cure Rates at Day 14 mITT Population – Phase 2, Phase 3



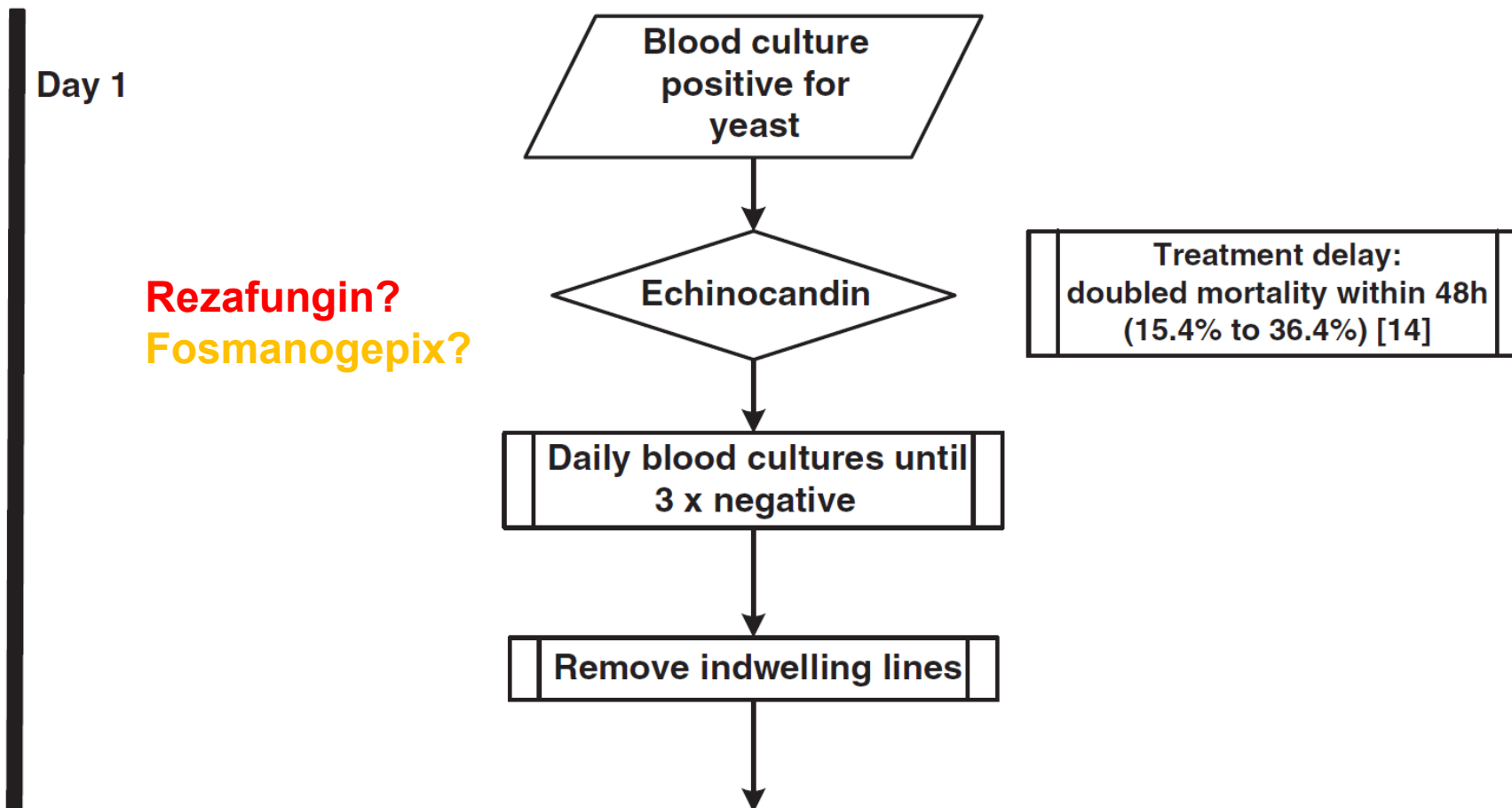
NI=non-inferiority.

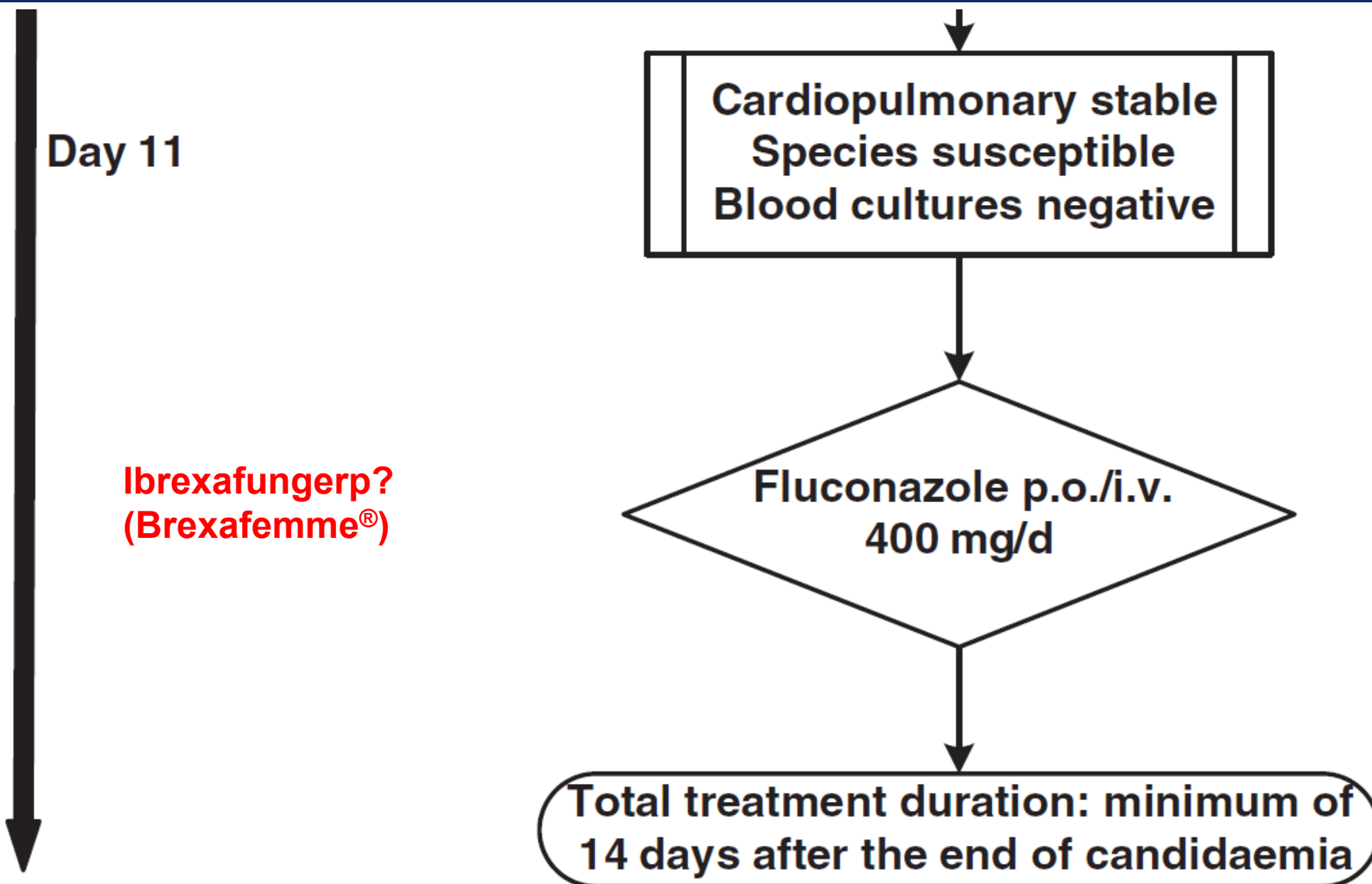
^aOverall Cure (Phase 2): resolution of systemic signs attributable to candidemia or invasive candidiasis AND mycological eradication as demonstrated by a single tissue/fluid culture or 2 negative blood cultures at least 12 hours apart.

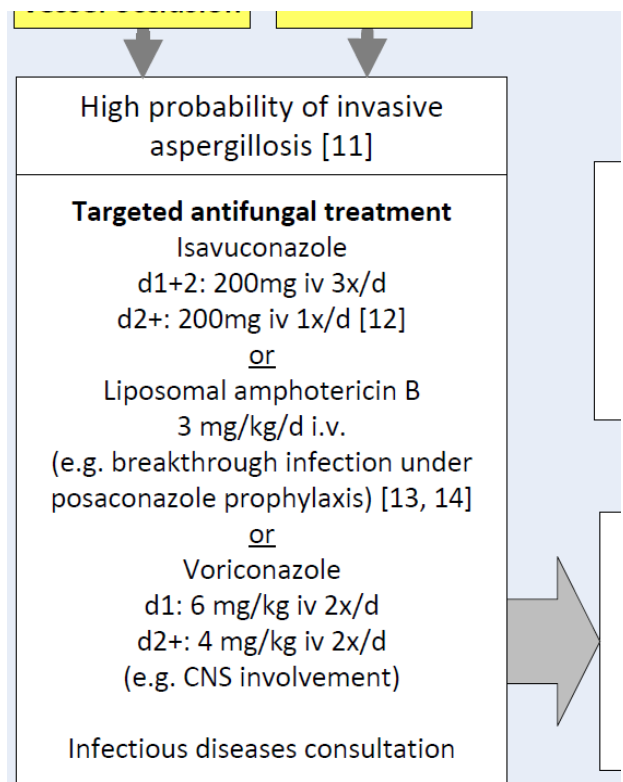
^bGlobal Cure (Phase 3): investigator assessment of clinical cure AND mycological eradication as demonstrated by a single negative blood or tissue/fluid culture AND (if pertinent) improvement or resolution of evidence of invasive candidiasis on radiographic imaging.



Rezafungin?



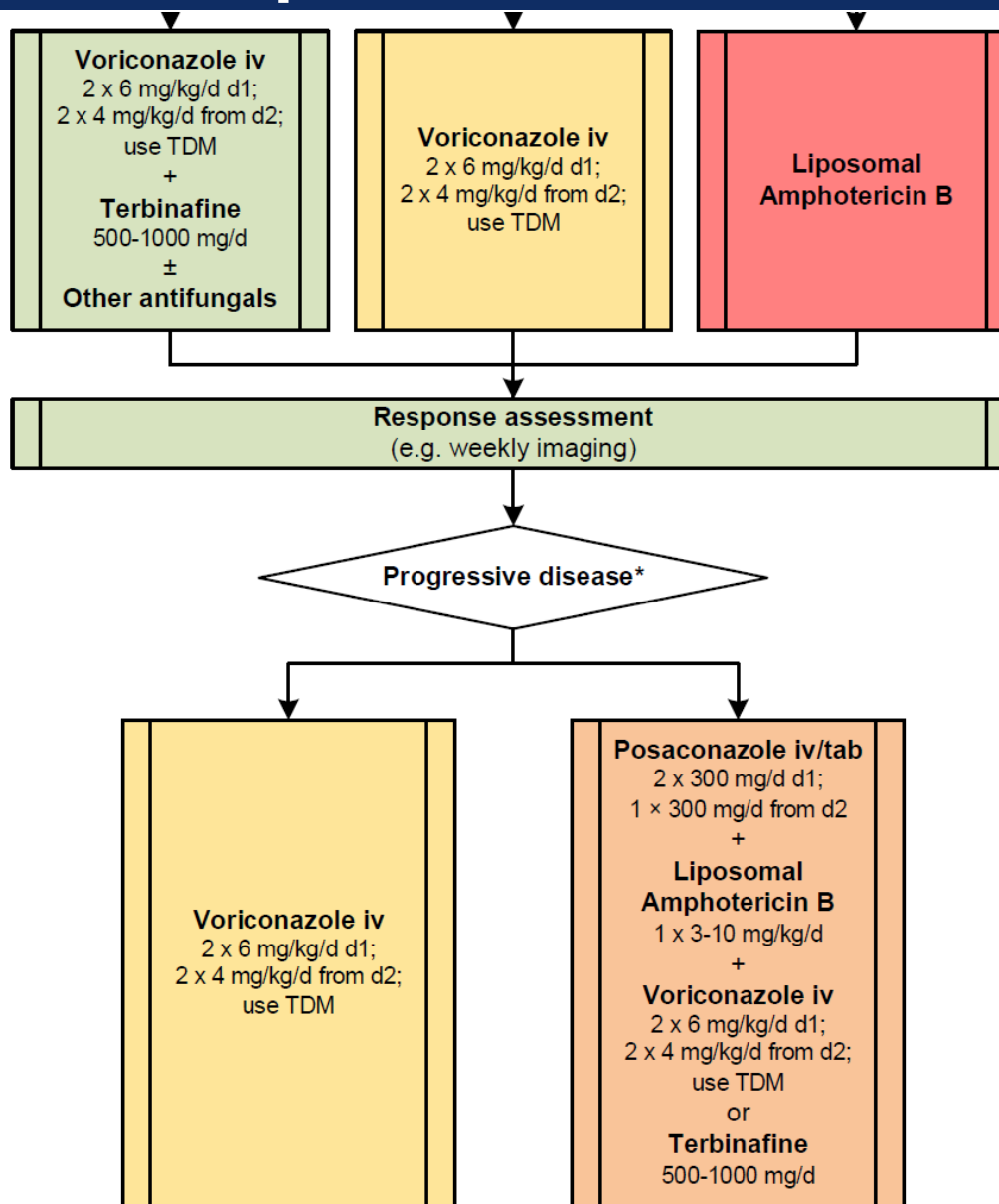




Ibrexafungerp?
Olorofim?
Rezafungin?
Fosmanogepix?
GR-2397?



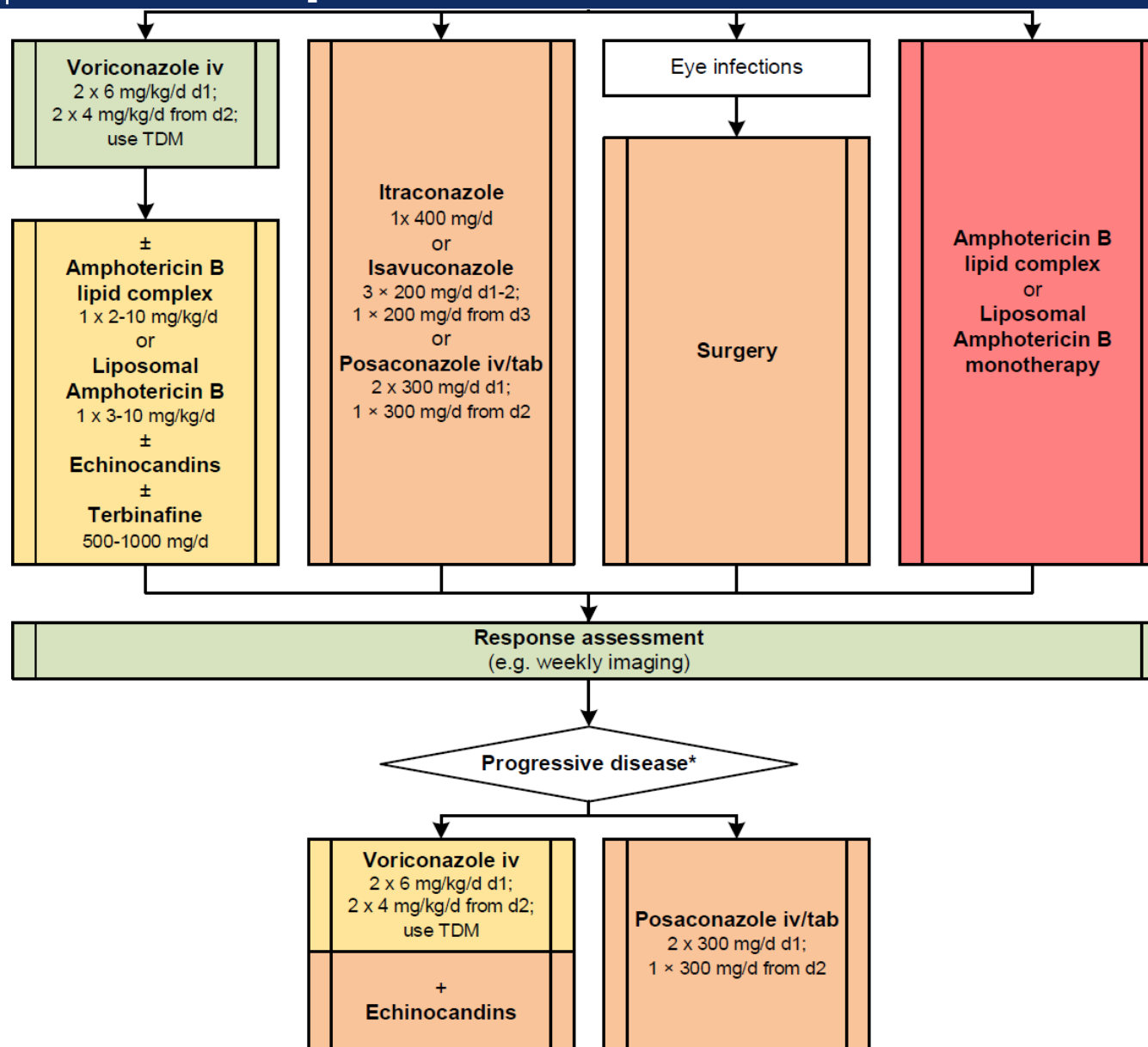
Treatment Pathway for Antifungal Management of Lomentosporiosis



Olorofim?



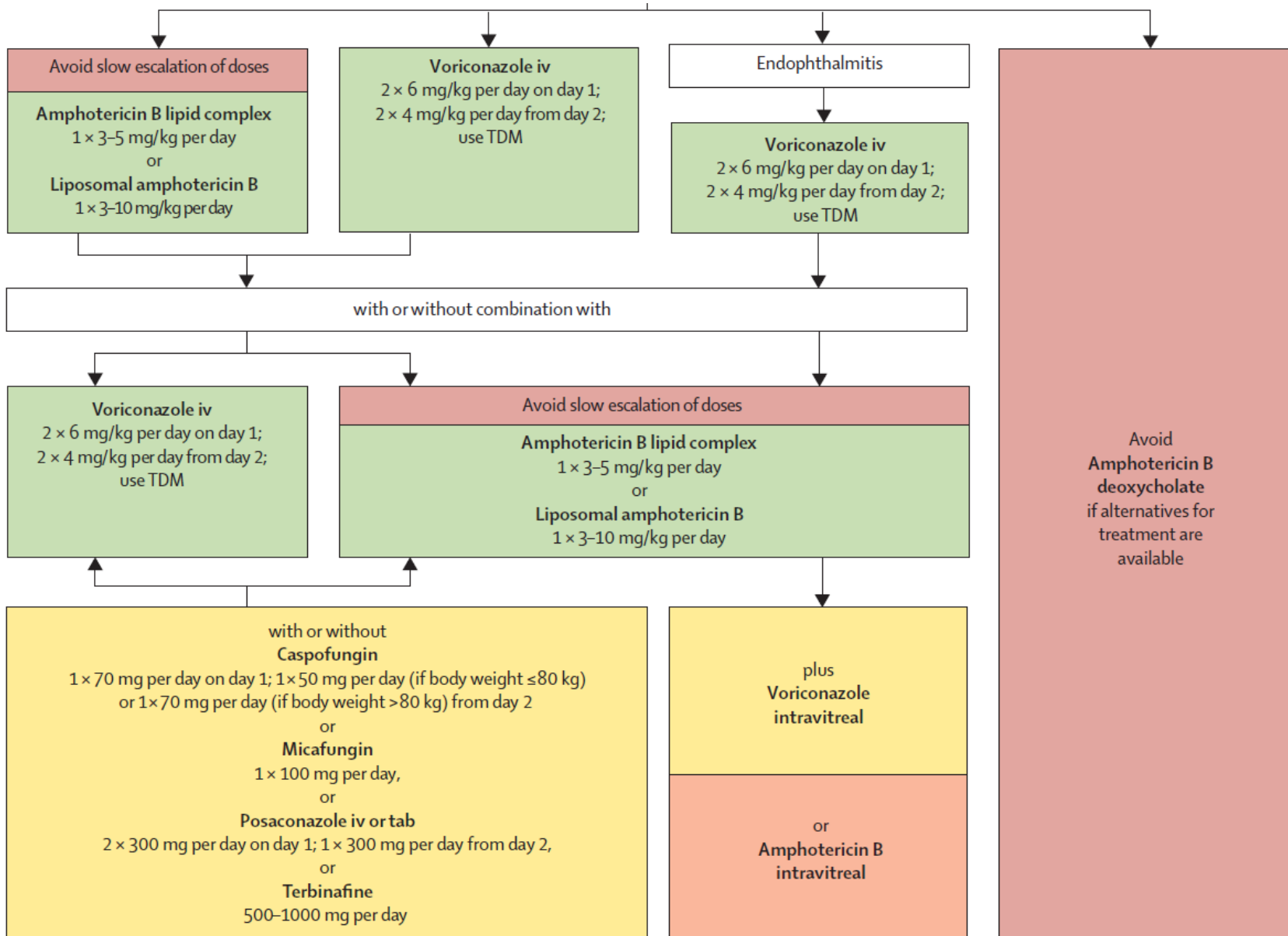
Treatment Pathway for Antifungal Management of Scedosporiosis



Olorofim?
Fosmanogepix?

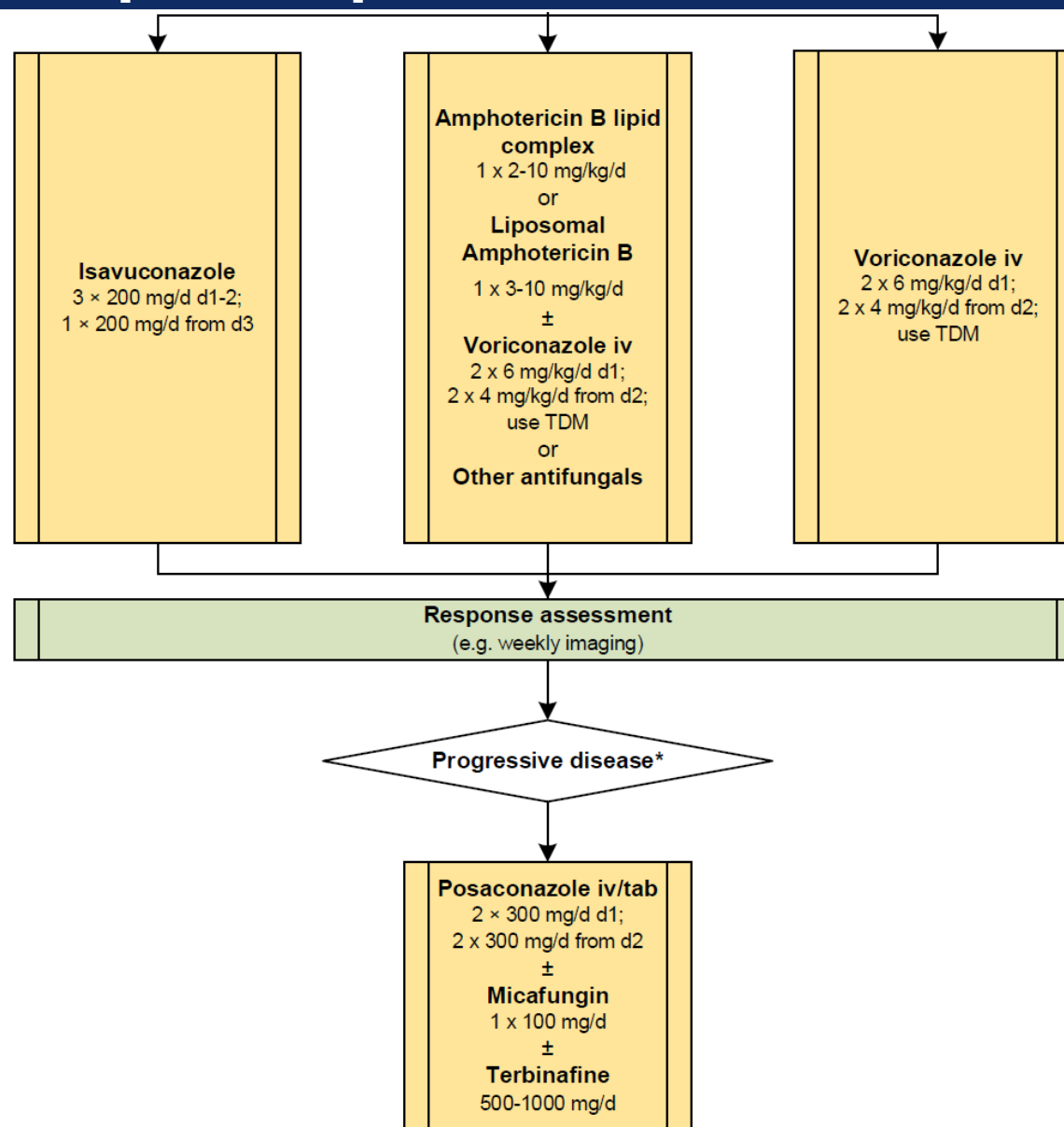


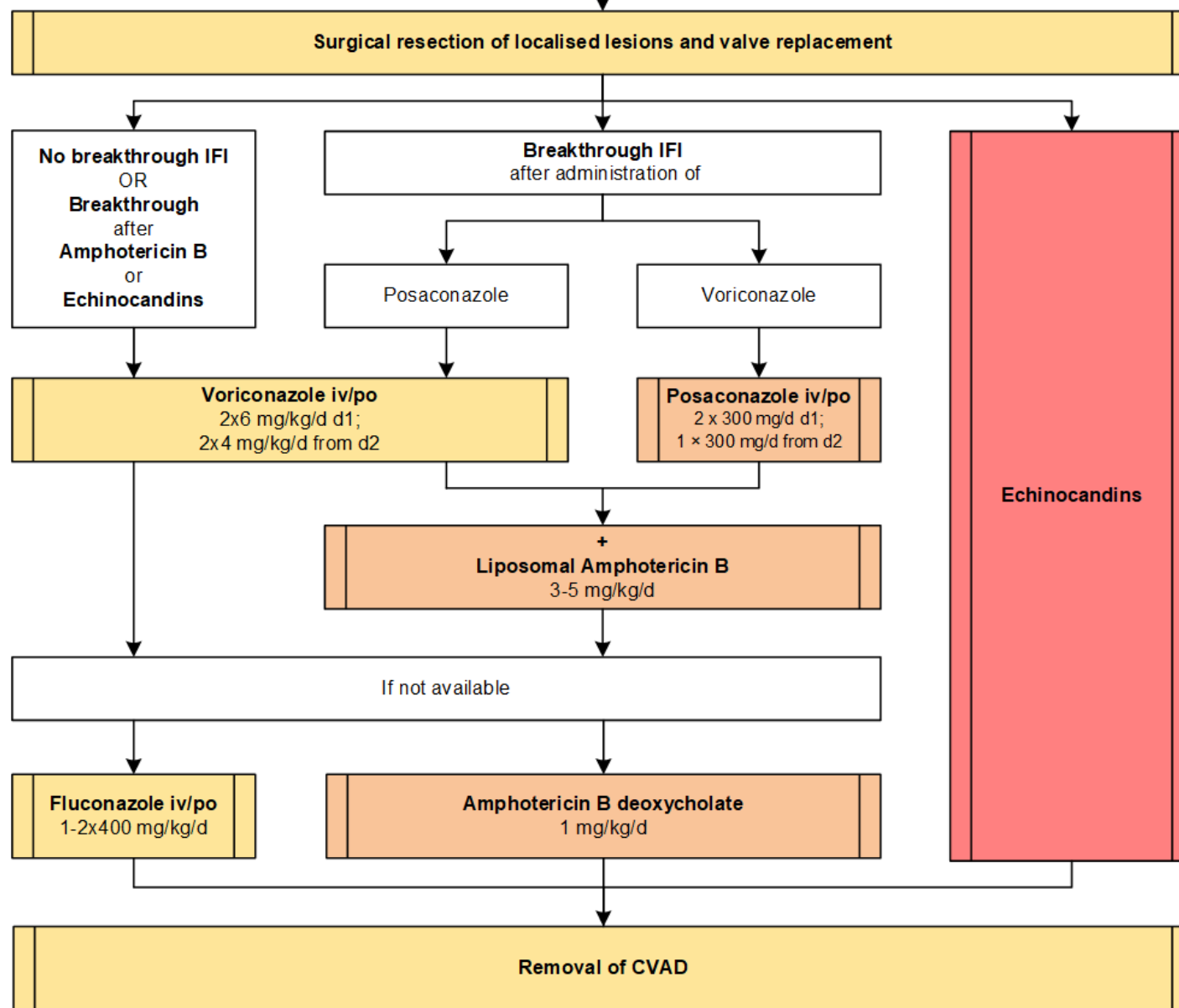
Fosmanogepix?





Ibrexafungerp?
Olorofim?





Ibrexafungerp?
Olorofim?

Legend:

- strongly recommended
- moderately recommended
- marginally recommended
- recommended against



YouTube DE infectious diseases in motion

National Societies Endorsing the Guideline

Global Mucormycosis Guideline. Cornely OA et al. Lancet ID 2019. in press

13:54 / 15:41

IDIM: ECMM MSG-ERC Mucor Guideline - Published





Fragen & Antworten