Turletricin (EL219/SF001), a novel, once weekly, non-nephrotoxic polyene takes a novel clinical development approach

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ESCMID Global 2026 Pipeline Session
Saturday 18th April, 15.00

Conflicts of interest

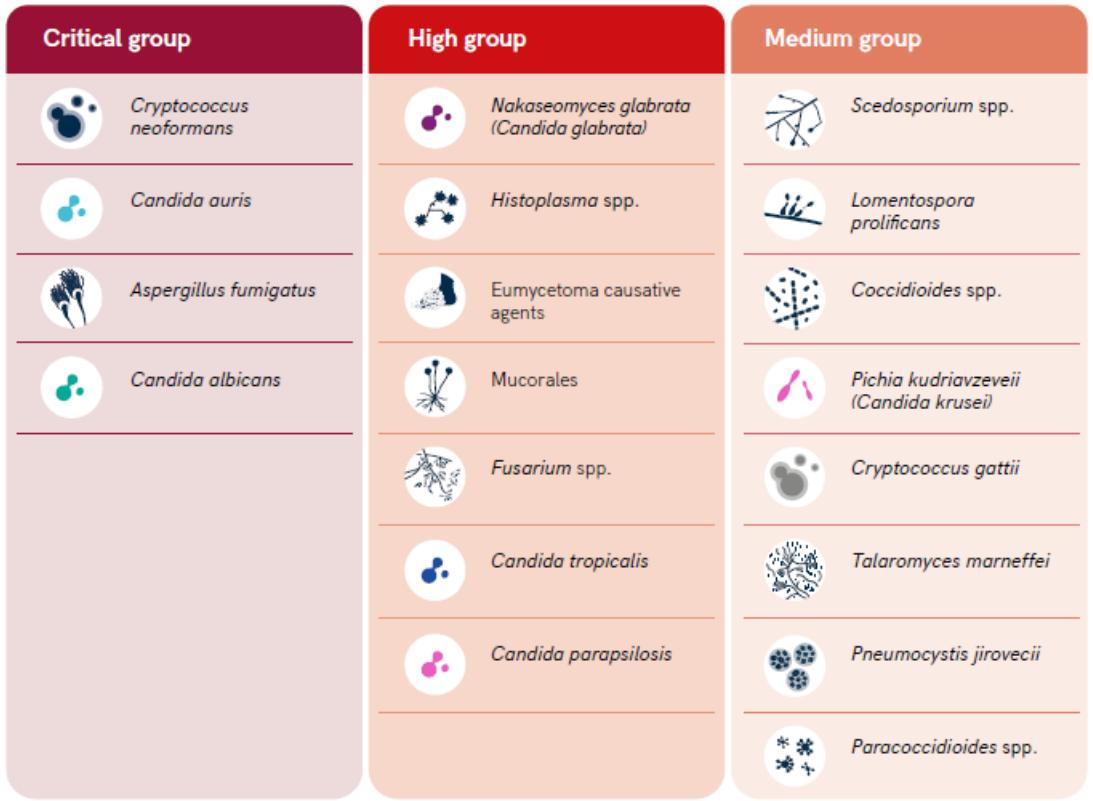
Kieren Marr is an employee of Elion Therapeutics and has equity in Elion Therapeutics & Pearl Diagnostics

Johan Maertens received grants, speaker's fee, ad board honoraria and/or travel support from (in alphabetical order)

- Amplyx
- Astellas
- Basilea Pharmaceuticals
- Bio-Rad laboratories
- Cidara
- Elion
- F2G
- Gilead Sciences
- IMMY
- MSD
- Mundipharma
- OLM Diagnostics
- PathoNostics
- Pfizer Inc.
- Pulmocide
- Scynexis
- Takeda
- Vical

The current antifungal armamentarium: issues and shortcomings (unmet need)

2022 WHO Fungal Priority Pathogen List (FPPL)



Antifungal resistance: the silent pandemic

- **Intrinsic and acquired**
  - *Lomentospora prolificans*
  - *Scedosporium* species
  - *Scopulariopsis*
  - *Fusarium* species
  - Mucorales species
  - *Candidozyma auris:* panfungal-R
  - *Candida parapsilosis*: fluconazole-R
  - *Aspergillus fumigatus*: (pan)azole-R
    - One Health challenge

https://iris.who.int/server/api/core/bitstreams/69af4379-4f27-4ac4-8973-74d7b52af7bd/content

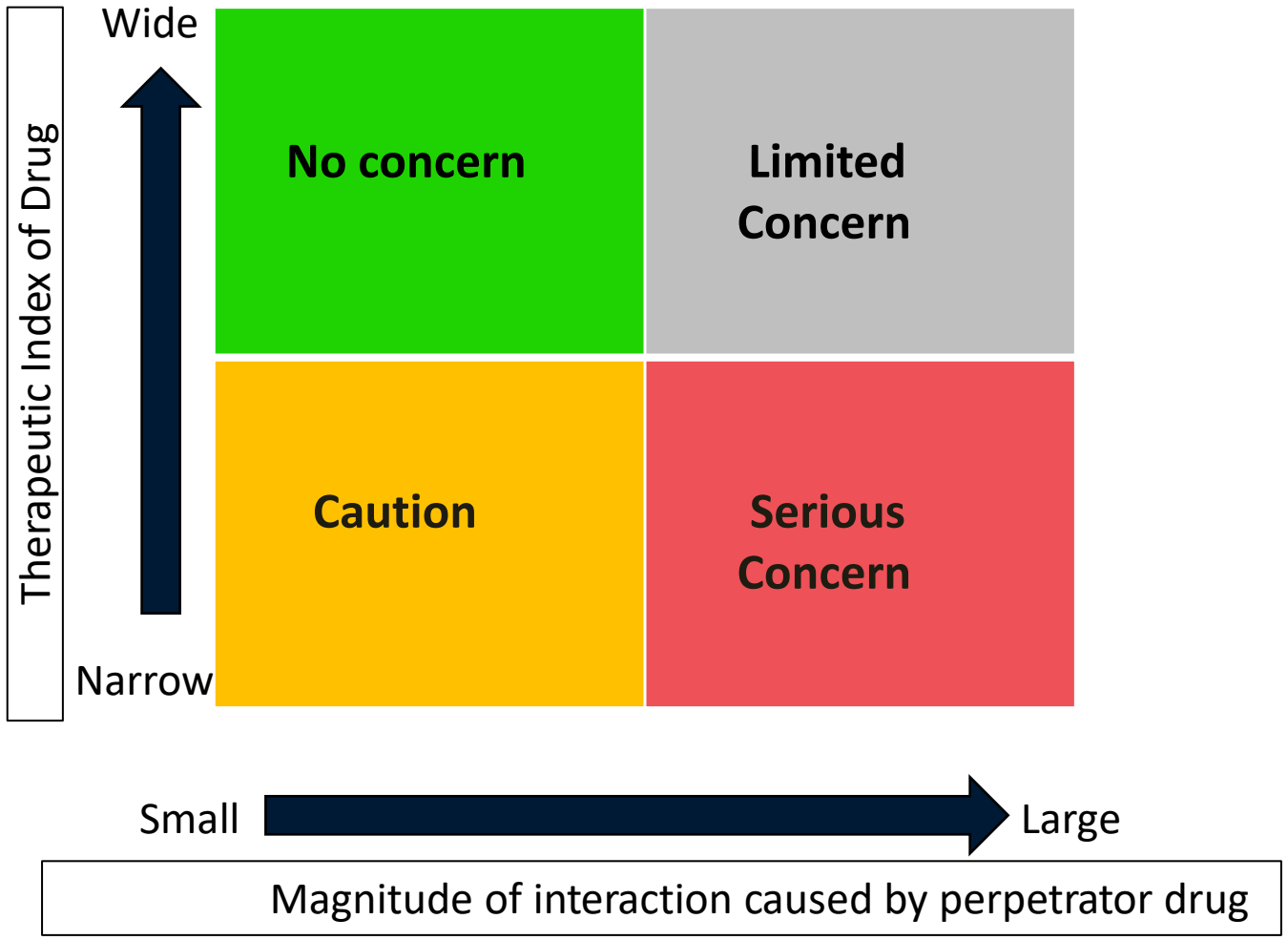
Bagga R et al. Microorganisms 2026; 14: 599

The current antifungal armamentarium: issues and shortcomings (unmet need)

- **Known or predicted resistance of the infecting isolate to (all) licensed agents:**
  - *Lomentospora prolificans*
  - Azole-resistant *Aspergillus fumigatus* and cryptic species
  - Echinocandin-resistant *Candida* species, including *C*. auris
  - Mixed fungal infections (e.g., *Aspergillus*/Mucorales)
- **Intolerance to available therapy:** e.g., increase in serum creatinine with an amphotericin, persistent visual disturbances with voriconazole, periostitis, phototoxicity (and skin cancer), neuropathy, allergic reaction with any compound, or other recognized drug-related AE (hepatic!)
- **Inability to manage DDIs:** e.g., strong inhibitors of CYP 450 enzymes, esp. 3A4
- **Inability to produce or maintain therapeutic drug levels**
- **Poor penetration in sanctuary sites** (e.g., central nervous system, eye, biofilm)
- **An IV-only option (e.g., an amphotericin) has produced a clinical response, and oral or out-patient follow-up is not feasible.**
- **Failure of (all) available therapy and tolerance.**

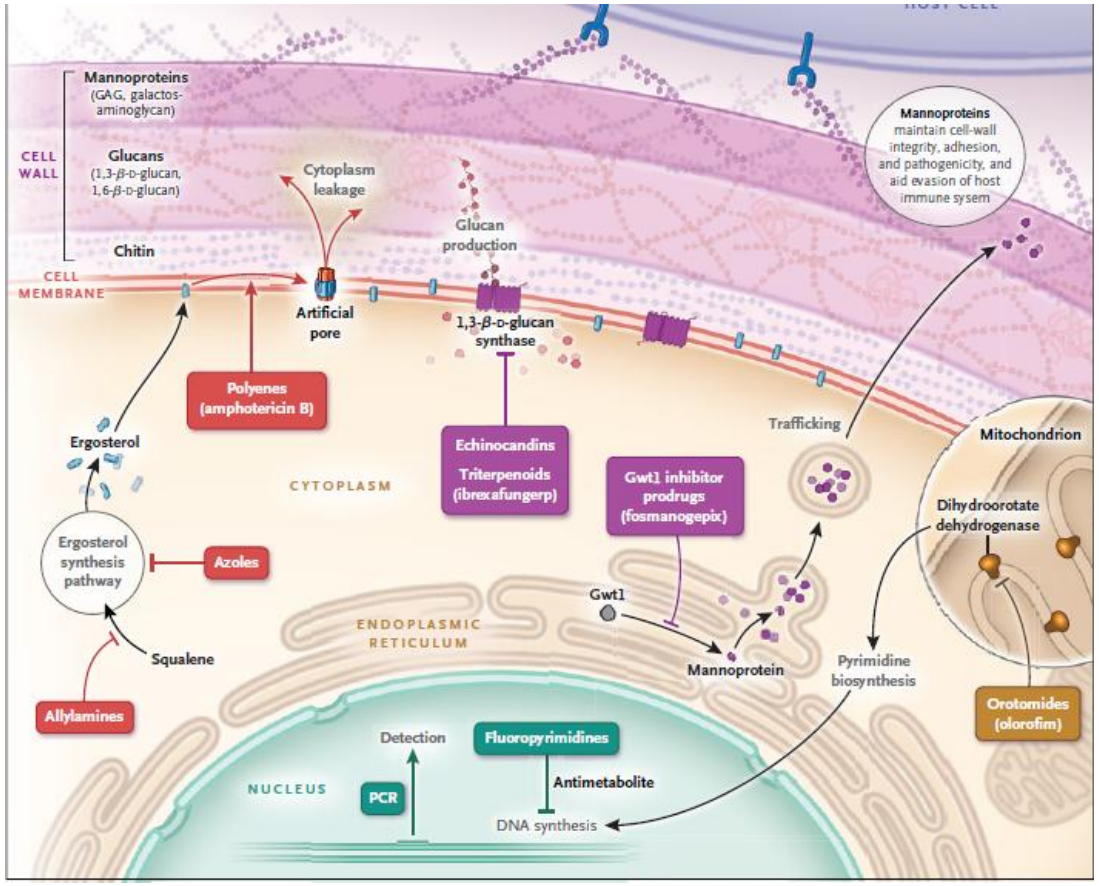
The problem of drug-drug interactions with azoles in a changing landscape

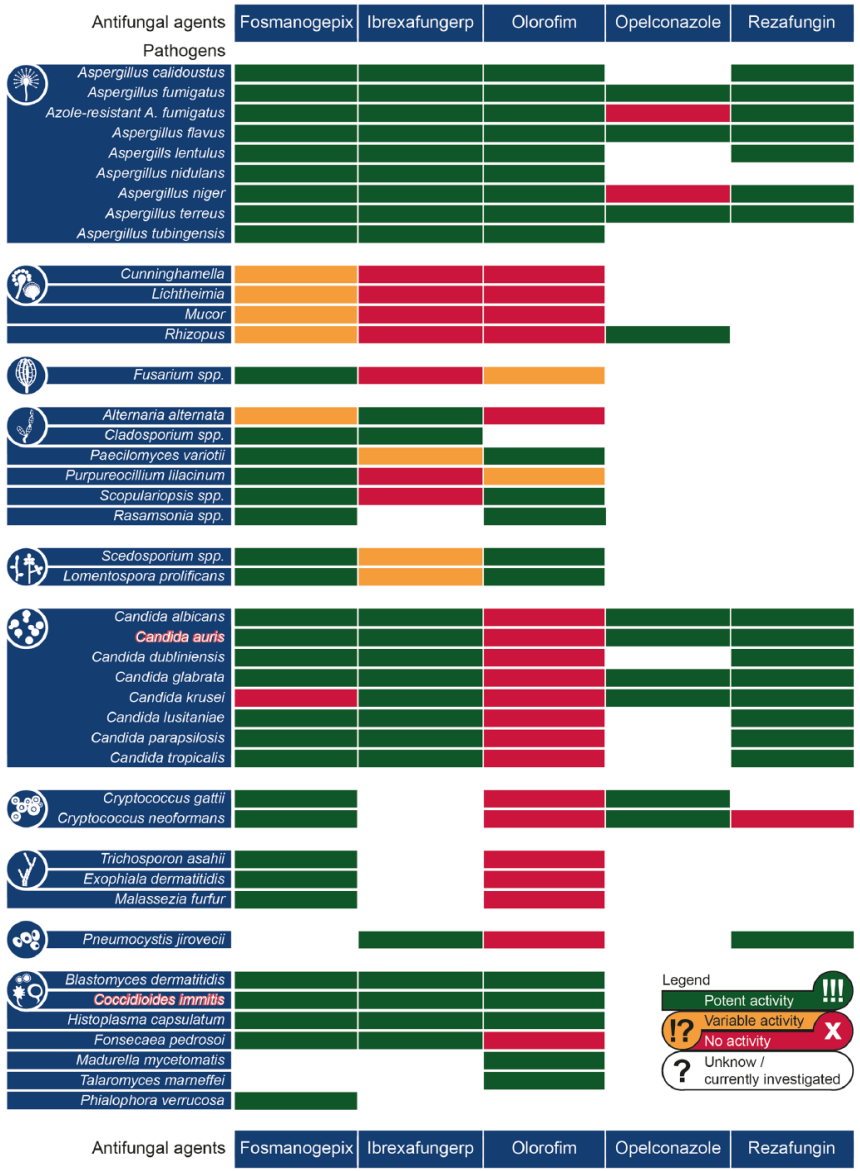
- Midostaurin
- Gilteritinib
- Sorafenib
- Quizartinib
- Enasidenib
- Ivosidenib
- Venetoclax
- Glasdegib
- Ruxolitinib
- Ibrutinib
- Acalabrutinib
- Imatinib
- Dasatinib
- Ponatinib
- Bosutinib
- Nilotinib
- Asciminib
- …



Brüggemann RJM, et al. Clin Infect Dis 2009; 48: 1441-1458
Wilson DT, et al. Therapeutics and Clinical Risk Management 2016:12 1197–1206

The antifungal pipeline: unmet needs

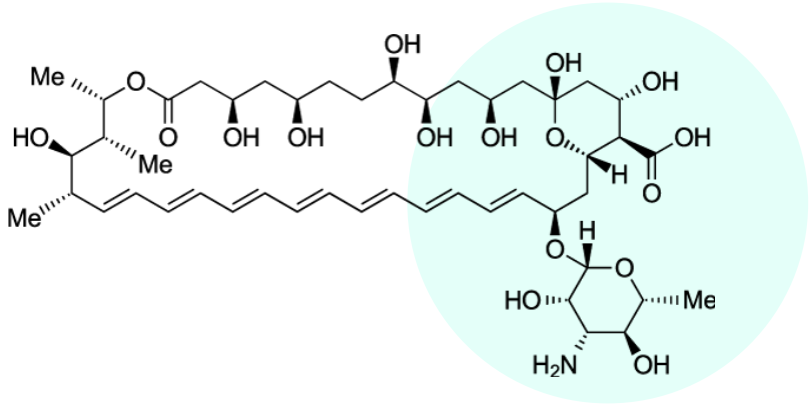




Thompson GR and Young JH. ***NEJM***. 2021; 385(16):1496-1509

Hoenigl M, et al. Drugs 2021; 81: 1703

Next-generation polyene rationally designed for reduced toxicity

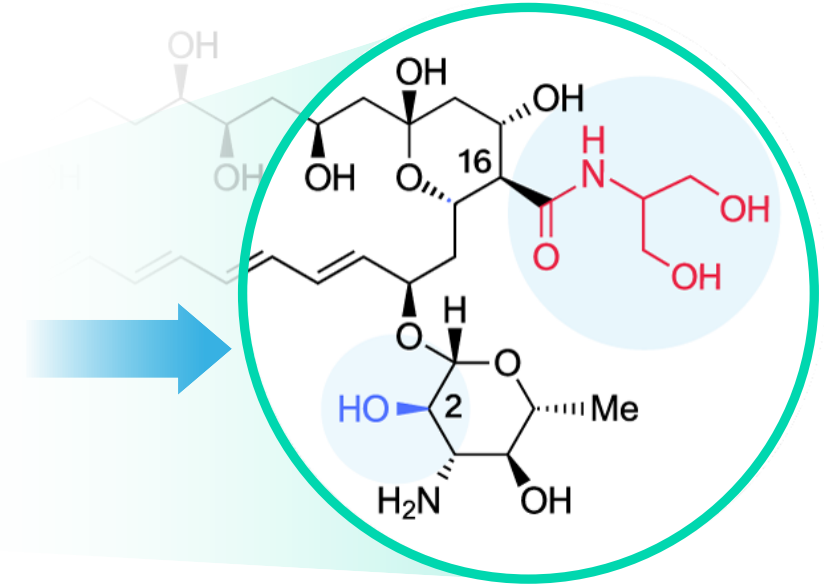


Amphotericin B (AmB)

⊕ potent, broad-spectrum, fungicidal with low potential for resistance
⊖ targets sterols in both human and fungal cells; renal toxicity

Modifications to the Chemical Structure

By inverting the carbinol center, toxicity is reduced and ergosterol extraction is preserved through the conversion of carboxylic acid to serinol amide



Turletricin (EL219/SF001)

⊕ potent, broad-spectrum fungicidal with low potential for resistance; potential for reduced renal toxicity

Maji A, et al., *Nature*, 2023.

Active against pathogenic yeasts, moulds, endemic dimorphs

Species (n)	EL219	AmB	Isavuconazole	Posaconazole	Voriconazole
Candida albicans (10)	0.125 – 1	0.25 – 1	≤0.03 – >16	≤0.03 – >16	≤0.03 – >16
Candida auris (10)	0.25 – 1	0.5 – 2	≤0.03 – 0.5	≤0.03 – 0.25	≤0.03 – 4
Cryptococcus neoformans (10)	0.125 – 0.25	0.5 – 1	0.125 – 2	0.06 – 0.25	≤0.03 – 1
Aspergillus fumigatus (6)	0.5 – 1	0.25 – 4	0.25 – >16	≤0.03 – 1	0.25 – >16
Aspergillus terreus (6)	0.5 – 2	2 – 4	1 – 8	0.06 – 0.25	0.5 – 2
Aspergillus calidoustus (6)	0.5 – 1	1 – 2	4	>16	8
Aspergillus lentulus (6)	2 – 4	1 – 4	1 – 4	0.25 – 0.5	4 – 8
Mucor circinelloides (10)	0.25 – 0.5	≤0.03 - 0.125	>16	0.5 – 4	>16
Fusarium oxysporum (6)	2 – 4	1 – 2	≥16	2 – >16	4 – 16
Coccidioides immitis (6)	0.06 – 0.125	≤0.03 - 0.125	0.125 – >16	≤0.03 – 4	0.06 – 4
Blastomyces dermatitidis (6)	0.125 – 0.25	≤0.03 - 0.06	≤0.03 – 0.25	≤0.03 – 0.06	≤0.03 – 0.5
Histoplasma capsulatum (6)	0.06 – 0.25	≤0.03 - 0.06	≤0.03 – 0.06	≤0.03 – 0.06	≤0.03 – 0.06

Data represent MIC (µg/mL) range values read at 100% growth inhibition for EL219 and LAMB and at 50% growth inhibition for azoles.
EL219=micellar formulation of EL219 in a 1:3 molar ratio with DSG-PEG2000; AMB=amphotericin B

NOTE: The use of commercial drug formulations herein and known polyene physical-chemical properties that confer nonspecific binding have necessitated in-process efforts to establish drug substance-only modified CLSI and EUCAST MIC testing methodologies for use with EL219 going forward.

ELION THERAPEUTICS

Maji et al., *Nature*, 2023

Turletricin Nonclinical ADME similar to AmB but with long half-life

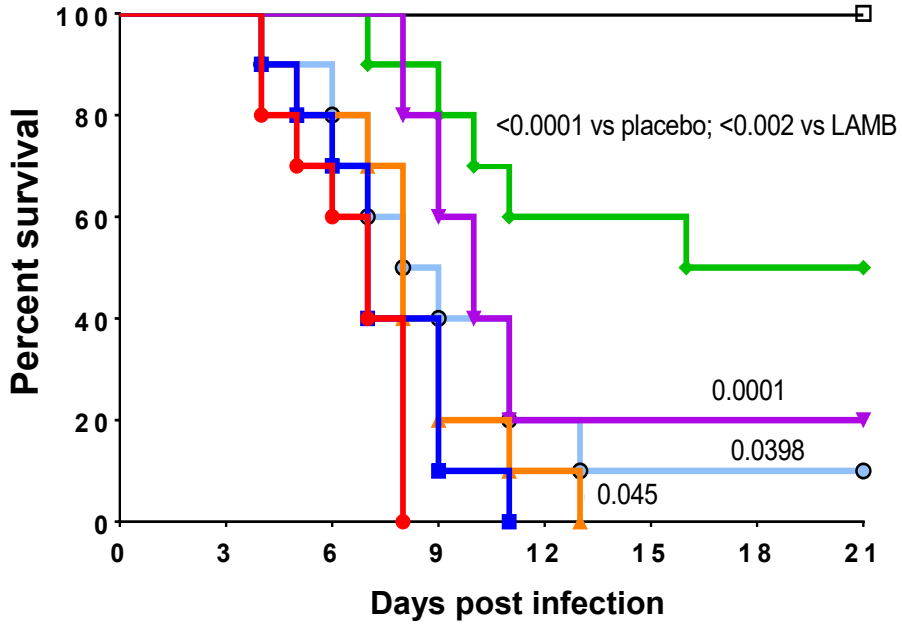
- Highly protein bound (>94%)
- Plasma $T_{1/2}$ 23 hrs (rat); longer in tissues
- Liver > Spleen > **Lung** > Kidney > Heart > Brain
- No significant metabolism (25% excreted in urine)
- No interactions with CYP isoforms
- Mouse models using *Candida* spp and *A. fumigatus* both show equivalent correlations of **AUC:MIC** and **C_{max}:MIC** as predictive PD drivers

Enables once weekly dosing

Turletricin is active in pulmonary aspergillosis models, including with strains considered resistant to AmB

Improved survival and tissue fungal burden in immunosuppressed mouse model of aspergillosis compared to LAMB at clinically relevant doses

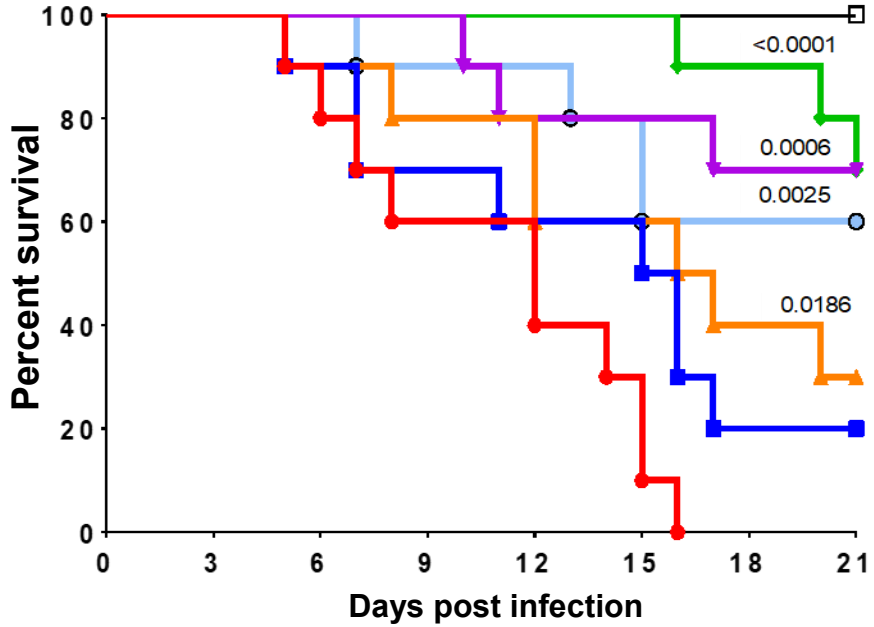
***Aspergillus fumigatus* (AF293)**



n=10 mice/group

- Uninfected
- EL219 30 mg/kg
- EL219 7.5 mg/kg
- EL219 1.5 mg/kg
- EL219 0.3 mg/kg
- LAMB 5 mg/kg
- Placebo

***Aspergillus calidoustus* (Ac-6)**



All treatments administered IV QD x 4 days starting 16 h after infection by intranasal inhalation

All treatments administered x 7 days starting 16 h after infection by intratracheal instillation

LAMB=liposomal amphotericin B.

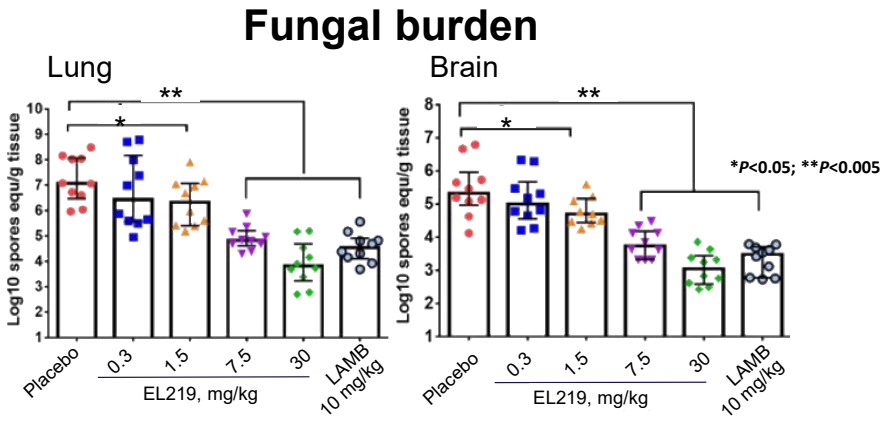
Youssef et al, *Antimicrobial Agents and Chemotherapy*, 2026

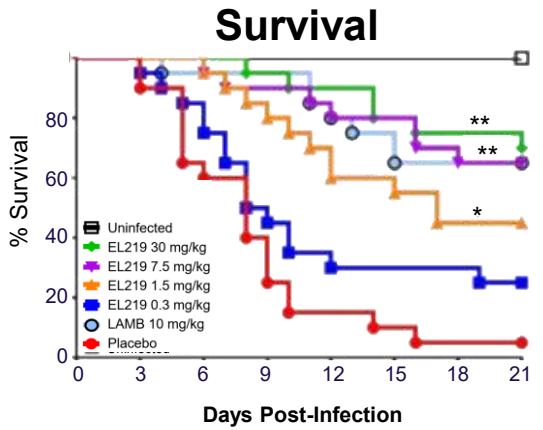
Turletricin has good *in vivo* efficacy against mucormycoses

Improved survival and tissue fungal burden in immunosuppressed mouse model of difficult to treat mucormycoses

Rhizopus delemar

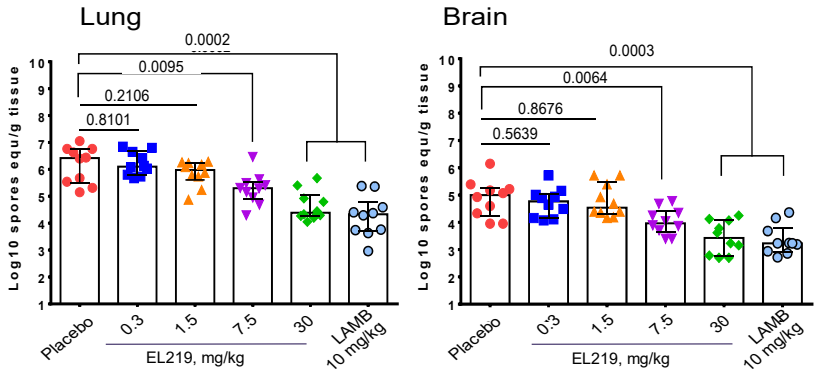
(n=20 mice/group)

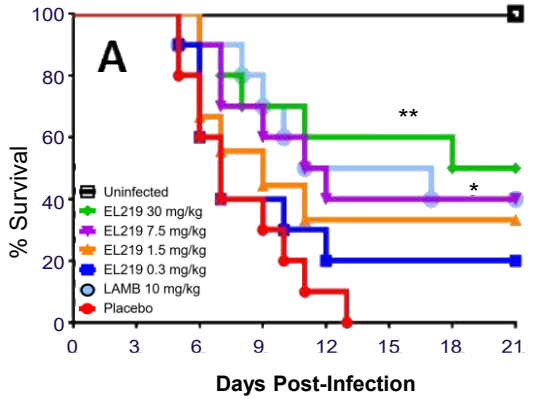




Mucor circinelloides

(n=10 mice/group)





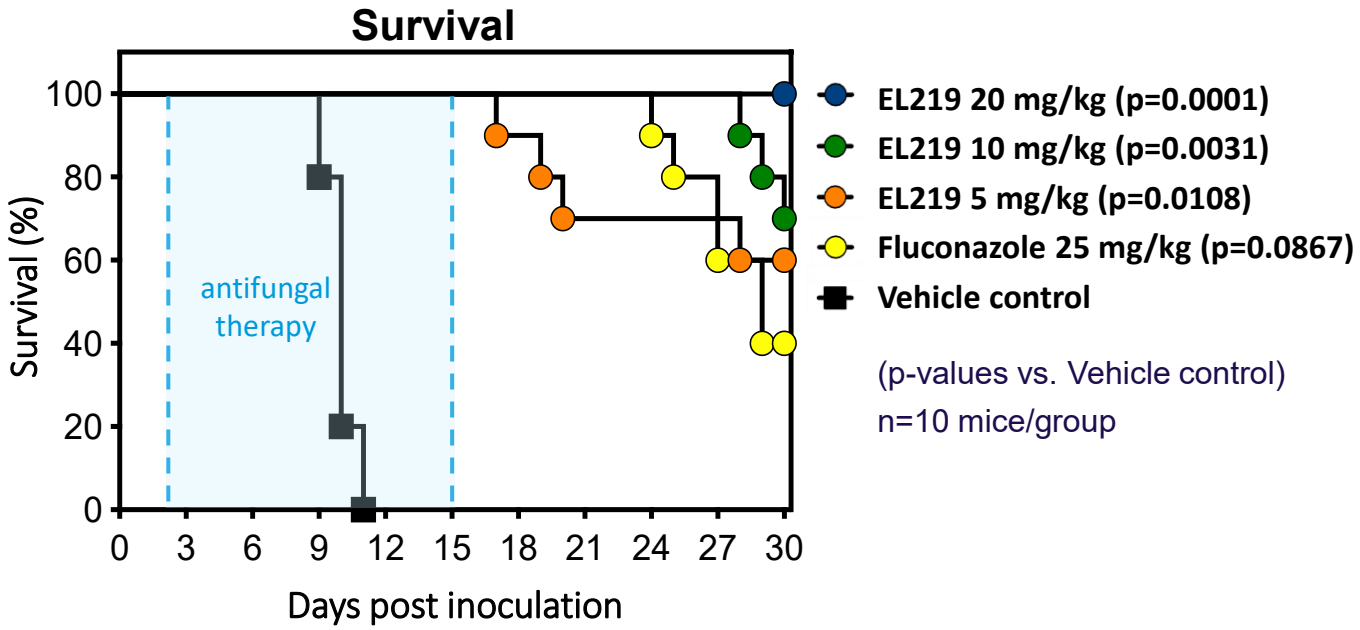
*P<0.05; **P<0.005 vs. placebo and 0.3 mg/kg EL219

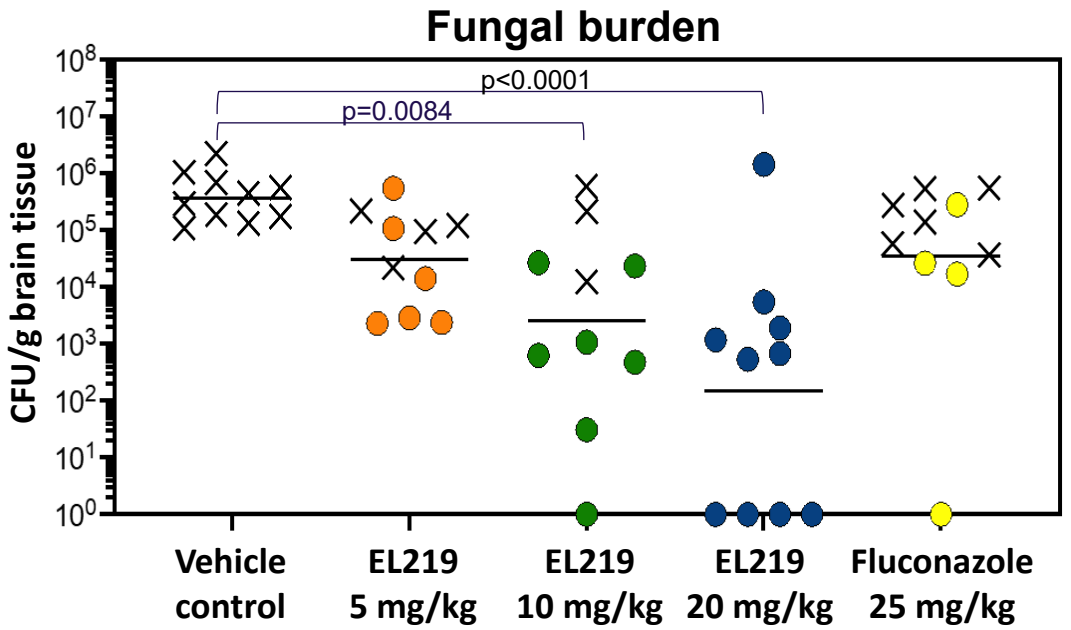
LAMB=liposomal amphotericin B.
Maji et al., *Nature*, 2023

Turletricin is fully protective *in vivo* against CNS coccidioidomycosis

Complete protection and brain fungal bioburden clearance in a subset of mice conferred by EL219 at a clinically relevant dose in a difficult to treat CNS coccidioidomycosis model

***Coccidioides immitis* (95-2478)**





Drugs dosed days 2-15 post-intracranial inoculation
(EL219: IP, QD; FLU: PO, BID)

EL219 repeat 20 mg/kg dosing in mice = 1.6 mg/kg human equivalent

Wiederhold et al, *Antimicrobial Agents and Chemotherapy*, 2026

Clinical Summary: Safety Overview

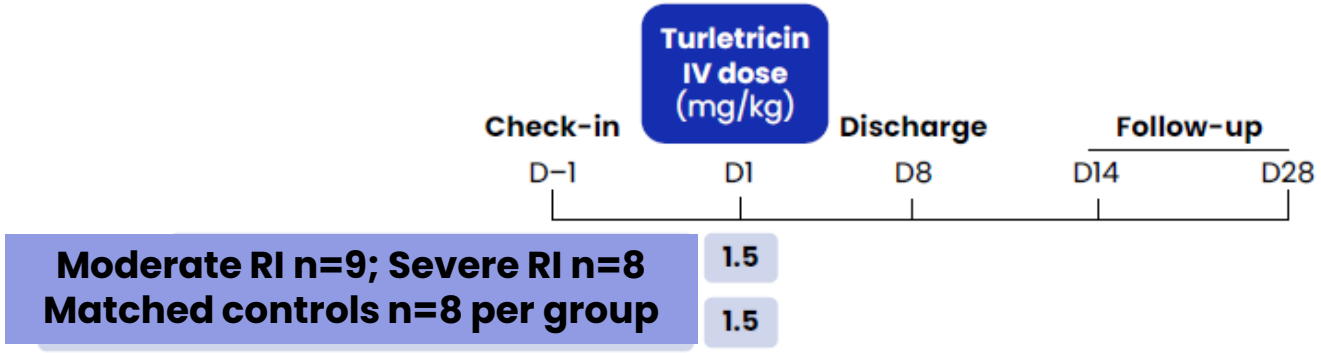
- Turletricin has been dosed in >130 people over Phase 1 SAD, MAD, Renal Insufficiency studies, Phase 2, and Expanded Access using single doses as high as 3 mg/kg and for durations as long as 23 weeks.
  - No dose-limiting SAEs have been observed and the drug has been well tolerated.
- Turletricin has not caused classic toxicities caused by polyene cholesterol binding (acute and chronic nephrotoxicity, electrolyte wasting, anemia).
- Turletricin has not caused acute inflammatory infusion-related reactions (IRR) most commonly associated with polyene therapy (fever, chills, rigors).
- The most common AEs are histamine-like IRRs (tingling, pruritic), which occur with high rates of drug dosing and are prevented with slower infusions (up to 2 hour) and pre-hydration.
- Two people have received drug in expanded access, 1 for 6 months, no toxicities apparent
- Half-life >60 hrs, enabling once-weekly administration

Clinical Summary: Phase 1 SAD, MAD, Renal Insufficiency

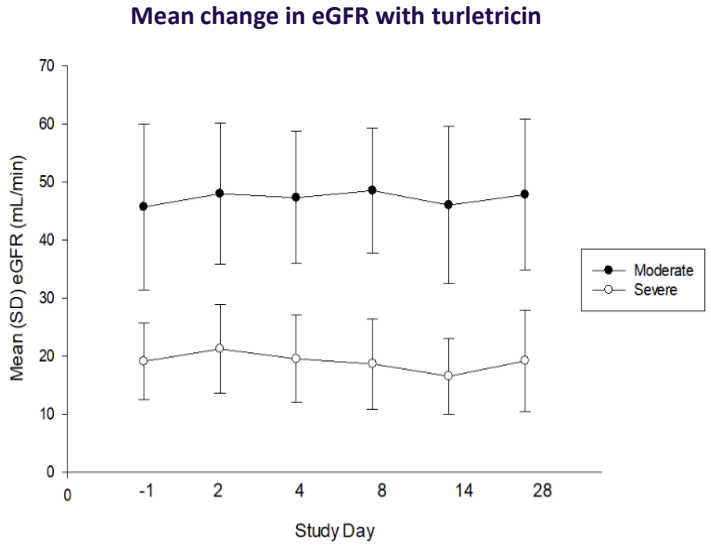
- SAD (n=48; 36 turletricin/ 12 placebo) & MAD (2-week, n=24; 18 turletricin; 6 placebo)
  - No SAEs or discontinue of drug.
  - Treatment emergent AEs (TEAE) were mild and transient and occurred in 22/54 (41%) healthy participants. 12 were infusion-related reactions. 10 considered related to turletricin
    - IRR were mild and transient, mainly histamine-like in character (e.g. tingling and pruritis).
- Renal insufficiency (n=17 dosed with turletricin)
  - In people with moderate (eGFR 30 – 59 ml/hr, n=9) and severe (eGFR <30 ml/hr, n=8) renal insufficiency who received EL219, no additional renal toxicities or lab abnormalities occurred

Renal Impairment Study confirmed Renal Safety and Established no need for Dose Modification

- Open-label study of participants with moderate or severe RI[#] matched with healthy controls receiving a single 1.5 mg/kg dose.
- 2 people developed TEAEs considered related to the drug -- IRRs that occurred with drug administered at a higher than specified infusion rate.



[#]Moderate RI = eGFR 30-60 ml/min
Severe RI – eGFR <30ml/min
Healthy eGFR = >90ml/min



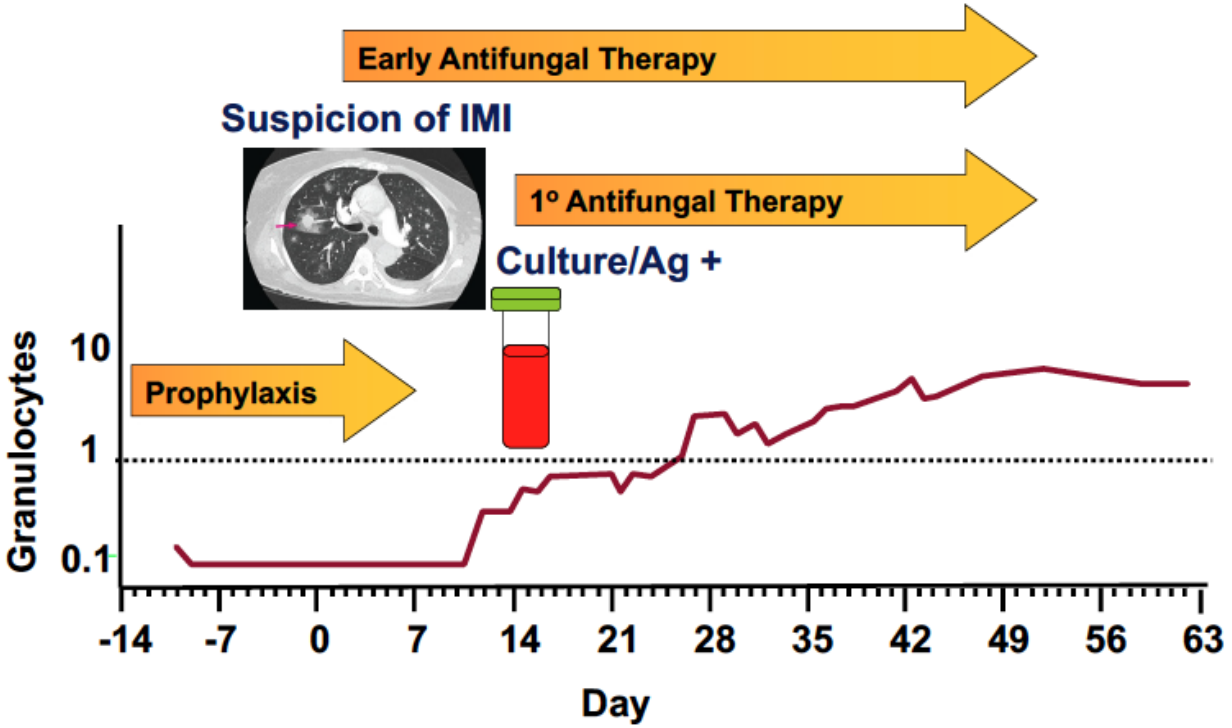
Please visit our poster : Pharmacokinetics and safety of turletricin (EL219), a novel next generation once weekly polyene antifungal, in participants with severe renal impairment. Sunday 12:00 - 13:30; sector B, row 8, station 28

Clinical Summary: Phase 2 Studies are Ongoing

- Given IRRs associated with infusion, Phase 2 turletricin dosing duration was extended from 1 hr to 1.5 – 2 hr, and included prehydration with 100 mL saline.
- Phase 2 HIV and cryptococcal meningitis, ongoing in Uganda
  - 40 people with crypto dosed with turletricin to date; Protocol met safety & efficacy criteria to proceed (DSMB)
  - High doses, longer duration of induction therapy (ongoing trial)
- Phase 2 Early Antifungal Therapy (TREAT-1 study) ongoing in U.S. and Canada (EU soon)
  - Early Antifungal Therapy (EAT) – new indication based on Phase 3 SECURE (isavu) design

Early Antifungal Therapy of Suspected IMI – a New Indication

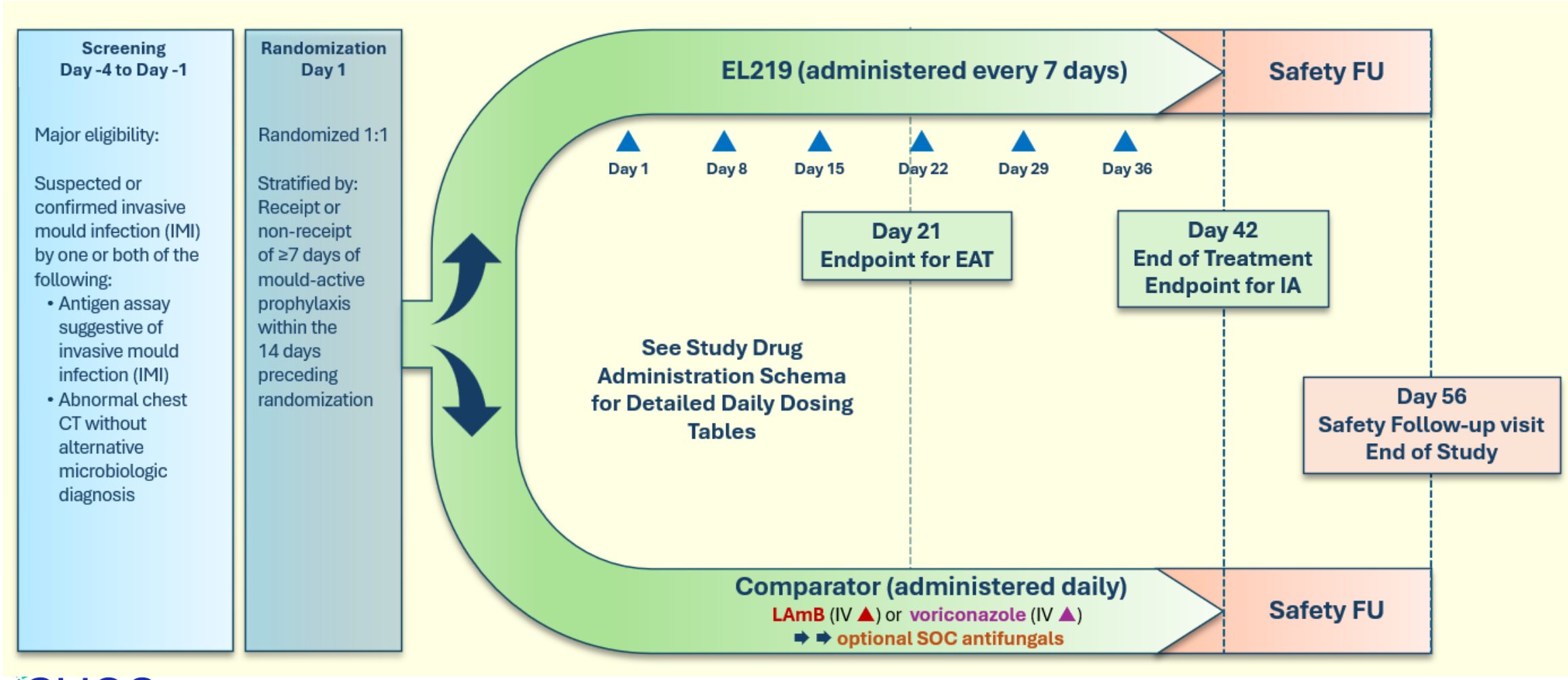
- Classic IA therapy trials– mITT analysis of people with confirmed (EORTC/MSG) IA
- Phase 3 SECURE study (isavu vs. vori) – ITT analysis (50% proven/probable, 40% possible IMI, and 10% without evidence of infection)
  - EU summary of product characteristics: posology described as *early targeted therapy* (pre-emptive or diagnostic-driven therapy), which may be instituted pending confirmation of the disease from specific diagnostic tests.



Maertens JA et a; Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016 Feb 20; 387(10020):760-9.

Early Antifungal Therapy – Trial Design

[Study Details | NCT07215273 | Study of EL219 vs Standard of Care for Early Antifungal Therapy of Suspected Invasive Mould Infections | ClinicalTrials.gov]



The current antifungal armamentarium: issues and shortcomings (unmet need)

Characteristics of turletricin: addresses areas of unmet need

- Broad spectrum of activity
- Fungicidal activity
- Good tissue penetration (including biofilms)
- No identified drug-drug interactions
- No need for therapeutic drug monitoring
- Low level of resistance
- Once weekly IV dosing (no oral formulation)
- Reduced renal toxicity/no electrolyte disturbances
- No hepatic toxicity
- (no agricultural use)

Anticipated clinical use (pending confirmation from [large] clinical trials)

Specific populations

- Patients with (pre-existing) renal insufficiency
- Patients with difficult-to-manage drug-drug interactions

Indications

- Early antifungal treatment in immunocompromised patients (possible IFI?)
- Empirical use in persistent febrile neutropenia
- Treatment of complicated yeast infections (e.g., abdominal candidiasis, eye and CNS, endocarditis, UTI)
- Treatment of probable/proven mold infections (including azole-R aspergillosis, mixed fungal infections)
- Long-term treatment of complex IFIs
- Severe cryptococcal disease
- Combination antifungal therapy in specific settings

Presenter's opinion