

Taylor Sandison, Jeffrey B. Locke, Shawn Flanagan, Kieren A. Marr

Elion Therapeutics, Inc., Boston, MA



## INTRODUCTION/BACKGROUND

- Invasive fungal infections (IFIs) are increasing in incidence and cause substantial morbidity and mortality. IFIs are a significant concern among the growing number of immunocompromised patients and those receiving immunosuppressive therapies [1].
- Amphotericin B (AmB), and liposomal formulations of AmB, are potent, efficacious antifungal agents, but their use is limited by toxicity, especially nephrotoxicity [1].
- Turletricin (EL219, formerly known as SF001), a novel AmB derivative, is a next-generation polyene antifungal, structurally modified to enhance specificity to fungal sterols [2].
- Two informed structural modifications to AmB were made to generate turletricin:
  - Epimerization of the mycosamine C2' carbinol shifts binding specificity from cholesterol and ergosterol to ergosterol only.
  - Amidation of the C16 carboxylic acid group restores antifungal activity lost due to the C2' stereocenter inversion.



### 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

### EL219

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

- Turletricin's improved safety profile over AmB enables micellar formulation (1:3 molar ratio of EL219:DSG-PEG2000) rather than necessitating the use of lipids or liposomes to alter PK properties for toxicity mitigation.
- In nonclinical studies, EL219 demonstrated broad-spectrum antifungal activity, low resistance potential, long half-life, efficacy vs key moulds, and few toxicities [2-7].
- EL219 is in clinical development for early antifungal therapy of suspected pulmonary mould infections, treatment of invasive aspergillosis, and treatment of cryptococcosis.
- Herein, we present a selected summary of nonclinical and Phase 1 clinical data supporting turletricin's current investigation as a once-weekly polyene in two Phase 2 clinical trials for treatment of cryptococcal meningitis (PLATFORM-CM) and early antifungal therapy for suspected invasive mould infections (TREAT-1).

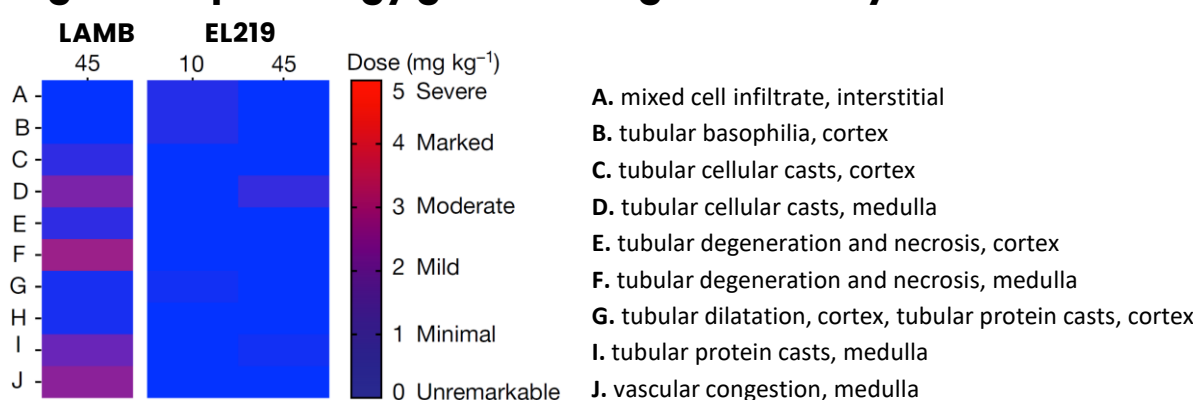
## METHODS

- Detailed methods for the datasets presented in this review can be found in the cited references [2-7] and ClinicalTrials.gov NCT identifiers.

## RESULTS

### Nonclinical Overview

Fig 1. Histopathology grade changes in kidneys



- Mouse kidney histopathology heatmaps demonstrate nephrotoxicity mitigation conferred by EL219's selective binding to ergosterol vs cholesterol

## RESULTS (con't)

Table 1. Antifungal activity profile

Species (n)	EL219	LAMB	Isavuconazole	Posaconazole	Voriconazole
<i>C. albicans</i> (10)	0.125 - 1	0.25 - 2	≤0.03 - >16	≤0.03 - >16	≤0.03 - >16
<i>C. auris</i> (10)	0.25 - 1	1 - 8	≤0.03 - 0.5	≤0.03 - 0.25	≤0.03 - 4
<i>C. neoformans</i> (10)	0.125 - 0.25	0.25 - 1	0.125 - 2	0.06 - 0.25	≤0.03 - 1
<i>A. fumigatus</i> (6)	0.5 - 1	0.06 - 0.5	0.25 - >16	≤0.03 - 1	0.25 - >16
<i>A. terreus</i> (6)	0.5 - 2	1 - >16	1 - 8	0.06 - 0.25	0.5 - 2
<i>A. calidoustus</i> (6)	0.5 - 1	>16	4	>16	8
<i>A. lentulus</i> (6)	2 - 4	4 - >16	1 - 4	0.25 - 0.5	4 - 8
<i>M. circinelloides</i> (10)	0.25 - 0.5	≤0.03 - 0.125	>16	0.5 - 4	>16
<i>R. arrhizus</i> (6)	0.25 - 1	≤0.03	1 - 4	≤0.03 - 0.25	2 - 4
<i>F. oxysporum</i> (6)	2 - 4	>16	>16	2 - >16	4 - 16
<i>C. immitis</i> (6)	0.06 - 0.125	≤0.03 - 0.5	0.125 - >16	≤0.03 - 4	0.06 - 4
<i>B. dermatitidis</i> (6)	0.125 - 0.25	≤0.03	≤0.03 - 0.25	≤0.03 - 0.06	≤0.03 - 0.5
<i>H. capsulatum</i> (6)	0.06 - 0.25	≤0.03	≤0.03 - 0.06	≤0.03 - 0.06	≤0.03 - 0.06

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

- EL219 has antifungal spectrum and potency similar to LAMB, with potential advantages against non-polyene-susceptible *Aspergillus* species.
- Because commercial drug formulations of EL219 (DSG-PEG2k micelles) and AmB (liposomal) were used here and there are known issues around polyene class nonspecific binding, future MIC testing will utilize drug substances and explore the viability of a modified MIC methodology to mitigate binding.

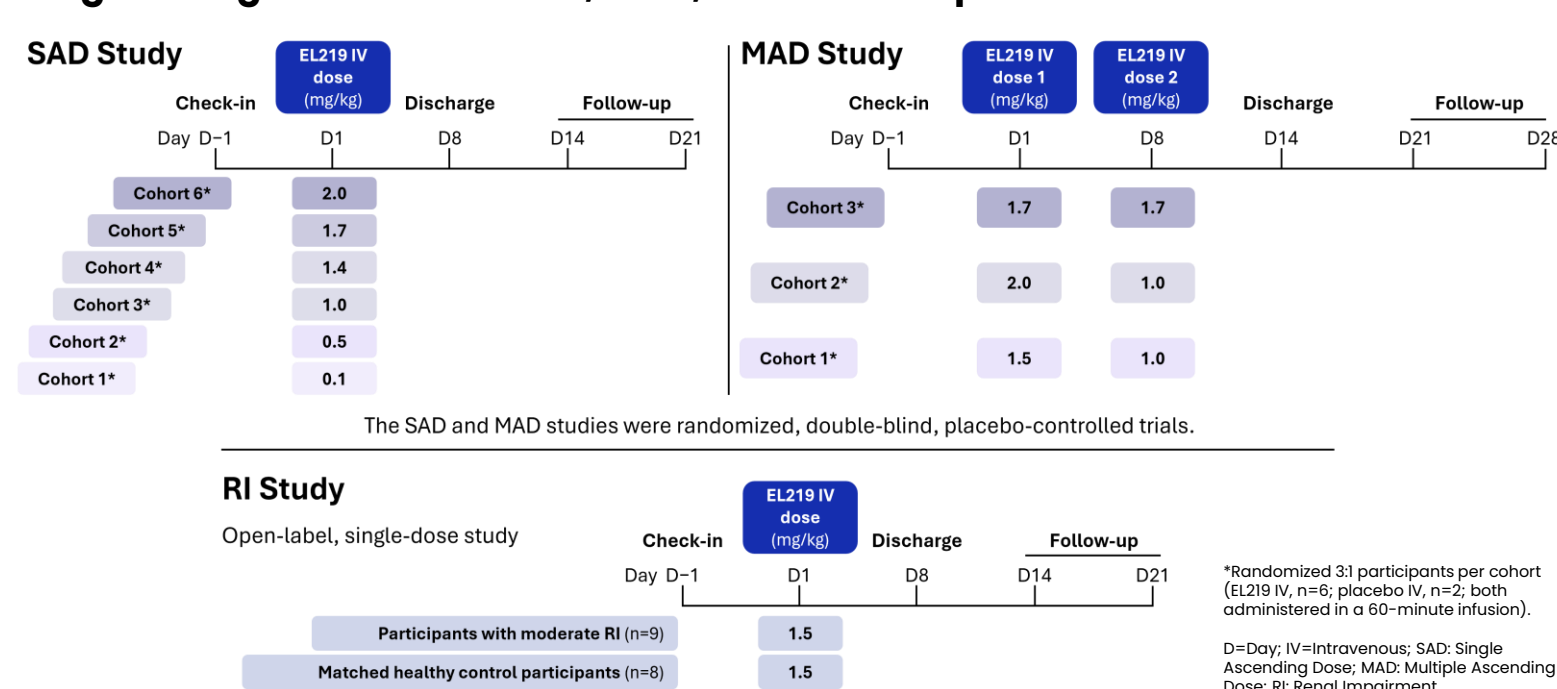
Table 2. In vitro and in vivo properties summary

In vitro	Spectrum/potency	Active against clinically relevant yeasts and molds Limited activity vs. <i>Scedosporium</i> , <i>Lomentospora</i> , <i>Cunninghamella</i> More potent compared to AmB, including against polyene-nonsusceptible <i>Aspergillus</i> ( <i>A. lentulus</i> , <i>A. calidoustus</i> , <i>A. terreus</i> )
	Antifungal MOA	Fungicidal in yeast and mould time-kills
	Post-antifungal effect	In line with AmB
In vivo	Resistance	Spontaneous frequency and serial passage studies suggest low resistance potential in yeasts and moulds
	Protein binding	Highly protein bound (>94%)
	Plasma T <sub>1/2</sub>	T <sub>1/2</sub> 23 hrs (rat); longer in tissues
	Tissue concentrations	Liver > Spleen > Lung > Kidney > Heart > Brain
	Metabolism	No significant metabolism
	CYP interactions	No interactions with CYP isoforms

- EL219 demonstrates properties largely consistent with AmB across in-depth in vitro and in vivo/ADME profiling

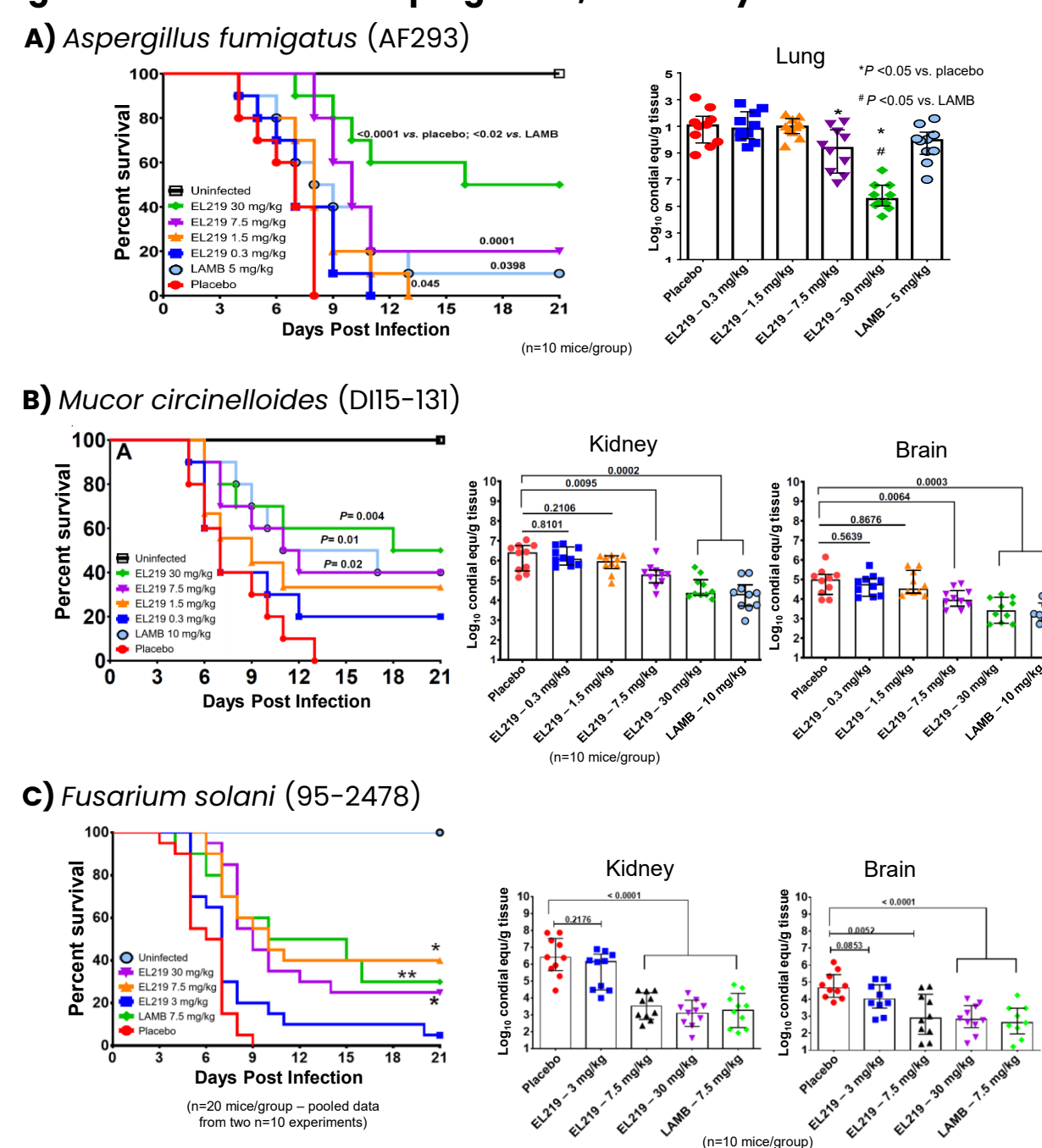
## Clinical Overview

Fig 3. Designs of Phase 1 SAD, MAD, and renal impairment studies



- EL219 is well tolerated.
  - In healthy adults at a single dose up to 2.0 mg/kg and at multiple doses up to a total of 3.4 mg/kg.
  - In adults with moderate (and severe) renal insufficiency at a single dose of 1.5 mg/kg with no need for dose adjustment.
- The majority of TEAEs were mild.
  - The most common TEAE was infusion-related reaction: histamine-like allergic reactions considered related to excipient (PEG) and the rate of infusion
    - All recovered/resolved, most without intervention.
    - A few received anti-histamine agents which were effective in diminishing symptoms.
  - No renal toxicities observed (serum Cr, eGFR stable), even in subjects with prior renal insufficiency.
- Half-life >60 hours and safety profile support a dose of 2 mg/kg in Week 1 followed by 1.5 mg/kg QW for Phase 2 studies.

Fig 2. Mouse models of aspergillosis, mucormycosis and fusariosis



- EL219 is efficacious in mouse models for key mould species including (A) *A. fumigatus*, (B) *M. circinelloides*, and (C) *F. solani*, with survival and bioburden reduction in lung, brain, and kidney on par with or better than LAMB at clinically relevant doses (i.e. EL219 at 30 mg/kg in mice = 2.4 mg/kg in man).

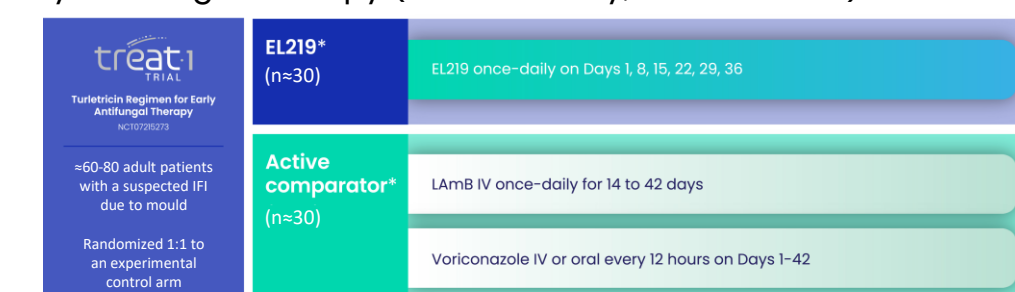
## RESULTS (con't)

### Designs of Phase 2 cryptococcal meningitis and early antifungal therapy studies

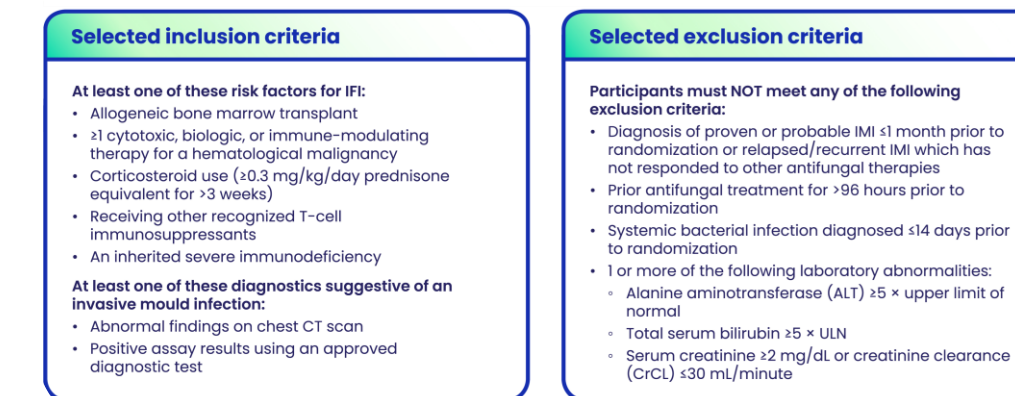
A) Cryptococcal meningitis (PLATFORM-CM study; NCT06666322)

- Site: Kampala, Uganda; n=40 1:1 LAMB (10 mg/kg) QW for 1 week vs EL219 QW for 2 weeks (2 and 1.5 mg/kg); both arms on top of standard of care fluconazole + 5 flucytosine.
- Primary efficacy endpoint: Rate of CSF *Cryptococcus* clearance quantified by change of log<sub>10</sub> *Cryptococcus* CFU/mL CSF/day as measured by fungal cultures over ~2 weeks.

B) Early Antifungal Therapy (TREAT-1 study; NCT07215273)



\*To maintain the blinding of the trial, patients in each treatment arm will receive placebo on a dosing schedule that corresponds with the medication given in the other arm.  
IFI: Invasive fungal infection; LAMB: Liposomal amphotericin B.



## CONCLUSIONS

- EL219 retains polyene class antifungal spectrum/potency, fungicidal activity, and low resistance potential.
- Rational design of EL219 to selectively bind fungal ergosterol over human cholesterol translates into a non-nephrotoxic profile as demonstrated in nonclinical and Phase 1 clinical data.
- A long half-life and the Phase 1 SAD/MAD safety profile support Phase 2 dosing at the highest regimens evaluated (2 mg/kg in Week 1 followed by 1.5 mg/kg QW).
- No changes are expected in dosing EL219 for use in adults with moderate RI.
- Clinical investigation of EL219 will continue with ongoing enrollment of Phase 2 studies for cryptococcal meningitis and early antifungal therapy.

## REFERENCES

- Branda F, et al. *Infect Dis Rep* 2025;17:91. <https://doi.org/10.3390/idr17040091>
- Maji A, et al. *Nature* 2023;623:1079-1085. <https://doi.org/10.1038/s41586-023-06710-4>
- Lepak AJ, et al. *Antimicrob Agents Chemother* 2024;68:e0163123. <https://doi.org/10.1128/aac.01631-23>
- Gebremariam T, et al. *Antimicrob Agents Chemother* 2025;69:e0180224. <https://doi.org/10.1128/aac.01802-24>
- Vahedi-Shahandashti R, Lass-Flörl C. *Antimicrob Agents Chemother* 2025;69:e0032225. <https://doi.org/10.1128/aac.00322-25>
- Youssef EG, et al. *Antimicrob Agents Chemother* 2026; 70(1):e0140025. <https://doi.org/10.1128/aac.01400-25>
- Sandison T, et al. *IDWeek* 2025; poster P399

## ACKNOWLEDGMENTS

This study was funded by Elion Therapeutics. All authors are employees of Elion Therapeutics.