Turletricin (EL219), a long-acting, non-nephrotoxic polyene antifungal

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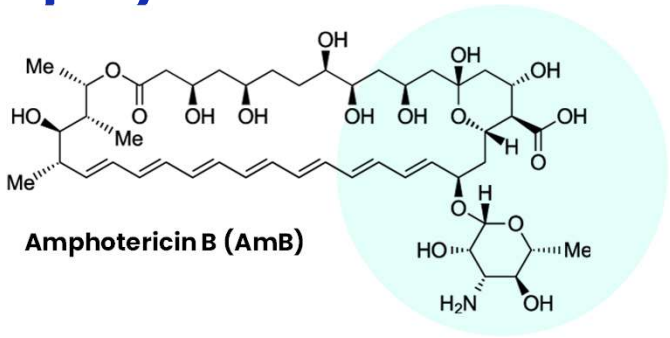
First non-nephrotoxic, broad-spectrum polyene

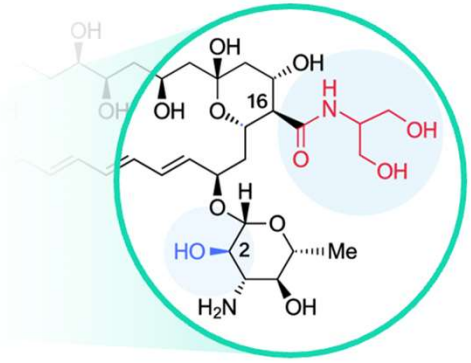
- Amphotericin - the 1st antifungal (1960's)
- Kidney toxicity and inflammatory infusion reactions
- Lipid formulations introduced in 1990's as 'work around' for toxicities
- Turletricin (EL219) - rationally designed, specific to fungal sterol
- The 1st novel polyene - broad spectrum, once weekly administered for suspected pulmonary mould infection
- Well tolerated in Phase 1 and 2a studies
  - Not renal toxic



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

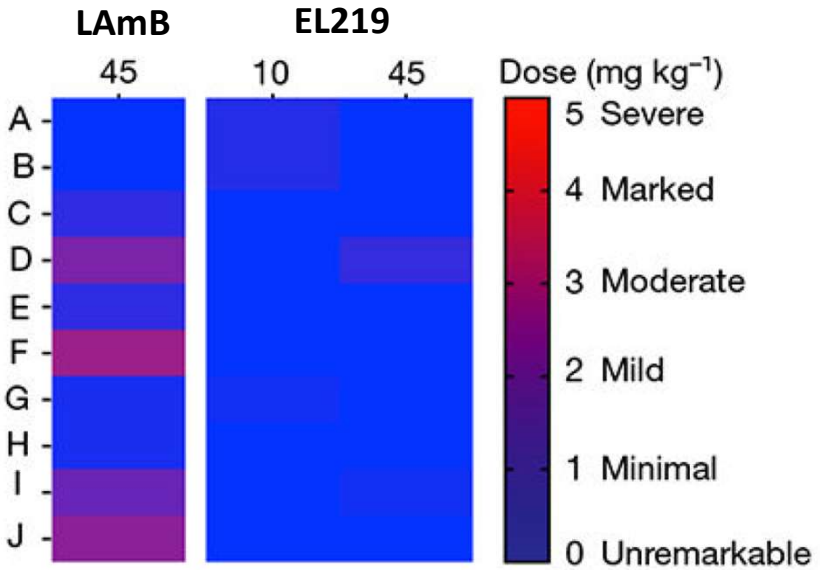


EL219

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

Turletricin's rational design confers reduced renal toxicity

- Histopathology grade changes in kidneys



A. mixed cell infiltrate, interstitial
B. tubular basophilia, cortex
C. tubular cellular casts, cortex
D. tubular cellular casts, medulla
E. tubular degeneration and necrosis, cortex
F. tubular degeneration and necrosis, medulla
G. tubular dilatation, cortex, tubular protein casts, cortex
I. tubular protein casts, medulla
J. vascular congestion, medulla

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

Turletricin microbiology similar to AmB but with activity against classically AmB – resistant species

- **Spectrum/potency**
  - Active against clinically relevant yeasts and molds
  - Limited activity vs. *Scedosporium*, *Lomentospora*, *Cunninghamella*
  - More potent compared to AmB, including against resistant *A. lentulus*, *A. calidoustus*, *A. terreus*
- **Antifungal MOA**
  - Time-kills show cidal activity against yeasts and molds
- **Post-antifungal effect**
  - PAFE in line with Ambisome
- **Resistance**
  - Spontaneous frequency and serial passage studies suggest low resistance potential in yeasts and moulds
  - Unlike azoles or new drugs in development (DHODH and Gwt1), no agriculture-based MOA analogs driving environmental resistance

Active against pathogenic yeasts, moulds, endemic dimorphs

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

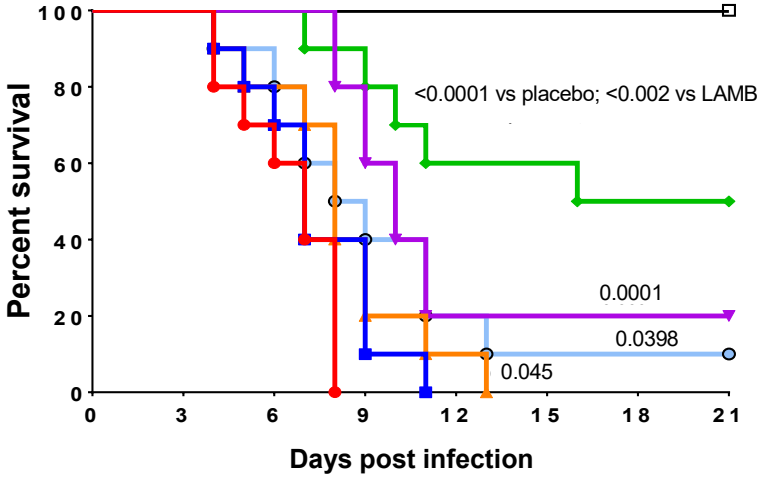
Data represent MIC (µg/mL) range values read at 100% growth inhibition for EL219 and LAMB and at 50% growth inhibition for azoles.
EL219=micellar formulation of EL219 in a 1:3 molar ratio with DSG-PEG2000; LAMB=liposomal amphotericin B

NOTE: The use of commercial drug formulations herein and known polyene physical-chemical properties that confer nonspecific binding have necessitated efforts to establish a drug substance-only modified MIC testing methodology for use going forward capable of generating accurate and reproducible susceptibility values.

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

In vivo efficacy of EL219 treatment against the most common pulmonary lung infection is robust in mouse models

Survival following *Aspergillus fumigatus* (AF293) infection

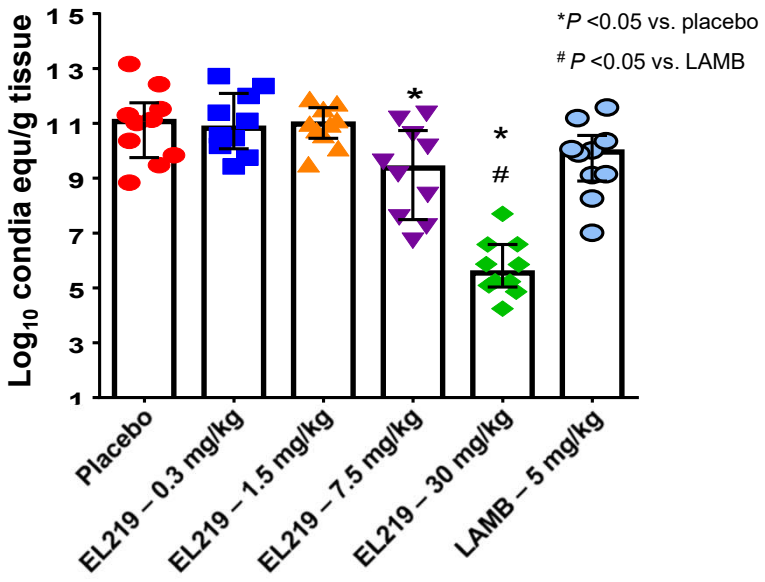


n=10 mice/group

- 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

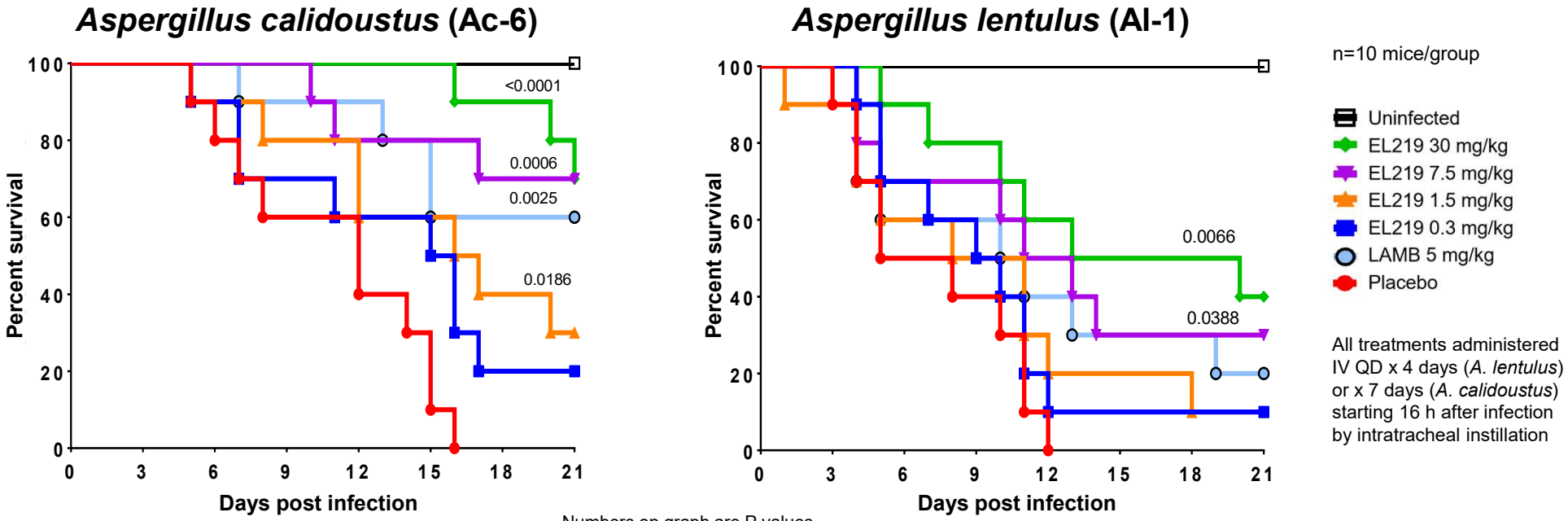
All treatments administered IV QD x 4 days starting 16 h after infection by intranasal inhalation

Fungal burden on Day 4



LAMB=liposomal amphotericin B.
Gebremariam T, et al. *Antimicrobial Agents and Chemotherapy*, 2026.

EL219 retains *in vivo* efficacy against AmB-Resistant *Aspergillus* spp.



Numbers on graph are P values vs. placebo-treated mice.

LAMB=liposomal amphotericin B.

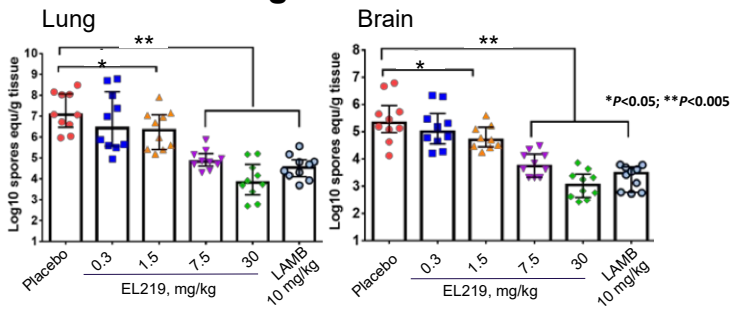
Gebremariam T, et al. *Antimicrobial Agents and Chemotherapy*, 2026.

EL219 has good *in vivo* efficacy against mucormycoses

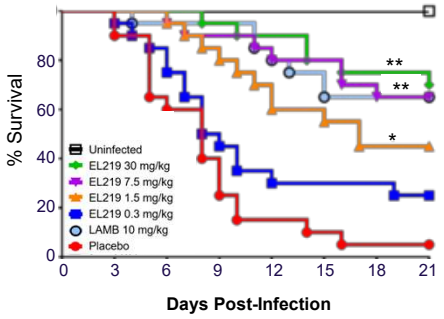
Rhizopus delemar

(n=20 mice/group)

Fungal burden

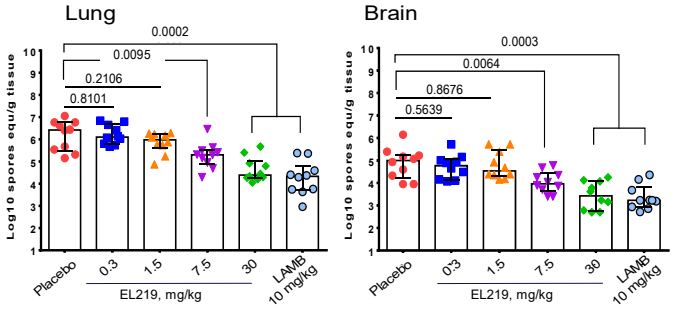


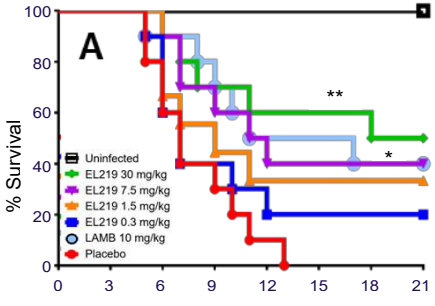
Survival



Mucor circinelloides

(n=10 mice/group)





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

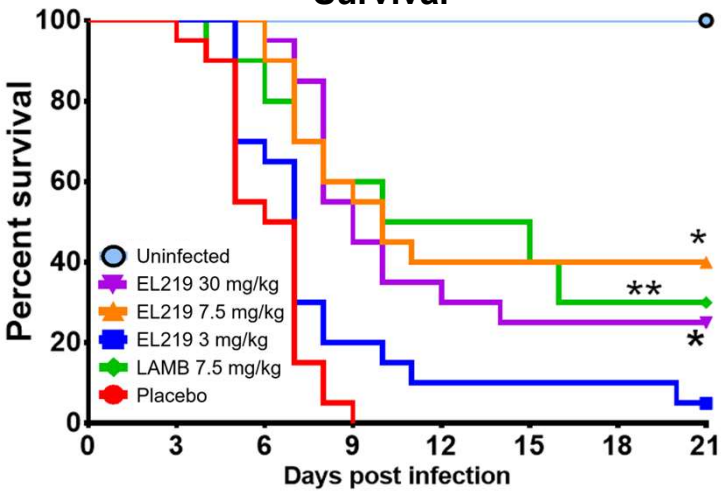
LAMB=liposomal amphotericin B.
Maji A, et al., *Nature*, 2023.

EL219 is efficacious *in vivo* against fusariosis

Improved survival and tissue fungal burden in an immunosuppressed mouse model of disseminated fusariosis

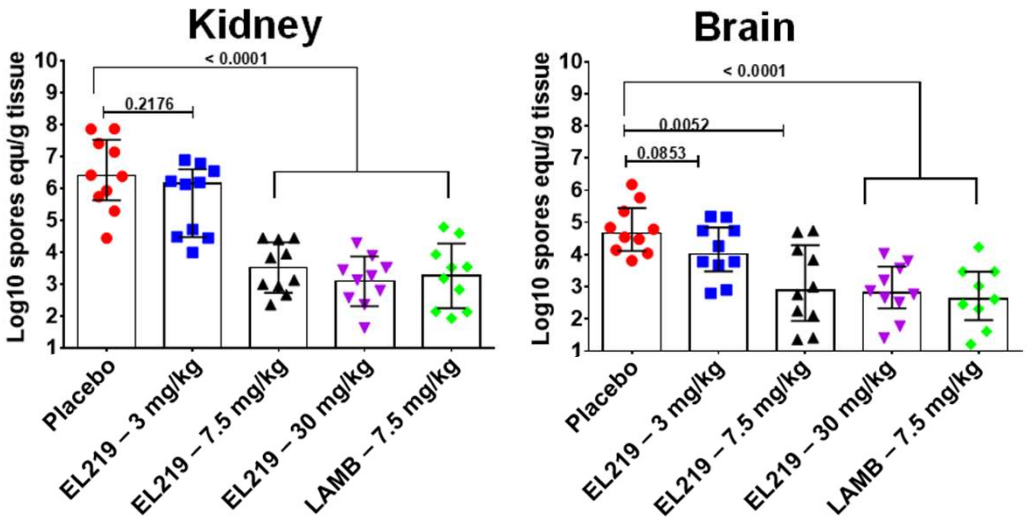
***Fusarium solani* (95-2478)**

Survival



(n=20 mice/group – pooled data from two n=10 experiments)

Fungal burden



(n=10 mice/group)

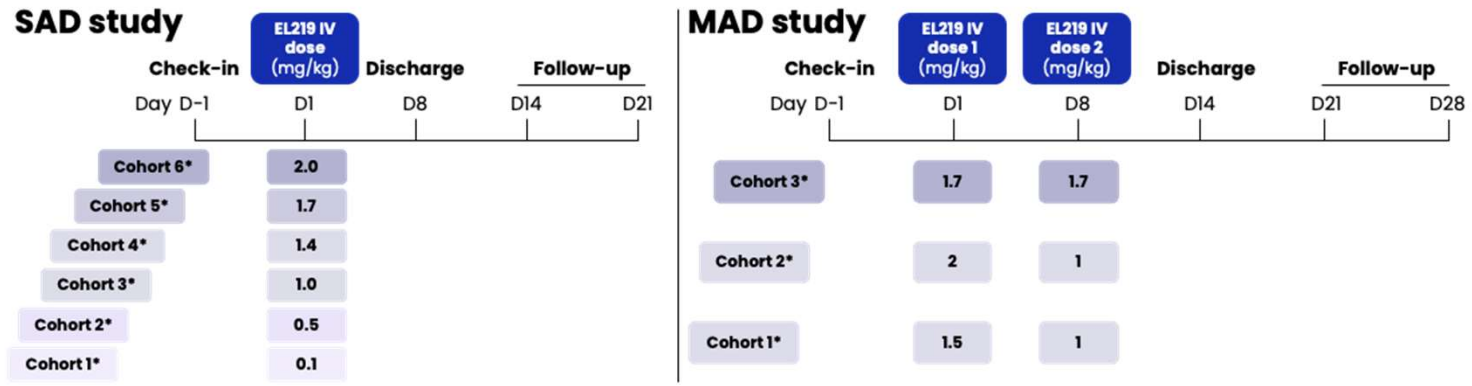
LAMB=liposomal amphotericin B.

Gebremariam T, et al, *Antimicrobial Agents and Chemotherapy*, 2025

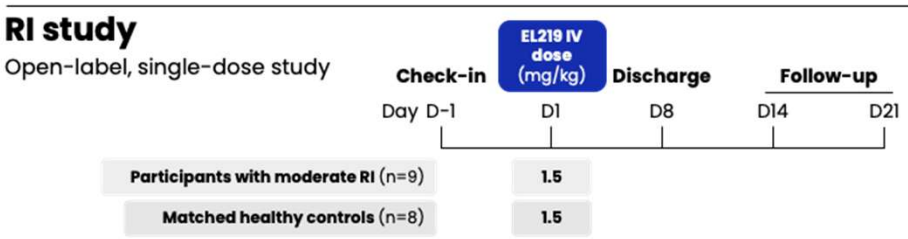
EL219 Nonclinical ADME similar to AmB but with long half-life

- Highly protein bound (>94%)
- Plasma $T_{1/2}$ 23 hrs (rat); longer in tissues
- Liver > Spleen > **Lung** > Kidney > Heart > Brain
- No significant metabolism
- No interactions with CYP isoforms
- Once weekly dosing

Phase 1 Clinical studies overview



The SAD and MAD studies were randomised, double-blind, placebo-controlled trials.



*Randomised 3:1 participants per cohort (EL219 IV, n=6; placebo IV, n=2; both administered in a 60-minute infusion).
D=Day; IV=intravenous; MAD=multiple ascending dose; SAD=single ascending dose.

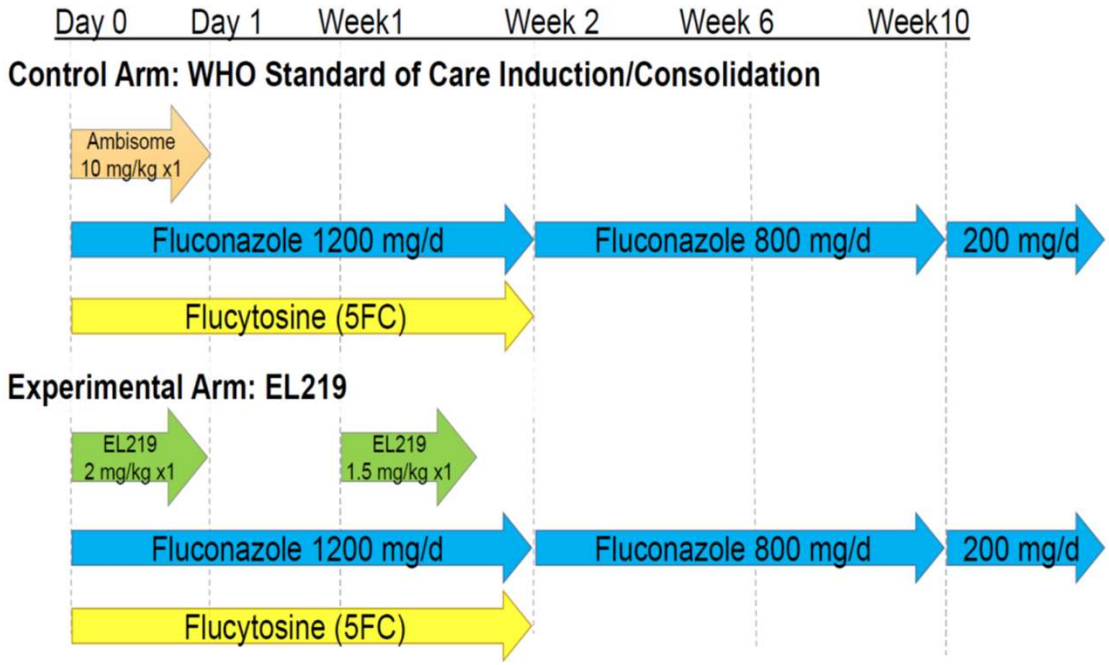
- SAD: Single Ascending Dose
- MAD: Multiple Ascending Dose
- RI: Renal Impairment

Results of Phase 1 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
  - TEAEs were mild and during infusion: histamine-like allergic reactions considered related to excipient (PEG)
    - All recovered/resolved, few received anti-histamine
    - Rate- associated
  - No renal toxicities (serum Cr, eGFR stable)
- 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

*2 participants with moderate RI experienced AEs that were considered related to the study drug (both IRRs). Both of these involved drug administration errors whereby EL219 was infused at 1.73× the protocol-designated rate (protocol-specified infusion time was 60 [± 10] minutes); one of these was severe and led to withdrawal of the study drug after 2 minutes, resulting in the recruitment of additional participant.

PLATFORM-CM Study Design: Phase II Open label



Population and Randomization

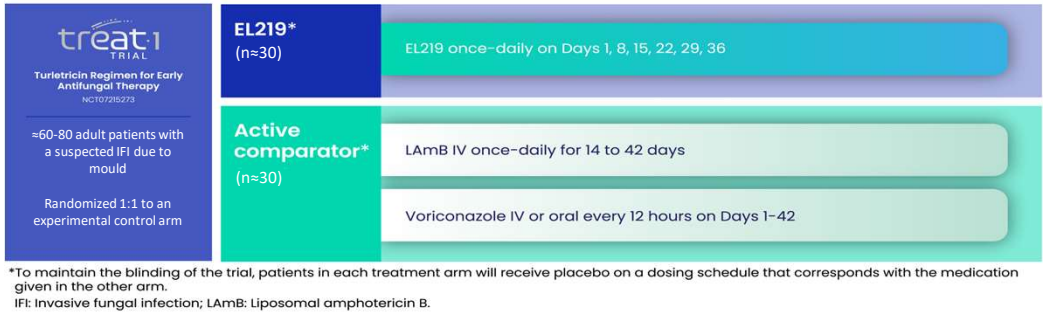
- Site: Kampala, Uganda
- Hospitalized PLWHA with CrAg+ cryptococcal meningitis
- Phase 2: n=40 1:1 SOC vs EL219 QW for 2 weeks (2 and 1.5 mg/kg)+ fluconazole + flucytosine

Endpoints

- **Primary efficacy for Phase II:** Rate of CSF *Cryptococcus* clearance (Early Fungicidal Activity: EFA) quantified by change of log10 *Cryptococcus* CFU/mL CSF/day as measured by CSF fungal cultures over ~2 weeks
- **Key Secondary Endpoint:** Desirability of Outcome Response as ordinal ranked maximum score tested by Win Ratio
- **Safety Endpoints:** incidence of Grade 1-5 lab abnormalities; SAEs; study drug discontinuation, dose reduction, or interruption due to toxicity or clinical AE by grade

https://clinicaltrials.gov/study/NCT06666322

Lead Indication: Early Antifungal Therapy in people with suspected Invasive Aspergillosis



*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.

Primary outcome measures

- **All-cause mortality at day 42**
- **Serious adverse events**
- **Treatment-emergent adverse events**

Selected inclusion criteria

At least one of these risk factors for IFI:
- Allogeneic bone marrow transplant
- ≥1 cytotoxic, biologic, or immune-modulating therapy for a hematological malignancy
- Corticosteroid use (≥0.3 mg/kg/day prednisone equivalent for >3 weeks)
- Receiving other recognized T-cell immunosuppressants
- An inherited severe immunodeficiency

At least one of these diagnostics suggestive of an invasive mould infection:
- Abnormal findings on chest CT scan
- Positive assay results using an approved diagnostic test

Selected exclusion criteria

Participants must NOT meet any of the following exclusion criteria:
- Diagnosis of proven or probable IMI ≤1 month prior to randomization or relapsed/recurrent IMI which has not responded to other antifungal therapies
- Prior antifungal treatment for >96 hours prior to randomization
- Systemic bacterial infection diagnosed ≤14 days prior to randomization
- 1 or more of the following laboratory abnormalities:
  - Alanine aminotransferase (ALT) ≥5 × upper limit of normal
  - Total serum bilirubin ≥5 × ULN
  - Serum creatinine ≥2 mg/dL or creatinine clearance (CrCL) ≤30 mL/minute

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

Thank You!

