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Pharmacokinetics of EL219 (SF001), a novel, next-generation polyene antifungal: Results from the Phase 1 dose-escalation trials in healthy adults and Phase 1 open-label study in adults with moderate renal impairment

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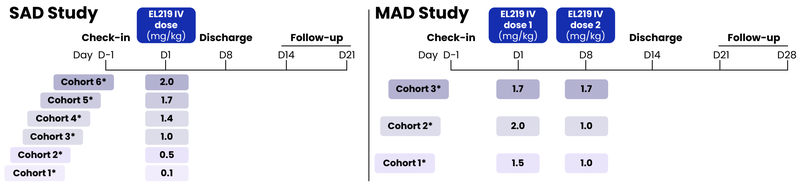
INTRODUCTION

- Invasive fungal infections (IFIs) are increasing in incidence and cause substantial morbidity and mortality [1]. 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 nephrotoxicity [1].
- EL219 (formerly known as SF001), an AmB derivative, is a novel, next-generation polyene antifungal, structurally modified to enhance specificity to fungal sterols [2].
  - EL219 is in clinical development for early antifungal therapy of suspected pulmonary mold infections, treatment of invasive aspergillosis, and treatment of cryptococcosis.
  - In nonclinical studies, EL219 demonstrated broad-spectrum antifungal activity, in vivo efficacy, and few toxicities [2-5].
- Here, we report pharmacokinetic (PK) results from three Phase 1 studies of EL219.

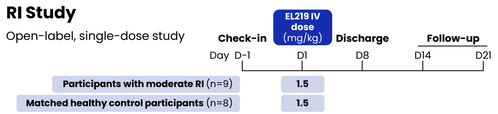
METHODS

- The PK of EL219 was assessed in three studies in adult volunteer participants (**Fig. 1**).
  - In two randomized, double-blind, placebo-controlled trials, participants were administered EL219 at various doses (up to 2.0 mg/kg) or placebo, to assess the safety of single and multiple doses of EL219.
  - In an open-label study, participants with moderate renal impairment (RI; estimated glomerular filtration rate [eGFR]: 30–<60 mL/min) and healthy control participants matched for sex, age, race, and body weight received a single 1.5-mg/kg dose of EL219.
- The primary objective of all three studies was to assess the safety, tolerability, and PK profile of EL219.

Figure 1. Designs of the EL219 Phase 1 SAD, MAD, and RI Studies



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



*Randomized 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.

Safety Assessments

- Adverse events (AEs), laboratory assessments (hematology, chemistry, urinalysis), electrocardiograms, and vital signs were monitored throughout the studies, including at follow-up (SAD study: D21 ± 1 day; MAD and RI studies: D28 ± 1 day).

PK Assessments

- Samples to evaluate the PK of EL219 were collected pre-dose and at multiple timepoints post-dose. Drug concentrations were analyzed using a validated liquid chromatography–tandem mass spectrometry method.
- PK parameter computations were calculated using Phoenix® WinNonlin® software, and descriptive statistics were generated using SAS® (v9.4).

RESULTS

- Demographic and clinical characteristics of the study populations are shown in **Table 1**.

Table 1. Baseline Demographic and Clinical Characteristics

Parameter	SAD Study (N=48)	MAD Study (N=24)	RI Study	
			Moderate RI (n=9)*	Healthy (n=8)
Age, mean ± SD years	37.0 ± 9.5	34.3 ± 9.6	64.3 ± 5.8	58.8 ± 3.5
Sex, n (%)				
Female	13 (27.1)	10 (41.7)	3 (33.3)	2 (25.0)
Male	35 (72.9)	14 (58.3)	6 (66.7)	6 (75.0)
Not Hispanic or Latino, n (%)	47 (97.9)	21 (87.5)	5 (55.6)	3 (37.5)
Race†				
White	26 (54.2)	11 (45.8)	2 (25.0)	2 (25.0)
Black	15 (31.3)	11 (45.8)	6 (75.0)	6 (75.0)
White, American Indian, or Alaska Native	1 (2.1)	1 (4.2)	0	0
Asian	0	1 (4.2)	0	0
BMI, mean ± SD kg/m^2	27.0 ± 3.1	26.8 ± 2.9	28.9 ± 3.7	29.3 ± 3.1
eGFR, mean ± SD mL/min	NR	NR	44.9 ± 10.9	112.3 ± 14.0

*Race and BMI data were unavailable for one participant; one participant did not receive the full infusion and was therefore excluded from the PK analysis. †Self-reported. The SAD study also enrolled participants from the following self-reported race categories: American Indian or Alaska Native; Black or African American, American Indian, or Alaska Native; Native Hawaiian or Other Pacific Islander (n=1 each); White, Black, or African American (n=3).
BMI=body mass index; NR=not recorded; SD=standard deviation.

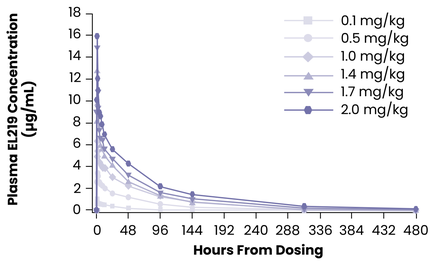
Safety

- EL219 was generally well tolerated in all three studies.
- Transient histamine-like allergic reactions, likely related to excipient (polyethylene glycol), occurred at higher doses or at higher infusion rates.
- Some participants showed evidence of mild, transient renal tubular abnormalities, consistent with drug aggregation.
  - These resolved without intervention or recurrence with additional dosing.
- No electrolyte abnormalities, anemia, or other safety abnormalities were observed, even in the setting of moderate RI.

Pharmacokinetics

- Plasma EL219 concentrations remained quantifiable for weeks (**Fig. 2**).
- Exposures as measured by area under the concentration-time curve (AUC) and maximum concentration (C_{max}) increased approximately proportionally with increasing dose, along with other single-dose PK parameters, as shown in **Table 2** for the 1- and 2-mg/kg dose groups.
- Most notably, EL219 demonstrated a long half-life (>60 hours following single-dose administration of 1.0 and 2.0 mg/kg, **Table 2**); urinary excretion was 20–25% as EL219.
- **Table 3** shows PK on D1 and D8 in the MAD study.

Figure 2. PK Profiles of EL219 in the SAD Study



Data are arithmetic mean values.

Table 2. PK of EL219 in the SAD Study

Parameter*	SAD Study	
	1.0 mg/kg (n=6)	2.0 mg/kg (n=6)
AUC_{0-inf} (µg*h/mL)	359.6 (31.6)	744.6 (27.8)
C_{max} (µg/mL)	7.4 (76.0)	15.7 (22.0)
$t_{1/2}$ (h)	62.35 ± 7.88	88.10 ± 21.37
CL (L/h)	0.225 ± 0.060	0.223 ± 0.057
V_d (L)	20.0 ± 5.31	27.3 ± 5.68

*AUC and C_{max} values are presented as geometric mean (geometric CV%); all other parameters are presented as arithmetic mean ± SD.
CL=clearance; CV=coefficient of variation; $t_{1/2}$=half-life; V_d=volume of distribution.

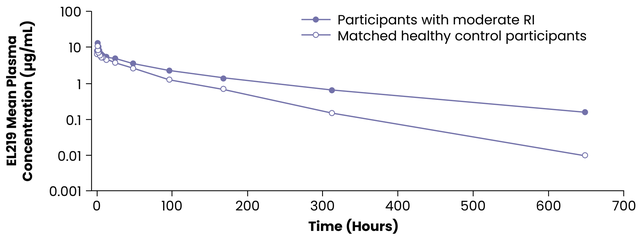
Table 3. PK of EL219 in the MAD Study

Parameter*	Timepoint	1.5/1.0 mg/kg (n=6)	2.0/1.0 mg/kg (n=5)†	1.7/1.7 mg/kg (n=5)†
AUC_{0-168} (µg*h/mL)	Day 1	471.4 (14.6)	699.1 (12.3)	534.3 (14.1)
	Day 8	357.1 (16.1)	472.0 (22.0)	622.9 (17.6)
C_{max} (µg/mL)	Day 1	14.8 (15.4)	18.8 (14.5)	16.2 (12.2)
	Day 8	10.5 (7.4)	11.7 (9.2)	17.9 (7.0)

*AUC and C_{max} values are presented as geometric mean (geometric CV%). †One subject from each of the 2.0/1.0- and 1.7/1.7-mg/kg EL219 groups was excluded from summary statistics due to significant D8 infusion interruptions.

- Following administration of a 2nd dose in the MAD study, accumulation was ~17% in the 1.7/1.7-mg/kg group.
- Other dose regimens – 1.5/1.0 mg/kg and 2.0/1.0 mg/kg – provided higher first-dose (front-loaded) exposures.
- EL219 PK in adults with moderate RI showed a trend toward slower elimination, but there were no clinically meaningful changes compared with matched-control participants (**Fig. 3**).

Figure 3. PK Profile of EL219 Following Dosing in RI or Healthy Adults



CONCLUSIONS

- Across three studies, EL219 was well tolerated with no safety concerns.
- EL219 demonstrated a long half-life, enabling once-weekly dosing.
- No changes are expected in dosing EL219 for use in adults with moderate RI.
- These data further support the ongoing development of EL219 for antifungal therapy.
- Clinical investigation of EL219 will continue with the enrollment of a cohort of participants with severe RI to assess safety and PK, as well as Phase 2 studies on cryptococcal meningitis (ongoing) and early antifungal therapy (commencing in Q4 2025).

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DISCLOSURES

All authors are employees or consultants of Elion Therapeutics.