

Pharmacokinetic–pharmacodynamic analysis of anidulafungin in pediatric and adult patients with invasive fungal infections

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INTRODUCTION

- Anidulafungin is an intravenous (IV) echinocandin, synthesized from a fermentation product of *Aspergillus nidulans*, approved for the treatment of invasive candidiasis including candidemia (ICC) in adult patients worldwide.
 - The approved adult dosing regimen is a 200 mg loading dose followed by a once-daily (QD) 100 mg maintenance dose.
- The pharmacokinetic (PK) properties of anidulafungin have been previously evaluated in healthy adult subjects, patients with renal or hepatic impairment, patients with fungal infections, and in neutropenic pediatric (2 to 17 years of age), neonatal (<30 postnatal days), and infant (≥30 postnatal days) patients at high risk of invasive fungal infections.^{1–5}
- Anidulafungin exhibits linear and predictable PK in all of these populations.
- A trend towards a positive association between anidulafungin exposure and efficacy in patients with esophageal candidiasis or ICC was shown in a previous population PK/pharmacodynamic (PD) analysis of data from four studies in adult patients.⁶
- Also, the PK of anidulafungin was recently evaluated in a Phase 3b prospective, open-label, non-comparative study in pediatric patients (1 month to <18 years of age) with ICC (Study A8851008, NCT00761267).^{7,8}
- Here, we describe the PK and PK/PD relationships in a population analysis across a full range of adult and pediatric ages in patients with ICC.

OBJECTIVES

- The objectives of this study were to:
 - describe the PK of anidulafungin in pediatric and adult patients with ICC;
 - predict individual exposure parameters based on the final PK parameter estimates;
 - explore the relationship between anidulafungin exposure and key efficacy and safety endpoints; and
 - confirm if the proposed dosing regimen for pediatric patients is appropriate.

METHODS

Study design

- Data from four studies were evaluated in this analysis:
 - Pediatric investigator-initiated research (IIR) PK and safety study in neonates and infants <24 months of age with suspected serious infections, conducted by Duke University, Durham, NC, USA.
 - Pediatric clinical study (A8851008) in patients 1 month to <18 years of age with ICC.
 - Adult clinical study (A8851011) in neutropenic and non-neutropenic patients ≥18 years of age with *Candida* infections.
 - Adult clinical study (A8851019) in intensive care unit patients ≥18 years of age with ICC.
- In these studies, all pediatric patients received a 3 mg/kg (maximum 200 mg) IV loading dose followed by 1.5 mg/kg (maximum 100 mg) IV maintenance dose QD, and all adults received a 200 mg IV loading dose followed by 100 mg IV maintenance dose QD.

Study assessments

PK

- Data from all four studies were included in the PK analysis.
- Population PK analyses used a nonlinear mixed effects modeling approach (NONMEM) and first-order conditional estimation method with interaction (FOCEI).
- Exposure parameters (area under the curve over a 24-hour dosing interval at steady state [AUC_{0–24,ss}] and trough [minimum] concentration at steady state [C_{min,ss}]) were calculated using the individual parameter estimates from the final PK model and were summarized by age groups from all four studies and from the pediatric clinical study (A8851008) alone.

PK/PD efficacy and safety

- Exposure–efficacy and safety analyses included data from patients with PK in the three clinical studies (excluding the pediatric IIR study, which was primarily designed as a PK study).
- Exposure–efficacy and exposure–safety graphical analyses were used to estimate the probability of response.
 - Efficacy endpoints: global response at end-of-IV-treatment and end-of-treatment, and all-cause mortality at end-of-treatment and end-of-study.
- Safety endpoints: incidence of all-cause treatment-emergent hepatic and/or gastrointestinal (GI) adverse events (AEs) during treatment with anidulafungin.
- Anidulafungin exposures (AUC_{0–24,ss}) were examined graphically for five quantile groups (quantile ≤20%, >20%–40%, >40%–60%, >60%–80%, >80%) in all three clinical studies and also separately in the pediatric clinical study (A8851008).
- Exposure–response (safety endpoints) logistic regression modeling was performed using the maximum likelihood method once graphical analyses demonstrated a possible exposure–response relationship. The LAPLACE estimation method was used.
- No account of multiple AEs was taken, and data were treated as binary data for probability analyses with an assumption of independence of hepatic and GI AEs. Patients who had both GI and hepatic AEs were kept in both hepatic and GI AE groups.

RESULTS

PK

- A total of 163 patients (95 [58.3%] male and 68 [41.7%] female) were included in the PK analysis.
 - Of these, 14 patients from the pediatric IIR PK study, 66 from the pediatric clinical study (A8851008), and 83 from the two adult clinical studies provided 797 anidulafungin concentrations (391 from pediatric patients).
- Anidulafungin PK was best characterized by a 2-compartment disposition model with first order elimination. The goodness of fit plots are shown in **Figure 1**.
- Body weight was a covariate on clearance (CL) and intercompartmental clearance (Q), central volume of distribution (V_c), and peripheral volume of distribution (V_p).
 - No other covariates (e.g., age or sex) were identified as statistically significant.
- The estimated CL, V_c, V_p, and Q of a typical patient weighing 70 kg are shown in **Table 1**, together with the inter-individual variability for CL, V_c, V_p, and Q.

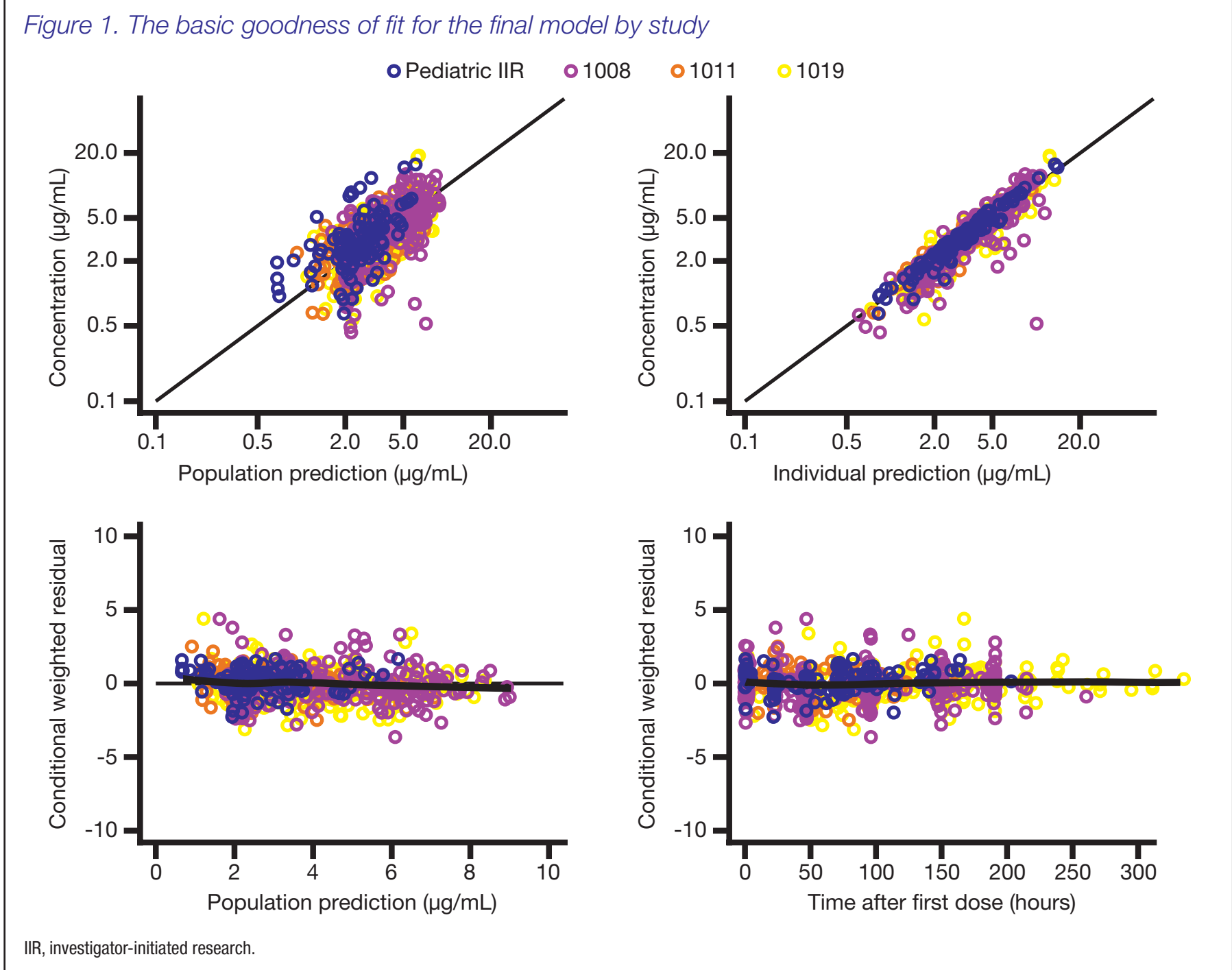


Table 1. Parameter estimates for the final model		
Parameter	Estimate (% RSE)	Shrinkage, %
CL ^a , L/h	1.16 (3.92)	–
Vc ^a , L	26.7 (6.5)	–
Q ^a , L/h	2.37 (15.2)	–
Vp ^a , L	22.4 (12.9)	–
WT on CL	0.915 (2.98)	–
WT on Vc	1.2 (4.95)	–
WT on Vp	0.769 (6.04)	–
IIV on CL, %	37.9 (7.31)	5.37
IIV on Vc, %	46.5 (19.9)	10.3
corr CL–Vc ^b	0.16 (0.0947)	–
IIV on Q, %	52.2 (18.6)	54.6
IIV on Vp, %	53.8 (14.5)	44.7
Residual error, %	21.2 (6.77)	15.9

^aThe estimate is for a patient weighing 70 kg; ^bEstimate of the covariance between CL and Vc. CL, clearance; corr, correlation; IIV, inter-individual variance; Q, inter-compartmental clearance; RSE, relative standard error; Vc, central volume of distribution; Vp, peripheral volume of distribution; WT, body weight.

- The final model generally predicted the data well across the studies, with a good match between the median, 5th and 95th percentiles for the observed and simulated data across the age groups, indicated by prediction–corrected visual predictive check plot (**Figure 2**).
- Predicted mean AUC_{0–24,ss} for maintenance doses; adult, 100 mg QD and pediatric, 1.5 mg/kg QD were 80.8, 82.9, 82.8, 86.8, and 91.1 µg·h/mL for neonates, children 1 month–<2 years, 2–<5 years, 5–<18 years, and adults ≥18 years of age, respectively.
 - Predicted exposures (AUC_{0–24,ss} and C_{min,ss}) and weight-corrected mean parameters were comparable across the five age groups (**Table 2**).

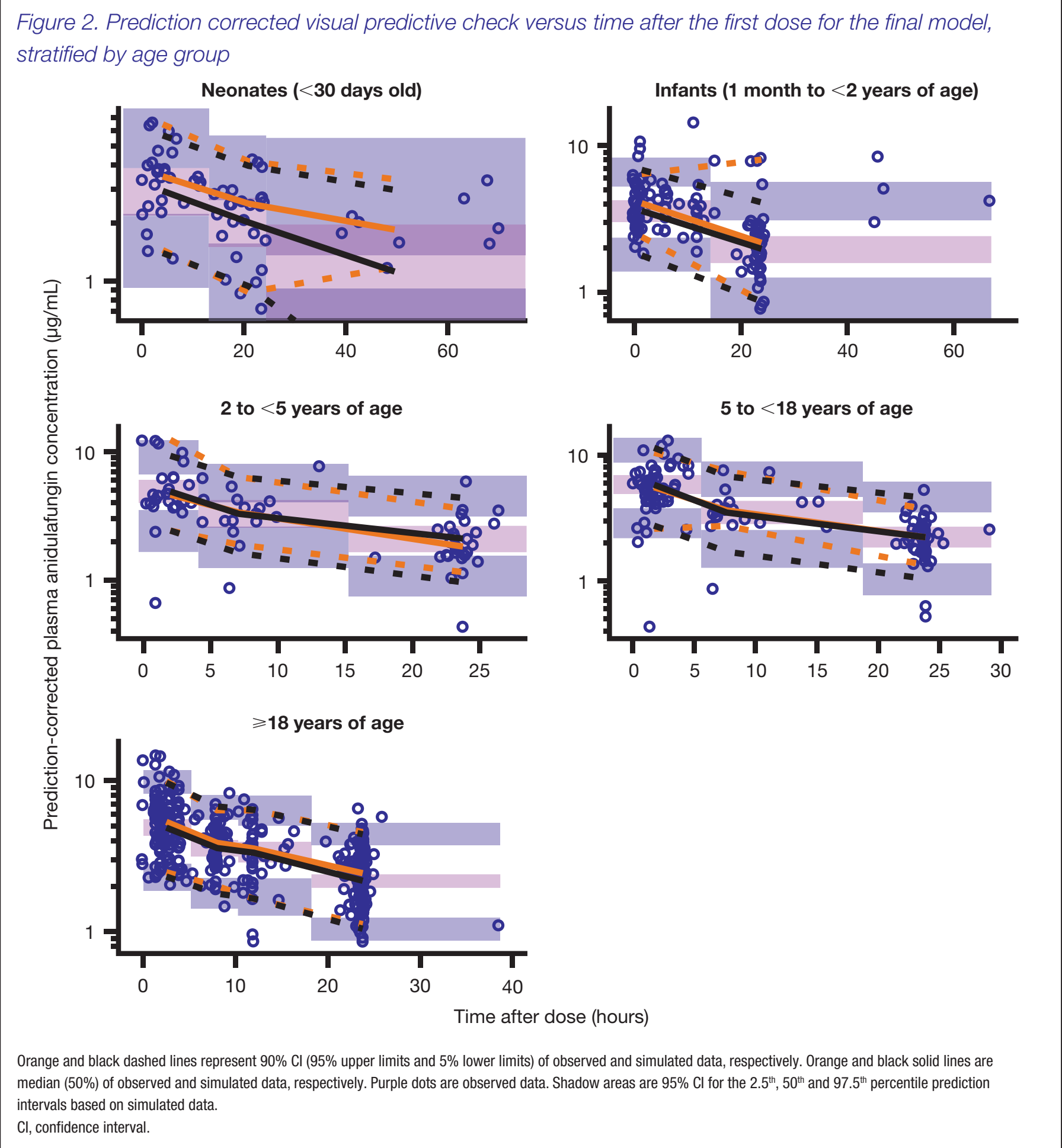


Table 2. Summary of estimated anidulafungin exposure and PK parameters in pediatric and adult patients by age groups (loading/maintenance doses for pediatric patients at 3.0/1.5 mg/kg QD or adults at 200/100 mg QD)					
	Neonates (<30 days old)	Infants (1 month to <2 years of age)	2 to <5 years of age	5 to <18 years of age	≥18 years of age
Number of patients	8	23	19	30	83
AUC _{0–24,ss} ^a , µg·h/mL					
Mean (SD)	80.77 (28.03)	82.91 (43.74)	82.81 (31.9)	86.77 (31.12)	91.11 (38.93)
Median (range)	83.87 (29.27–124.97)	67.52 (49.09–260.64)	80.01 (35.8–161.65)	80.49 (28.3–197.79)	85.09 (30.8–246.9)
90% CI	41.68, 114.78	50.13, 111.98	38.55, 138.86	57.85, 124.45	43.36, 154.72
C _{min,ss} ^a , µg/mL					
Mean (SD)	2.64 (0.99)	2.46 (1.44)	2.51 (1.11)	2.52 (0.96)	2.71 (1.31)
Median (range)	2.59 (0.81–4.09)	1.92 (1.17–8.12)	2.46 (1.01–5.36)	2.34 (0.62–5.9)	2.47 (0.87–9.06)
90% CI	1.28, 3.88	1.27, 3.69	1.02, 4.32	1.59, 3.76	1.31, 4.72
CL, L/h/kg					
Mean (SD)	0.023 (0.0125)	0.0208 (0.0064)	0.0214 (0.0088)	0.0198 (0.0079)	0.0175 (0.0065)
Median (range)	0.0197 (0.012–0.0525)	0.0212 (0.0058–0.0316)	0.0212 (0.0093–0.0487)	0.0193 (0.0093–0.053)	0.0162 (0.0068–0.0354)
90% CI	0.0136, 0.0422	0.013, 0.0304	0.0115, 0.0354	0.012, 0.0269	0.009, 0.0296
Vss, L/kg					
Mean (SD)	1.1023 (0.4085)	0.7731 (0.2301)	0.9049 (0.275)	0.7528 (0.158)	0.7526 (0.2234)
Median (range)	1.0166 (0.6036–1.6821)	0.7545 (0.2486–1.3173)	0.8847 (0.5911–1.717)	0.7815 (0.4996–1.1104)	0.7046 (0.3398–1.4875)
90% CI	0.6244, 1.6598	0.4764, 1.2678	0.6283, 1.4853	0.5084, 0.9509	0.4705, 1.1418

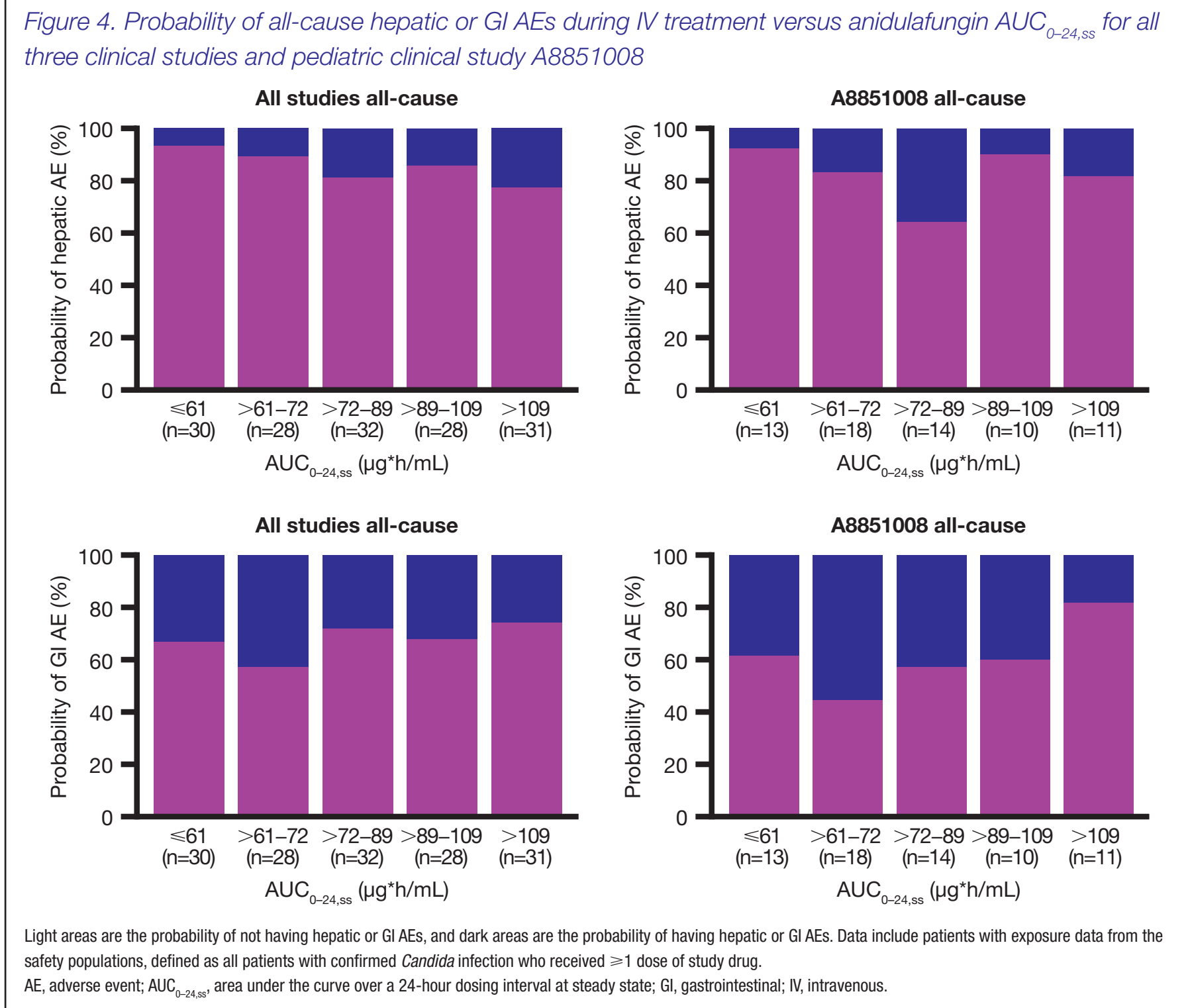
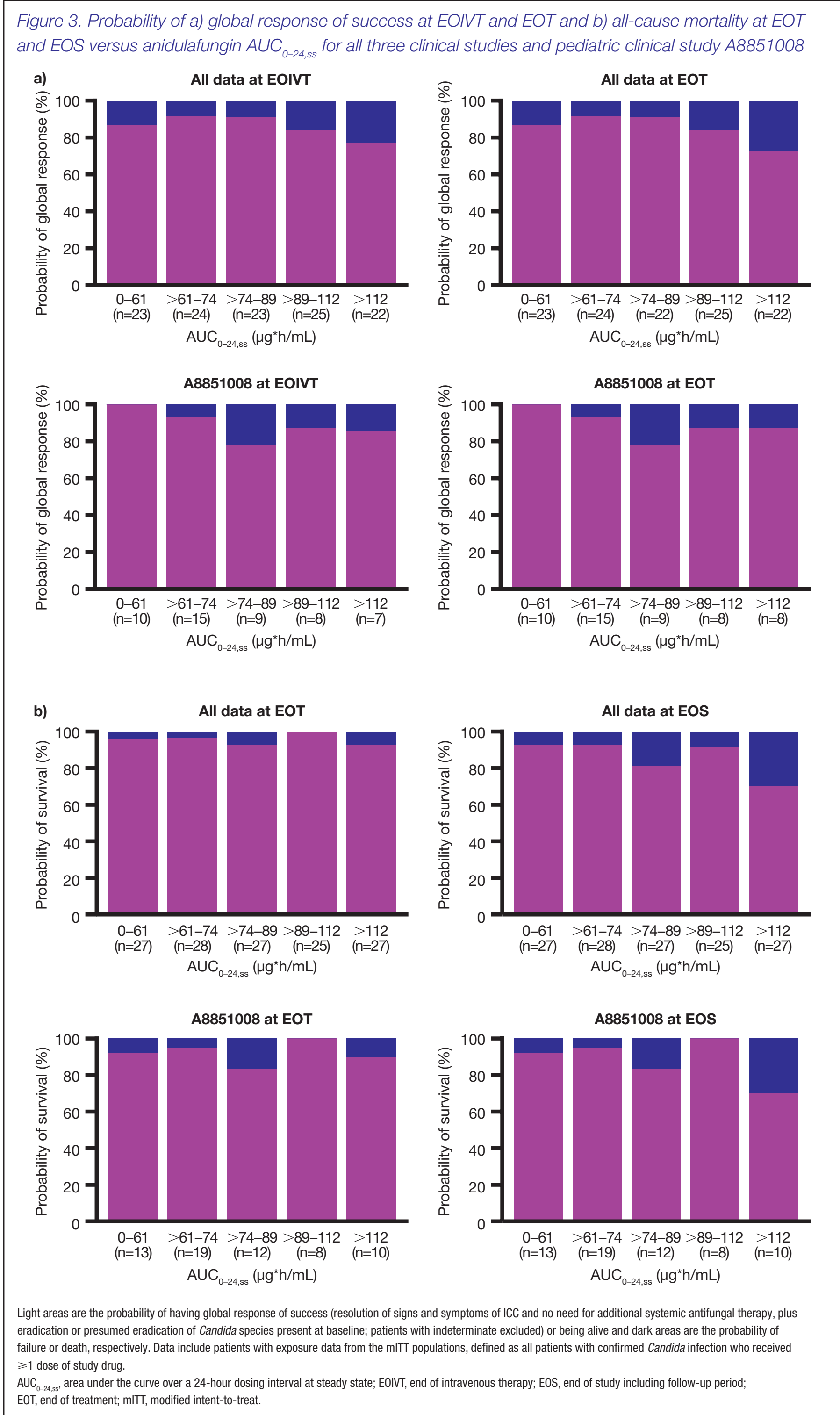
AUC_{0–24,ss}^a, area under the curve over a 24-hour dosing interval at steady state (maintenance dose); CI, confidence interval; CL, clearance; C_{min,ss}^a, minimum concentration at steady state (maintenance dose); QD, once daily; SD, standard deviation; Vss, volume of distribution at steady state.

PK/PD Efficacy

- Evaluation of data from all three clinical studies and pediatric clinical study (A8851008) alone showed that the probability of treatment failure (**Figure 3a**) or death (**Figure 3b**) does not appear to be related to low anidulafungin exposures.
- As there was no clear association observed between anidulafungin exposure quantiles and all-cause mortality or treatment failure, no further exposure–efficacy modeling analysis was performed.

PK/PD Safety

- There was a slight trend towards an increased incidence of all-cause hepatic AEs with higher exposure in the data from all three clinical studies, but not in the pediatric clinical study (A8851008) alone.
- There was no apparent relationship between exposure and all-cause GI AEs (**Figure 4**).
- None of the exposure parameters were identified as a statistically significant predictor for the incidence of hepatic or GI AEs using logistic regression.



CONCLUSIONS

- The proposed weight-based IV dosing regimen, a 3.0 mg/kg (maximum 200 mg) loading dose followed by 1.5 mg/kg (maximum 100 mg) maintenance dose QD, is considered appropriate for pediatric patients 1 month to <18 years of age.
 - The anidulafungin exposures achieved with this regimen are comparable to those of adult patients receiving the recommended dosing regimen (200 mg loading dose/100 mg maintenance dose QD).
- No statistically significant relationships between anidulafungin exposure parameters and efficacy/safety were identified in pediatric and adult patients with ICC.

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DISCLOSURES

RX, SR, RS, MT, HL-T, and LM are employees of Pfizer Inc. PL is a former employee of Pfizer Inc and current employee of Clinical Pharmacology, Linking Truth Technology Co Ltd.

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