Population pharmacokinetics of LXE408 in healthy volunteers and dose predictions for adult and pediatric patients with visceral leishmaniasis

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Introduction

- Leishmaniasis is a spectrum disease caused by protozoan parasites from >20 Leishmania species associated with three main clinical syndromes: cutaneous, mucocutaneous, and visceral leishmaniasis. Cutaneous leishmaniasis is the most common syndrome; however, visceral leishmaniasis (VL) is the most serious form of the disease and is fatal if left untreated. The estimated number of VL cases globally is 50,000 to 90,000 annually with children below the age of 15 years representing half of the affected VL patients and 7,500 deaths are estimated to occur per year worldwide.
- Available drugs to treat VL include liposomal amphotericin B (AmBisome), sodium stibogluconate/paromomycin combination and miltefosine. They either can result in severe adverse effects, insufficient efficacy or require a temperature-controlled supply chain and/or administration in specialized centers. Therefore, there is an unmet medical need for new treatments of VL.
- LXE408 is a first-in-class parasite-selective kinetoplastid proteasome inhibitor developed to treat VL patients.
- Recently, the first in human (FIH) study of LXE408 in healthy volunteers was completed; doses up to 600 mg once daily (QD) for 10 days were well tolerated.
- A phase II study has been recently initiated that evaluates two LXE408 regimens and active comparator (AmBisome) in VL patients (NCT05593666). The study is conducted in India.

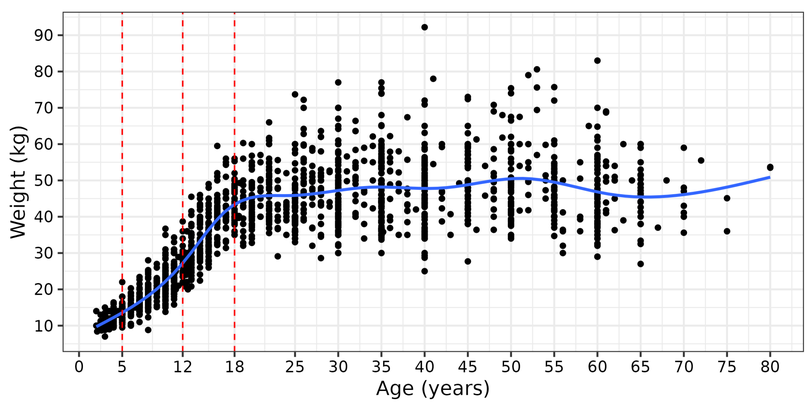
Objectives

- To describe the population pharmacokinetics of LXE408 after oral administration in healthy volunteers using data from the FIH study.
- To predict pharmacologically active doses for the phase II study in adult VL patients. To predict pediatric doses in patients ≥10 kg that match exposure of adults at the dose selected for phase II study in VL patients.

Methods

- The population PK (popPK) model was built using the nonlinear mixed-effects approach and was implemented in MonolixSuite 2021R2. The structural model was parameterized in terms of apparent clearance (CL/F), apparent volume of distribution (V/F), zero-order absorption duration (Tk0), lag time before absorption (Tlag) and relative bioavailability (F). Between-subject variability was introduced on all structural parameters. Residual unexplained variability was modeled using a proportional error model.
- The established popPK model was used for PK simulations of candidate doses for the phase II study. Between-subject variability was inflated by 30% to reflect higher expected variability in patients. Based on preclinical PKPD experiments, it was concluded that having free drug concentrations above the in-vitro EC50 value for 70% of time over the dosing interval correlated with efficacy in preclinical models of VL. This PKPD target was used for simulations to determine the pharmacologically active dose.
- Individual body weights of Asian VL patients from field study in India (Goyal 2018) were used for these simulations (see Figure 1).
- Once the dose for adult VL patients was selected, pediatric simulations were performed assuming allometric scaling of PK parameters with the aim to identify pediatric doses that result in similar exposure as the adult target dose.

Figure 1 Age and weight relationship of Asian VL patients



Weight and age data are from patients in the field study in India reported in (Goyal 2018). Blue line: smooth line through individual data; vertical red lines: 5, 12 and 18 years old

Results

- The final popPK model was a one-compartment disposition model with zero-order absorption and linear elimination. The observed dose under-proportional PK was captured in the model as dose effect on relative bioavailability F. Population parameter estimates are shown in Table 1. Body weight was introduced in the model as a covariate with fixed allometric coefficients of 0.75 for CL/F and 1 for V/F. The estimated dose effect on F was -0.245 on the log scale, indicating a decreasing bioavailability with increasing dose.
- The mean body weight of adult Asian VL patients used for these simulations was 47 kg. PK simulations estimated that doses in the range 65-100 mg QD would reach the preclinical PKPD target in 90-95% of adult VL patients (Figure 2). Nevertheless, since doses up to 600 mg QD for 10 days were well tolerated in healthy volunteers in the FIH study, a dose of 300 mg QD was selected for phase II study in adult VL patients to maximize potential treatment benefits.
- Pediatric simulations were performed assuming that the relative bioavailability of adults and children receiving the same dose is the same.
- Several dose adjustment schemes with fixed doses per weight band were considered for pediatric patients. The following dose adjustment scheme allowed an acceptable match of the adult target exposure, see Figure 3 for details:
  - 10 to <20 kg: 75 mg
  - 20 to <30 kg: 150 mg
  - ≥30 kg: 300 mg
- It should be noted that these preliminary simulations are exploratory in nature. Pediatric dose predictions will be iteratively updated with incoming data, such as PK data from adult VL patients, adolescent PK data, etc.

Table 1 LXE408 popPK model parameter estimates

Parameter	Estimate (%RSE)	Shrinkage (%)
Structural parameters		
Apparent clearance, CL/F (L/h)	5.39 (5%)	
Bioavailability, F (fixed to 1)	1 (fixed)	
Zero order absorption duration (h)	1.07 (8%)	
Absorption lag time (h)	0.243 (8%)	
Apparent volume of distribution, V/F (L)	142 (5%)	
Between-subject variability, standard deviations		
BSV on CL/F	0.277 (13%)	32%
BSV on F	0.302 (12%)	21%
BSV on Tk0	0.597 (10%)	20%
BSV on Tlag	0.458 (13%)	44%
BSV on V/F	0.219 (19%)	56%
Covariate effects		
Weight on CL/F	0.75 (fixed)	
Dose on F	-0.245 (12%)	
Weight on V/F	1 (fixed)	
Residual variability		
Proportional error (b)	0.198 (2%)	

%RSE: relative standard error expressed as percentage; Shrinkage was calculated manually, variance-based definition of shrinkage was used; BSV: between-subject variability; body weight was centered at 75 kg; dose was centered at 100 mg

Figure 2 Simulated dose-response for the PKPD target

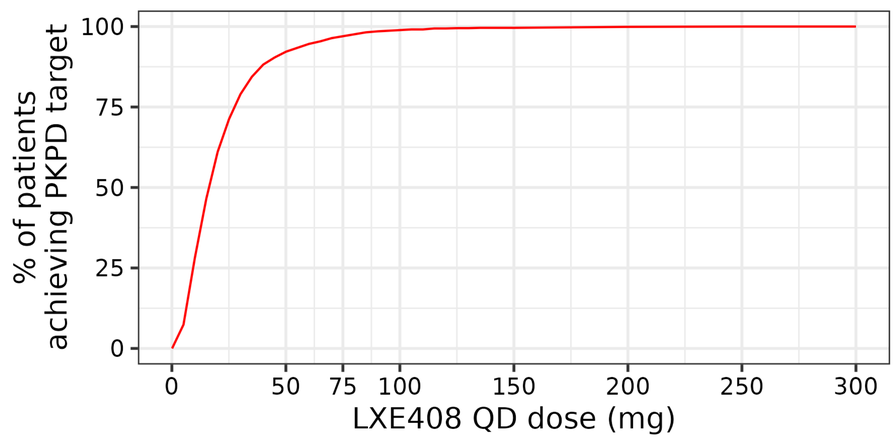
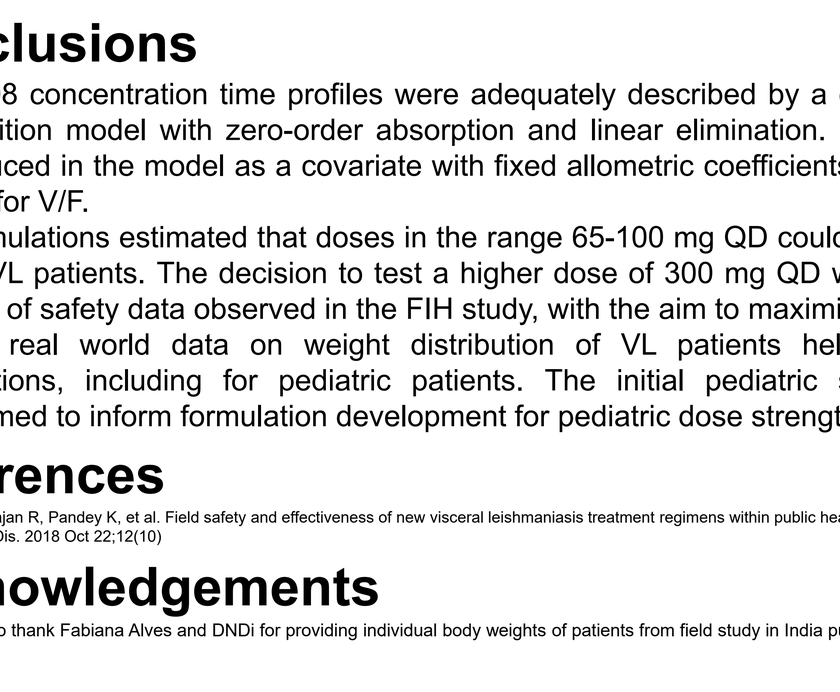


Figure 3 Simulated AUCtau,ss by body weight



Green shaded area: target exposure range (median and 5-95% percentiles) in adult VL patients receiving 300 mg QD dose; vertical error bars: exposure predictions for each given body weight from 10 to 30 kg

Conclusions

- LXE408 concentration time profiles were adequately described by a one-compartment disposition model with zero-order absorption and linear elimination. Body weight was introduced in the model as a covariate with fixed allometric coefficients of 0.75 for CL/F and 1 for V/F.
- PK simulations estimated that doses in the range 65-100 mg QD could be efficacious in adult VL patients. The decision to test a higher dose of 300 mg QD was based on the totality of safety data observed in the FIH study, with the aim to maximize efficacy.
- Using real world data on weight distribution of VL patients helped refine dose predictions, including for pediatric patients. The initial pediatric simulations were performed to inform formulation development for pediatric dose strengths.

References

[1] Goyal V, Mahajan R, Pandey K, et al. Field safety and effectiveness of new visceral leishmaniasis treatment regimens within public health facilities in Bihar, India. PLoS Negl Trop Dis. 2018 Oct 22;12(10)

Acknowledgements

We would like to thank Fabiana Alves and DNDi for providing individual body weights of patients from field study in India published in Goyal et al. 2018