Population pharmacokinetics of sutezolid and its main metabolite to characterize the exposure-response relationship in patients with pulmonary tuberculosis.

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Introduction

- Sutezolid is a novel oxazolidinone for treatment of multidrug-resistant tuberculosis.
- A potential alternative to linezolid, exhibiting comparable activity and a lower incidence of associated adverse events based on previous studies[1,2,3]."
- Metabolite may contribute to the overall efficacy[3].

Objective: Develop a parent-metabolite pharmacokinetic-pharmacodynamic model to characterize the exposure-response relationship for sutezolid in a phase IIb trial.

Methods and results

Pharmacokinetics

- A phase 2b, open-label, multicenter, randomized, controlled, clinical trial (SUDOCU) was performed[4].
- 75 participants were randomized in 5 dosing groups: 0mg, 600mg QD, 1200mg QD, 600mg BD, or 800mg BD of sutezolid, with a background of bedaquiline, delamanid, and moxifloxacin for 12 weeks.
- In total, 373 plasma concentrations each were available for both sutezolid and its metabolite.

Pharmacodynamics

- To determine the decrease in bacterial load over time on treatment, 1651 cultures were collected.
- The M3 method was used of observations that were above a selected censoring limit of 25 days.
- Bi-linear model with estimated node parameter was selected as structural model.

Exposure-response

- Linear and Emax exposure-response relationships were evaluated based on individual exposure-metrics during steady-state.

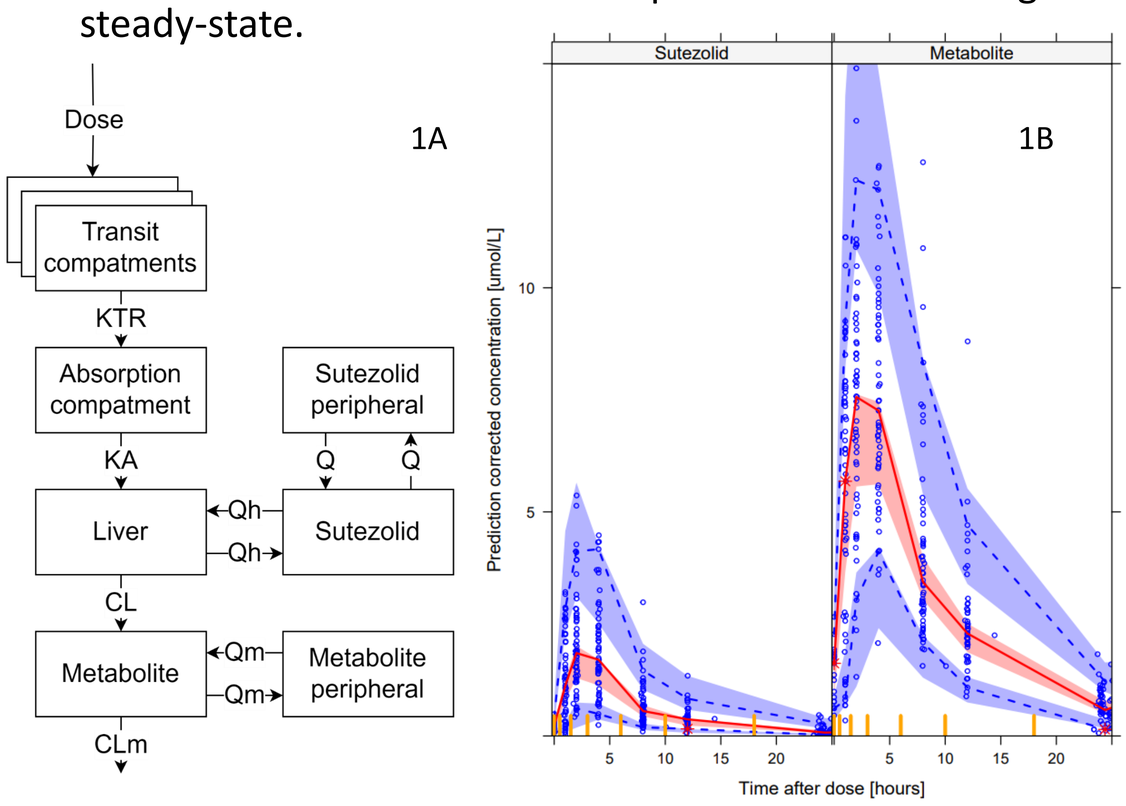

Figure1A: Schematic representation of the pharmacokinetic model of sutezolid and metabolite.
Figure 1B: Prediction corrected visual predictive check (VPC) of sutezolid (left) and metabolite (right).

Table 1: Estimated PK-PD model parameters.

Parameter	Estimate (RSE CV%)	IIV CV% (RSE CV%)
Pharmacokinetics		
Sutezolid		
Clearance/F (L/h)	352 (12%)	37.4 (15%)
Volume of distribution/F (L)	144 (7%)	-
Intercompartmental clearance/F (L/h)	17.7 (25%)	47.6[a] (20%)
Peripheral volume/F (L)	5440 (48%)	-
Absorption rate constant (/h)	0.769 (23%)	78.7 (17%)
Mean transit time (h)	0.385 (35%)	167.9 (31%)
Number of transit compartments	8 FIX	-
Proportional error (CV%)	29.5 (13%)	-
Bioavailability (%)	1 (FIXED)	36.2[b] (18%)
Fraction metabolized to main metabolite (%)	1 (FIXED)	-
Metabolite		
Clearance/(F*Fm) (L/h)	37.9 (6%)	12.2 (26%)
Volume of distribution/(F*Fm) (L)	179 (11%)	-
Intercompartmental clearance/(F*Fm) (L/h)	16.5 (16%)	47.6[a] (20%)
Peripheral volume/(F*Fm) (L)	3380 (19%)	-
Proportional error (CV%)	23.5 (11%)	
Correlation absorption rate constant – mean transit time (%)	35.6 (63%)	-
Correlation error sutezolid –error metabolite (%)	82.1 (10%)	-
Pharmacodynamics		
Baseline bacterial load (log10(h))	2.11 (1%)	6.5 (14%)
Slope 1 (log10(h)*day^{-1})	0.033 (11%)	47.1 (16%)
Slope 2 (log10(h)*day^{-1})	0.0098 (8%)	42.5 (19%)
Node (days)	8.3 (9%)	-
Additive error	0.021 (4%)	-
Lung damage effect (Ralph score) on slope2[c]	-0.58 (29%)	-
Correlation baseline bacterial load - slope 1 (%)	-51.4 (39%)	
Correlation replicate additive error (%)	22.5 (17%)	
Exposure-response		
Sutezolid effect on slope 1 and slope 2[d]	0.116 (55%)	-

a: The intercompartmental clearances for sutezolid and metabolite shared one estimated IIV. b: Inter-occasion variability. c: Covariate effect parameterized as: $(1+(value-value_{mean})/value_{mean} * Effect)$ d: exposure-response effect parameterized as: $(1+(exposure/exposure_{mean})*Effect$.

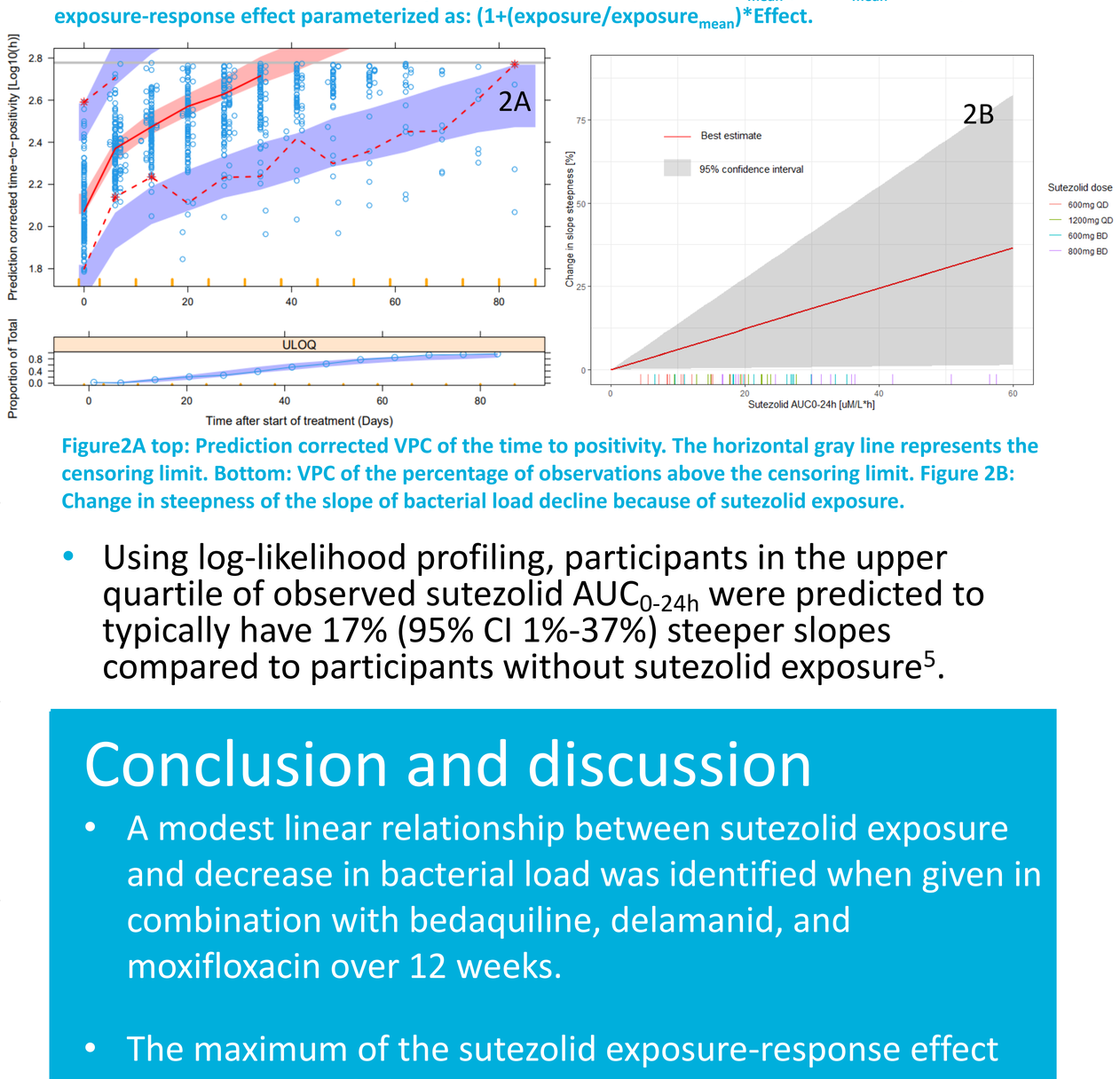

Figure2A top: Prediction corrected VPC of the time to positivity. The horizontal gray line represents the censoring limit. Bottom: VPC of the percentage of observations above the censoring limit. Figure 2B: Change in steepness of the slope of bacterial load decline because of sutezolid exposure.

- Using log-likelihood profiling, participants in the upper quartile of observed sutezolid $AUC_{0\text{-}24h}$ were predicted to typically have 17% (95% CI 1%-37%) steeper slopes compared to participants without sutezolid exposure[5].

Conclusion and discussion

- A modest linear relationship between sutezolid exposure and decrease in bacterial load was identified when given in combination with bedaquiline, delamanid, and moxifloxacin over 12 weeks.
- The maximum of the sutezolid exposure-response effect was not identifiable.
- No exposure-response relationship for the metabolite was detected.

1. Conradie. et al. N Engl J Med. 2022
2. Tasneen. et al. Antimicrob Agents Chemother. 2016
3. Wallis. et al. PLOS ONE. 2014
4. Heinrich. et al. CROI; Seattle. 2023
5. Sheiner. J Pharmacokinet Pharmacodyn. 1986

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