Population pharmacokinetics of clofazimine in a randomised controlled clinical trial for rifampicin-resistant tuberculosis

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Introduction

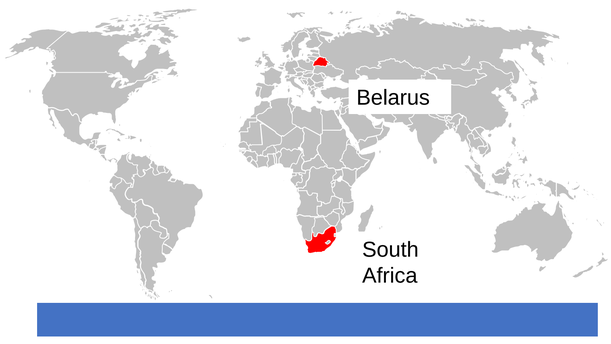
Clofazimine is a highly lipophilic riminophenazine antibiotic, with mechanism of action against *Mycobacterium tuberculosis* not completely known

- In the TB-PRACTECAL trial, participants received **clofazimine 100 mg daily for 24 weeks** as part of a **BPaLC** (bedaquiline, pretomanid, linezolid) regimen.

We aimed to characterise clofazimine pharmacokinetics in rifampicin-resistant TB patients enrolled in the TB-PRACTECAL clinical trial.

In case you missed:

TB-PRACTECAL showed that participants receiving 6-month oral **BPaLM** had 89% of favourable outcomes versus 52% in WHO-Standard of Care.
BPaL and BPaLC also proven to be effective and safe.[1]



Methods

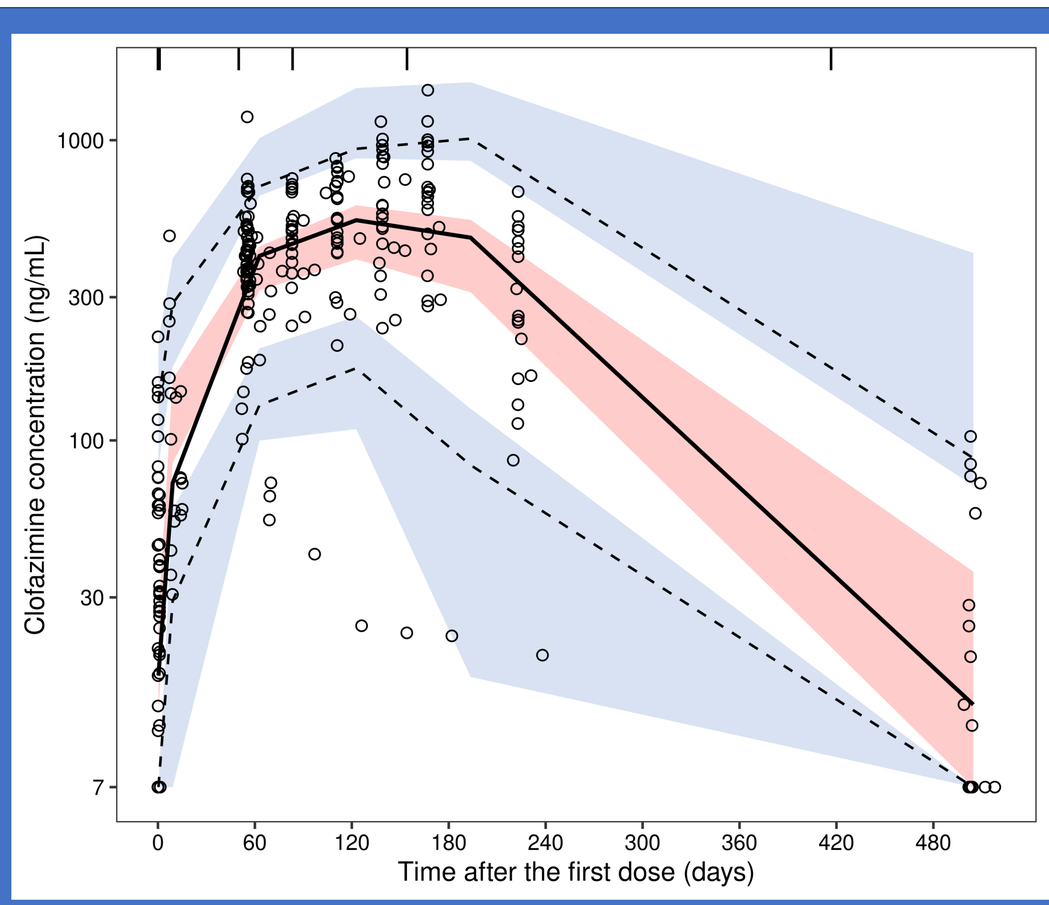
Participants from five sites in **South Africa and Belarus** without severe renal or hepatic function impairment, provided serial venous blood at:

- day 0 (0, 2, 23hrs),
- week 8 (0, 6.5, 23hrs)
- trough samples at week 12, 16, 20, 24, 32 and 72.

Quantification was conducted using HPLC MS-MS. Non-linear mixed effects modelling of the data was conducted using nlmixr2 package in r.

Results

	N (%)
Participants/obs	30/286
Female	7 (23)
HIV positive	10 (33)
Black/Caucasians	17 (57)/ 12 (40)
Mean BMI	19.7 kg/m2



Visual predictive check plot of the final clofazimine model

○ observed plasma concentrations; - median; --- 95% confidence interval; The pink and blue areas represent a simulation-based 95 % confidence interval for the median and for 5% and 95% percentiles, respectively

- A two-compartment, first order absorption and elimination model with fixed absorption rate constant (ka 0.67 h^{-1}) and lag time (0.62 hrs) [2] best described the data.
- Random effects on clearance (CL), central volume of distribution (Vc), peripheral volume of distribution (Vp) and inter-compartmental clearance (Q) were included in the model for inter-individual variability (IIV). Clearance and volume parameters were allometrically scaled by bodyweight.
- None of the tested covariates were retained in the backward step ($p<0.001$) of the stepwise covariate analysis.

Conclusions

An optimal design-led sparse sampling approach nested in a phase 3 randomised controlled trial enabled adequate characterisation of clofazimine's distribution and elimination phases. This allowed confirming clofazimine's long half-life in RR-TB patients.

Parameter	
ka [h-1]	0.67 (fixed) [1]
tlag [hrs]	0.62 (fixed) [1]
CL/F [L/hr]	6.84
Vc/F [L]	1750
Vp/F [L]	9150
Q/F [L/hr]	41.7
CL [%]	77.3%
Vc [%]	173%
Vp [%]	44.6%
Q [%]	82%
Median (range)	
C_{max} [µg/mL]	0.522 (0.005 – 1.10)
AUC_{0-24} [µg/mL]	11.4 (0.117 – 24.6)
C_{trough} [µg/mL]	0.471 (0.022 – 1.47)

Acknowledgements
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References
1. Faraj A et al. AAC 2020; 2. Nyang'wa BT et al. NEJM 2022.