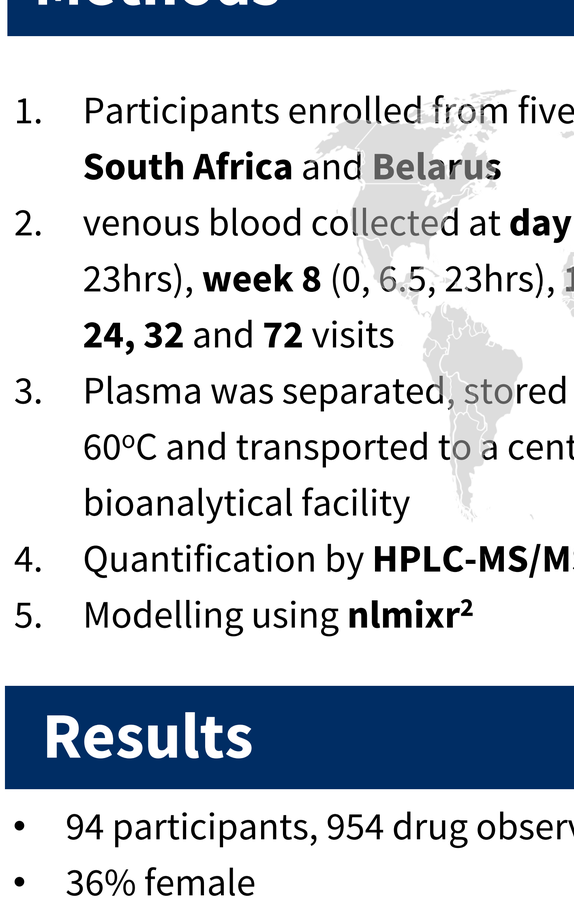
Fat-free mass affects the variability of **pretomanid AUC** and **Cmax** in **Rifampicin Resistant-TB** patients.

Introduction

Pretomanid is a nitroimidazole antibiotic with activity against both replicating and non-replicating Mycobacterium tuberculosis (TB) bacilli. We aimed to characterise pretomanid pharmacokinetics in rifampicin-resistant TB patients enrolled in the TB-PRACTECAL clinical trial. Participants received **pretomanid 200mg daily** as part of bedaquiline, pretomanid, linezolid +/- moxifloxacin +/- clofazimine regimens **for 24 weeks**.

Methods

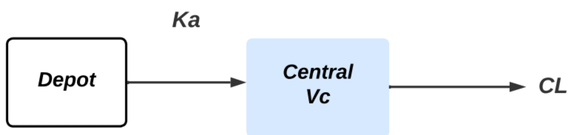
1. Participants enrolled from five sites in **South Africa** and **Belarus**
2. venous blood collected at **day 0** (0, 2, 23hrs), **week 8** (0, 6.5, 23hrs), **12, 16, 20, 24, 32** and **72** visits
3. Plasma was separated, stored at minus 60°C and transported to a central bioanalytical facility
4. Quantification by **HPLC-MS/MS**
5. Modelling using **nlmixr²**



Results

- 94 participants, 954 drug observations
- 36% female
- 42% with HIV
- No severe renal or hepatic abnormality

Final PK model



- One compartment, first order absorption and elimination model
- Covariates in forward-step ($p<0.05$)
  - BUN, Creatinine clearance, AST, race and treatment regimen
- Final covariates ($p<0.001$)
  - Fat-free mass

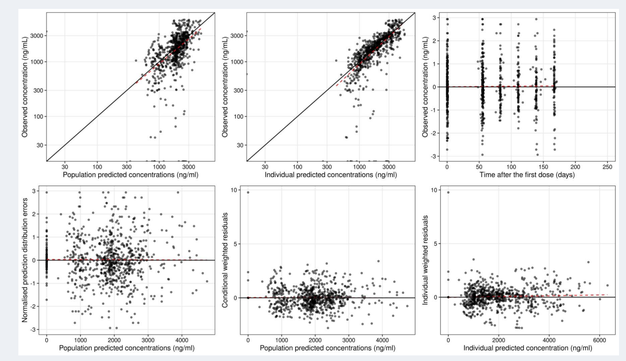
Parameter estimates

Model parameter	Estimate	95% confidence interval	Shrinkage
Ka (h^{-1})	0.316	0.233 - 0.429	
CL/F (L/hr)	3.08	2.86 - 3.32	32.7%
V/F (L)	103	85.6 - 124	35.1%
EB Estimates	**median**	**range**	
C_{max} (µg/mL)	3.18	1.38 – 6.35	
AUC_{0-24} (µg/mL)	63.8	30.9 – 139	
C_{min} (µg/mL)	1.97	0.065 - 7.70	

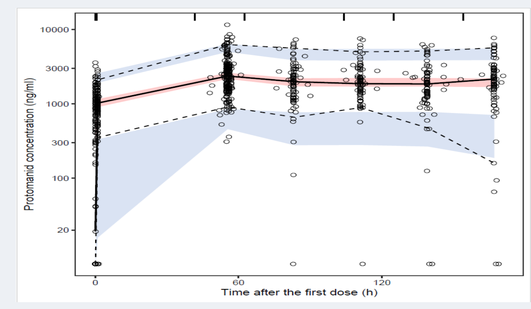
Conclusion

- Optimal design-led sparse sampling approach resulted in acceptable model
- Parameter estimates similar to those previously reported
- Need further exploration if pretomanid dose should be weight-banded to account for variability in exposure

TB Practecal
Innovating MDR-TB Treatment

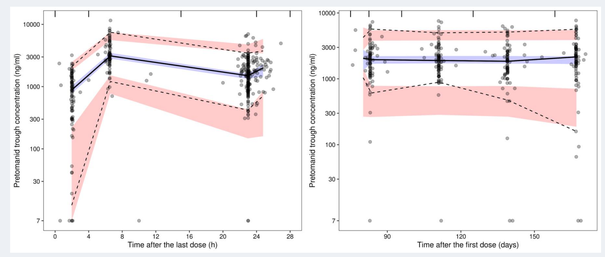


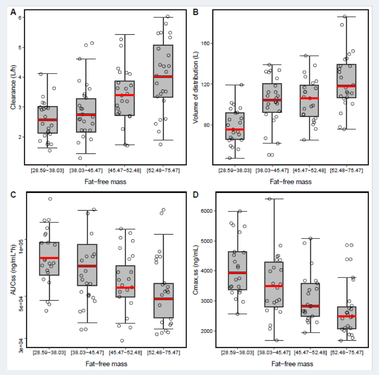
Goodness Of Fit plots clockwise from top left: DV vs PRED, DV vs IPRED, DV vs TAFD, IWRES vs IPRED, CWRES vs PRED, NPDE vs PRED



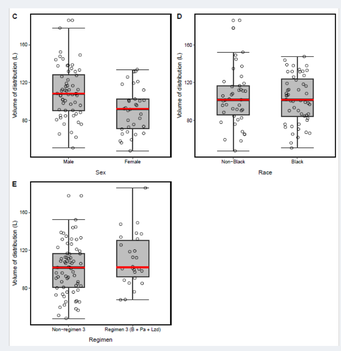
Visual Predictive Check plot of the final pretomanid model.

The black circles in the figure represents the observed plasma concentrations. Solid black line and dash black line represent the median and 95% confidence interval of observations, respectively. The purple area represents a simulation-based 95 % confidence interval for the median. Simulated prediction intervals for 5% and 95% percentiles are presented with pink





FFM vs clearance, volume of distribution, AUC and Cmax



Volume of distribution vs Sex, Race and regimen

Population pharmacokinetics of pretomanid in participants of a randomised controlled clinical trial for rifampicin-resistant tuberculosis.

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