9th SA TB Conference 2026

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Pharmacokinetics and safety of a novel clofazimine formulation and dosing strategy in children with rifampicin-resistant tuberculosis

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Background

- **~13,000** people develop rifampicin-resistant TB (RR-TB) annually in South Africa
- **~900** of these cases occur in **children** under 15 years
- The **WHO recommends** the inclusion of clofazimine as a core agent in RR-TB treatment regimens in children aged <15 years
- A 2025 global paediatric individual participant data meta-analysis reported that **45% of 20,395 children** treated for RR-TB **received clofazimine** as part of their treatment regimen
- **Limited data** on clofazimine's pharmacokinetics (PK) and safety in children

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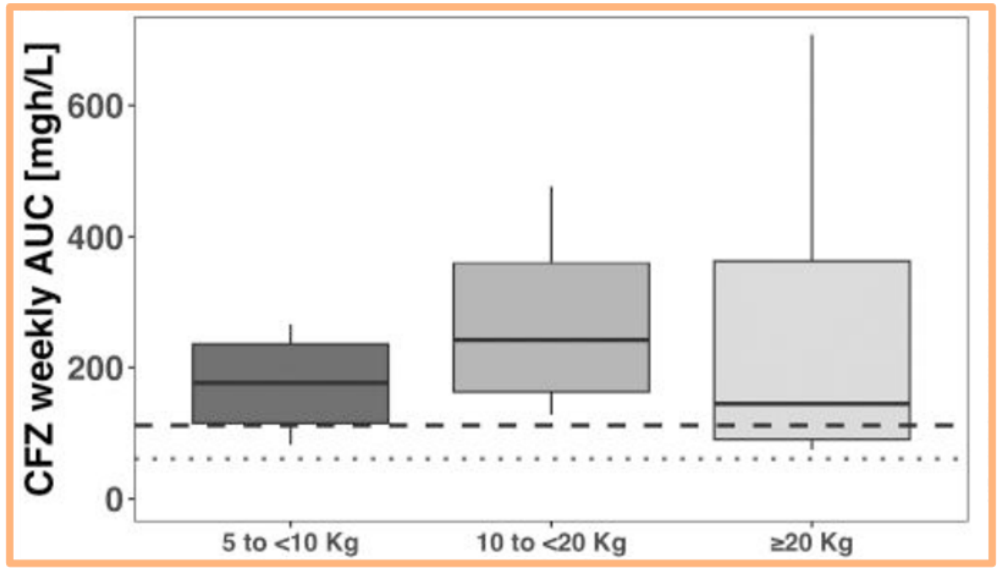
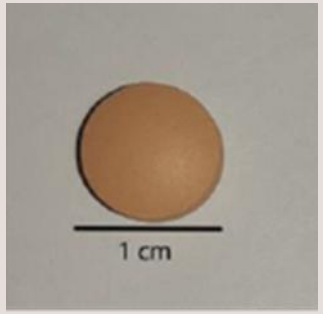
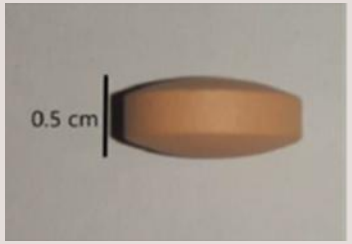


Hughes, J.A., et al., Pharmacokinetics and safety of clofazimine in children with rifampicin-resistant tuberculosis. J Infect Dis, 2025.

- This study builds on the previous **Clofazimine PK study**
- Which evaluated the pharmacokinetics, safety, and tolerability of **the 50 mg gel capsule formulation**
- **Which found that the exposures were higher than the adult target exposures**

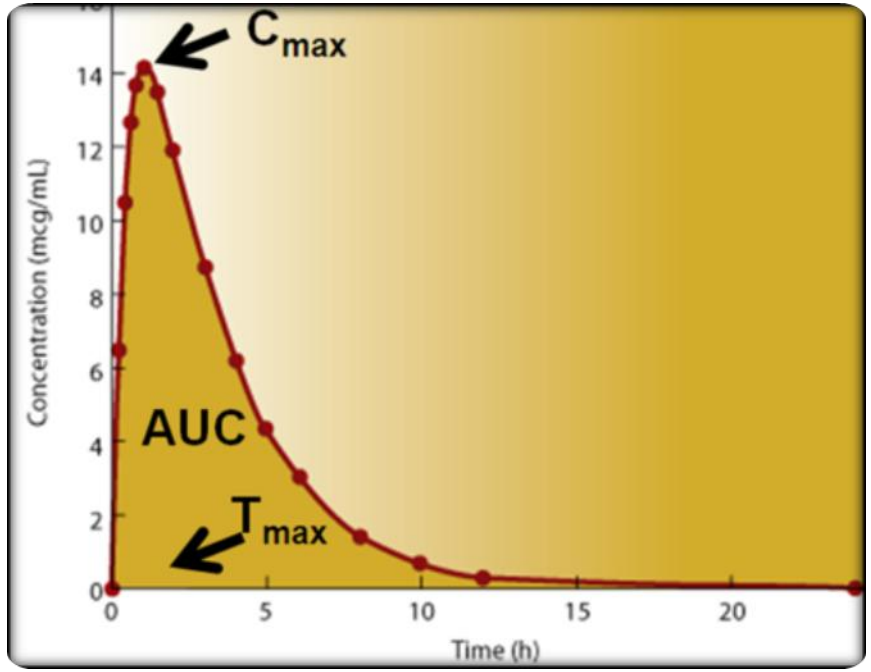
Routinely available CFZ formulation:	Study CFZ formulation:
Clofazimine Novartis 100mg 	Clofazimine Macleods 50mg  

The study aim was to evaluate:

- **Pharmacokinetics, safety and tolerability**
- **Novel 50 mg solid clofazimine tablet formulation**
- Children routinely treated for RR-TB
- **New daily dosing schedule**

Primary objectives

- Develop a **weight-banded dosing algorithm** to match adult clofazimine exposure (AUC)
- Target exposure:
  - **Daily AUC**: 15.9 mg/h/L
  - **Weekly steady-state AUC**: 111.8 mg/h/L (equivalent to 100 mg/day in adults)
- Assess **safety and tolerability** of clofazimine



Revised weight-banded dosing table

WHO weight bands (kg)	Clofazimine dose (mg)	Dosing frequency
3 to < 5 kg	15 mg	Daily
5 to < 7 kg	20 mg	Daily
7 to < 10 kg	25 mg	Daily
10 to < 16 kg	40 mg	Daily
16 to < 24 kg	50 mg	Daily
24 to < 30 kg	75 mg	Daily

Methods

- Open-label, single-arm, prospective study
- Conducted in Cape Town in 2024
- **Revised daily clofazimine dosing schedule in children weighing less than 30 kg**
- Based on **modelled pharmacokinetic data** from the Clofazimine PK study

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Methods

- Children were eligible if:
  - ✓ **under 18 years of age**,
  - ✓ **weighing less than 30 kg,**
  - ✓ **living with or without HIV,**
  - ✓ received **fewer than 12 weeks** of RR-TB treatment, including clofazimine

- Study duration = 12 weeks
- Gel capsule → daily-dosed clofazimine tablet
- Dispersed in water

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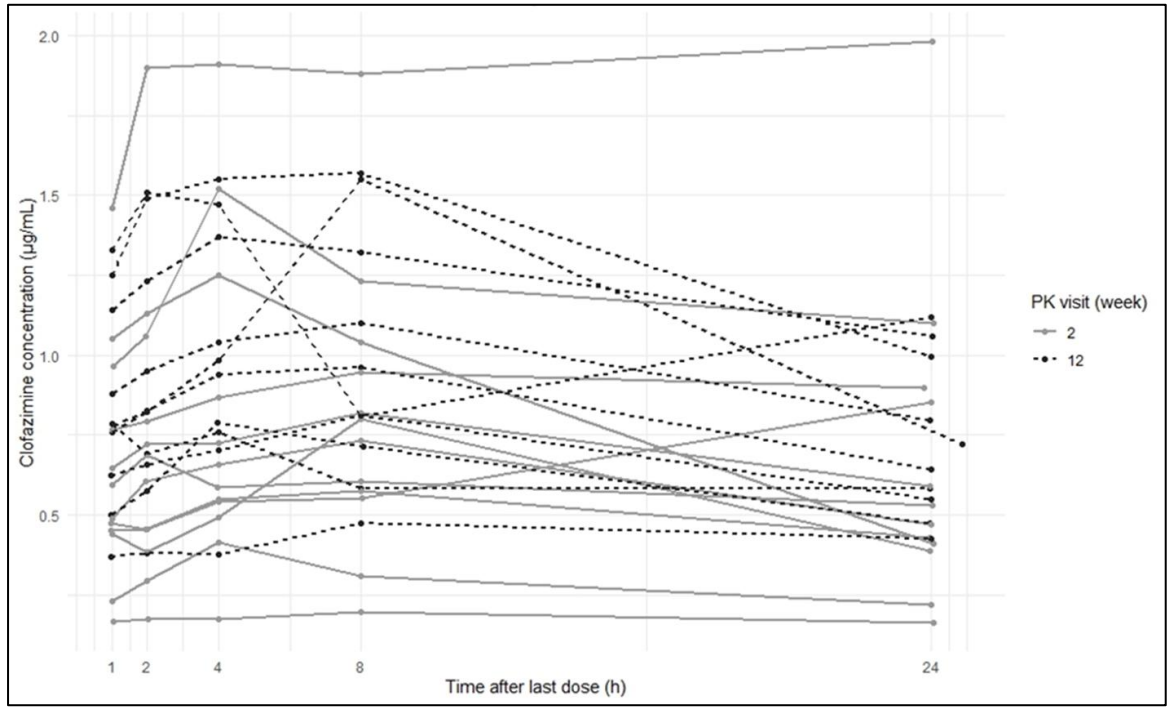
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PARTICIPANTS

	All Participants
	n=12 (%)
Male sex	5 (41.7)
Age in years: median (IQR)	2.8 (2.0, 5.0)
Weight in kg: median (IQR)	12.0 (10.5, 17.2)
PTB disease classification	
Clinically diagnosed	7 (58.3)
Microbiologically confirmed	5 (41.7)
Time on TB treatment before enrolment: weeks (IQR)	6.4 (3.0, 8.6)
Number of participants receiving bedaquiline (%)	12 (100.0)
Number of participants receiving delamanid (%)	1 (8.3)
Number of participants receiving levofloxacin (%)	11 (91.7)

PK RESULTS

Raw concentrations of clofazimine against time after last dose per visit week:



Model derived pharmacokinetic parameters

Parameter	Median	Range
$C_{max,}$ week 12 (µg/mL)	1.08	(0.464-1.53)
$T_{max,}$ week 12 (h)	8.17	(7.42-8.59)
$wAUC_{ss}$ (mg·h/L)	**107**	(76.7-273)
$AUC_{0\text{-}24h,,}$ week 2 (mg·h/L)	14.7	(4.23-45.2)
$AUC_{0\text{-}24h,}$ week 12 (mg·h/L)	22.9	(10.0-34.0)

Abbreviations: C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC, area-under-the curve; $wAUC_{ss}$, weekly steady-state area-under-the vurve.

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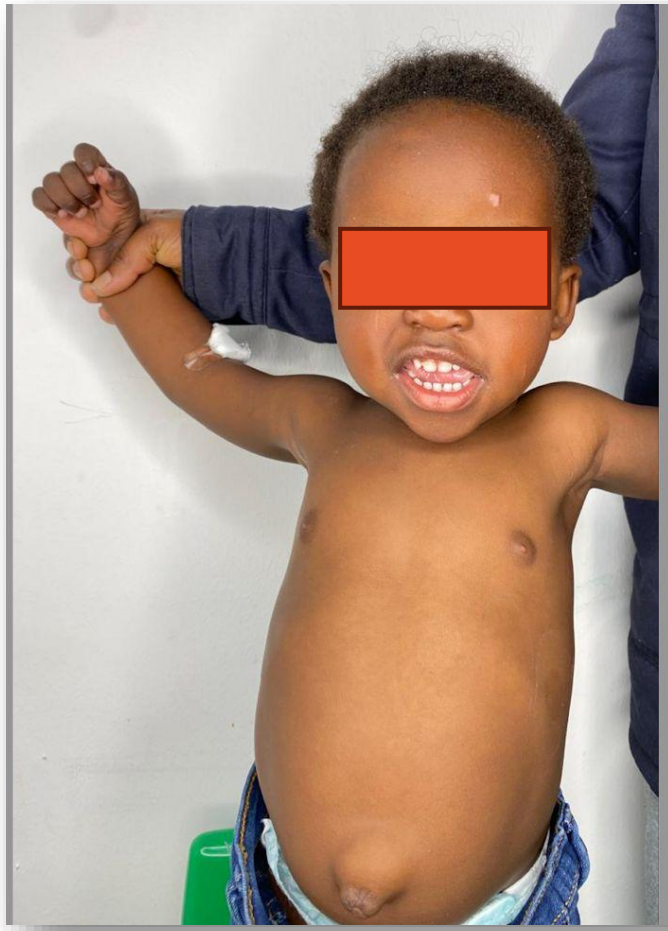
SAFETY RESULTS

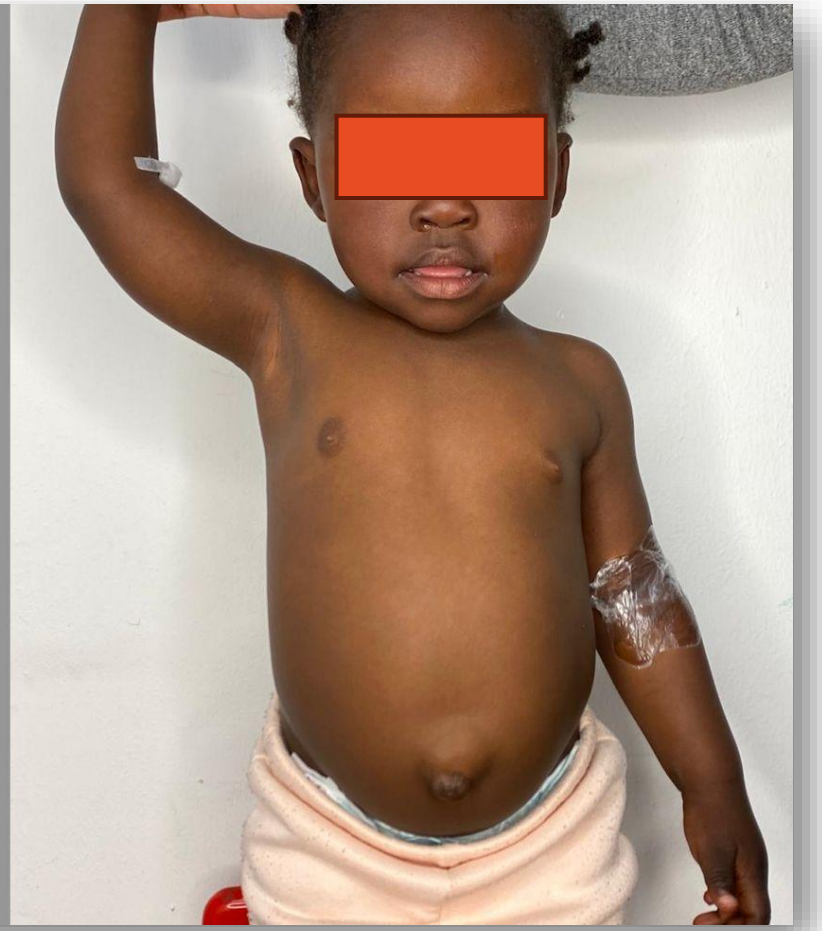
Frequency of adverse events at least possibly related to clofazimine

		Maximum Severity				
Organ System Classification	Number participants with event	Grade 1/ Mild	Grade 2/ Moderate	Grade 3/ Severe	Grade 4/Life-threatening	Total # events N=26
Eye disorders						
Discoloured sclerae	1	1	0	0	0	1
Skin disorders						
Skin hyperpigmentation	**10***	2	7	1	0	10
Ichthyosis	6	4	2	0	0	6
Pruritus	2	1	1	0	0	2
Xerosis	1	1	0	0	0	1
Hepatobiliary disorders						
Drug induced liver injury	**1**	0	0	1	0	1
Cardiac						
Prolonged QTcF (≥460ms)	**3**	5	0	0	0	5

SKINHYPERPIGMENTATION



Enrolment



Week 12 of study

*PHOTOGRAPH USED WITH PERMISSION

CONCLUSION

- Revised dosing strategy **successfully achieved the intended pharmacokinetic targets**
- Exhibited an **acceptable safety profile** in children
- Support **consideration of the revised once-daily** tablet strategy by **guideline groups and national TB programmes** for children <30 kg

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RECOMMENDATIONS

- **Larger, diverse cohorts** with representation across all weight bands, longer safety follow-up, and implementation data are needed
- **Combined analyses across existing paediatric and adult datasets**

These results contribute meaningfully to the growing body of evidence on clofazimine pharmacokinetics and safety in children

ACKNOWLEDGEMENTS

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- Entire CFZ study team at DTTC
- Participants and caregivers

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