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IMPAACT 2034: PHARMACOKINETICS, SAFETY, & ACCEPTABILITY OF SINGLE-DOSE PRETOMANID IN FEMALE CHILDREN WITH RIFAMPICIN-RESISTANT TUBERCULOSIS (RR-TB)

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Introduction

- **Pretomanid is approved in adults** for the treatment of rifampicin-resistant tuberculosis (TB)

Pretomanid is not available to children under age 14 years

- IMPAACT 2034 is a **first-in-children**, multisite, open label study investigating the **pharmacokinetics (PK), safety/tolerability, and acceptability of a single dose of pretomanid** in female children with rifampicin-resistant TB (RR-TB)
  - **10-mg and 50-mg dispersible, scored tablet formulations** were developed for **paediatric use** and used in this study; shown in healthy adults to achieve exposures similar to the adult marketed formulation

Design and Methods

- Female children with RR-TB (confirmed or probable) on optimized background regimen (OBR)
- All received a **single, weight band-based dose of pretomanid (3.2 to 6.3 mg/kg)**
- Procedures
  - Intensive PK sampling through 48 hours
    - PK data evaluated by noncompartmental analysis and population pharmacokinetic modeling
  - Acceptability questionnaires
  - Safety follow-up at 2 weeks

Enrolled at 3 sites in South Africa (n=26) & 1 site in Thailand (n=2)

Study Group (Weight range)	Pretomanid Dose (formulation)
1 (>31 kg)	≥40kg: 200 mg (adult) 31-<40kg: 100 mg (paeds)
2 (20-<31 kg)	100 mg (paeds)
3 (12-<20 kg)	75 mg (paeds)
4 (4-<12 kg)	8-<12kg: 50 mg (paeds) 6-<8kg: 35 mg (paeds) 4-<6kg: 20 mg (paeds)

Study Objectives

In children with RR-TB on an optimized background regimen:

Primary Objective

- Evaluation of the **PK of a single dose of pretomanid to identify modeled weight-based doses of pretomanid** for future evaluation in a multiple-dose study

Secondary Objectives

- **Safety and tolerability** of a single dose of pretomanid
- **Acceptability and palatability** of pretomanid formulations

Baseline characteristics of children (n=28)

Sex	Female	28 (100%)
Race	Black	26 (93%)
	Asian	2 (7%)
Age, years	Median (min, max)	5.0 (0.6, 17.6)
HIV status	Living with HIV	7 (25%)
Weight, kg	Median (min, max)	15.1 (6.9, 56.8)
Study Weight Group	**1** (≥31 kg)	8
	2 (20-<31 kg)	2
	3 (12-<20 kg)	8
	4 (4-<12 kg)	10

TB Diagnostic Criteria	Confirmed TB	13 (46%)
TB Disease Severity	Severe	10 (36%)
Pulmonary or Extrapulmonary Disease	Pulmonary TB	22 (79%)
	Extrapulmonary TB	2 (7%)
	Both	4 (14%)
OBR Included	Levofloxacin	24 (86%)
	Clofazimine	23 (82%)
	Terizidone	21 (75%)
	Linezolid	19 (68%)
	Bedaquiline	18 (64%)

Also: delamanid (13, 46%), isoniazid (3, 11%), aminosalicylate sodium (2, 7%), cycloserine (2, 7%), meropenem (1, 4%), ertapenem (1, 4%)

Safety

Safety, n (%)	Overall, n=28	Group 1 (≥31 kg), n=8	Group 2 (20-<31 kg), n=2	Group 3 (12-<20 kg), n=8	Group 4 (4-<12 kg), n=10
Grade 1 or higher AE	25 (89.3%)	6 (75%)	2 (100%)	7 (87.5%)	10 (100%)
Grade 3 or higher AE	2 (7.1%)	1 (12.5%)*	0 (0%)	0 (0%)	1 (10%)**
Grade 2 or higher AE related to study drug	1 (3.6%)	0 (0%)	0 (0%)	1 (12.5%)***	0 (0%)
SAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Hypoglycemia; **Neutropenia; ***Low GFR

QTcF Interval

Mean QTcF (ms)		Change in QTcF (ms)	Grade
Pre-dose	Post-dose		
445	466	21	0 → 1
468	456	-12	1 → 1

All other QTcF were normal; ΔQTc <50 ms

Acceptability & Palatability of Pretomanid

Adult 200 mg tablet		n=4
Ease of swallowing	Easy	4 (100%)
Taste	Good	1 (25%)
	Neutral	3 (75%)
Tablet size & shape	No issues	3 (75%)
	A little large but manageable	1 (25%)

Paediatric dispersible tablet		n=24
Ease of swallowing	Easy	21 (88%)
	Medium	2 (8%)
	Difficult	1 (4%)
Taste	Very good or good	11 (46%)
	Neutral	11 (46%)
	Bad or very bad	2 (8%)
Volume of liquid	No issues	23 (96%)
	Unmanageable	1 (4%)

Pharmacokinetics of Pretomanid in Children

Interim analysis performed to examine safety and confirm sample size adequate:

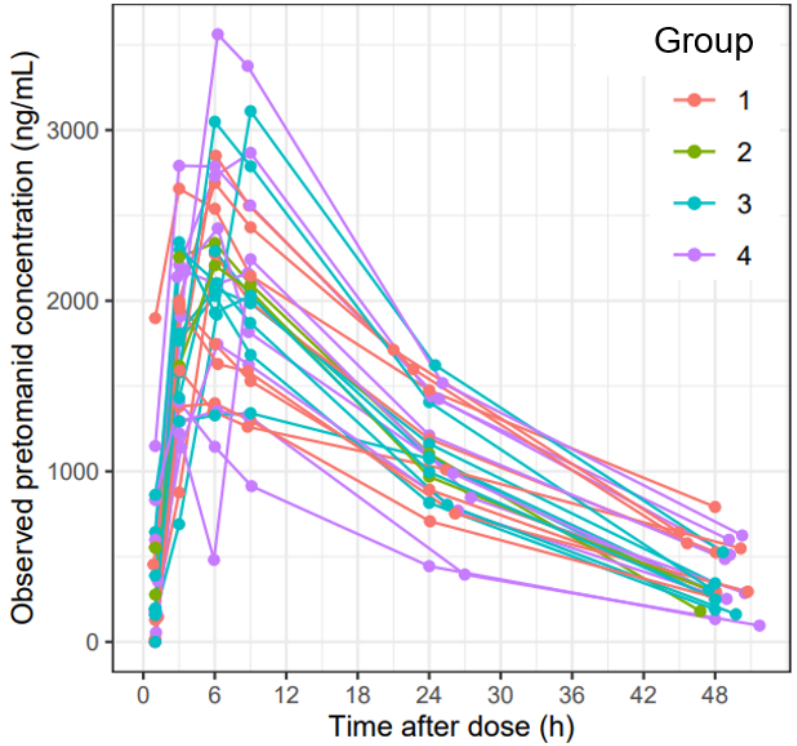
28 safety evaluable participants (of which 27 were PK evaluable)

A previously developed PK model based on data from 3 pretomanid studies in adults was used as the starting point for the PK analysis (ZeNix, Nix-TB, CL-011 [relative BA study for pediatric formulation]).

PK Parameter, median (range)	All (N=27)	Group 1 (n=8)	Group 2 (n=2)	Group 3 (n=8)	Group 4 (n=9)
C_{max} (ng/mL)	2275 (1341-3562)	2124 (1399-3850)	2272 (2207-2338)	2295 (2060-2520)	2243 (1354-3562)
$AUC_{0-\infty}$ (µg*h/mL) (model)	59.6 (28-95.9)	66.2 (45.9-94)	58.6 (58.1-59.1)	57.5 (46.8-85.5)	59.8 (28-95.9)

For reference, exposure median (range) in adult trials was:

C_{max} 1975 ng/mL (1120-3270) and **steady-state AUC_{0-24} 59.5 µg*h/mL** (28.7-117)



Conclusions

- **Safety** of a single dose of pretomanid was **acceptable** across all weight groups
- **Acceptability** of the pretomanid formulation, including the child-friendly dispersible tablet, was **favorable**
- Study doses achieved **exposures in children that were comparable** to those in healthy adults and adults treated for TB (C_{max} and AUC)
- In female children with RR-TB, the PK of a single dose of pretomanid was characterized with adequate precision to guide weight-based doses
  - ✓ There was sufficient statistical power to **select doses for a future multiple dose study in children**

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