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# Case Studies of Model-based Approaches used in Designing and Conducting Clinical Trials in Pregnant Women and Pediatrics

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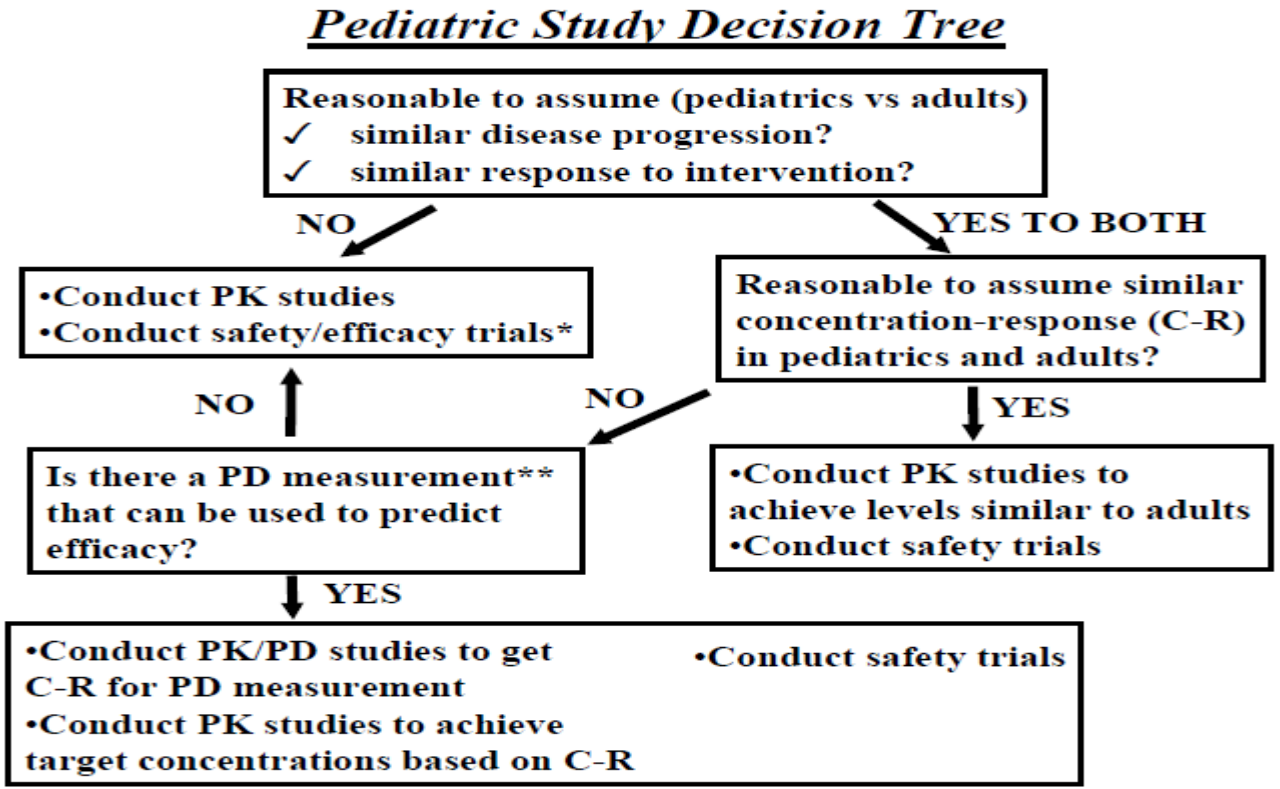
6/22/2016

# FDA recommended pediatric decision tree integration of PKPD




http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm073007.pdf

# What the models are used for?

- Dose Selection
  - Equivalence approach
  - Prior knowledge on clearance ontogeny
- Sample Size
  - Expectation to justify the choice of sample size for pediatric trials through modelling of adult  or relevant pediatric data and simulation of pediatric study
- Sampling Schedule
  - Timing and sampling frequency

# Outline

- **IMPAACT 2001 (PI: Jyoti Mathad)**

Dose Finding study of Rifapentine for Treatment of Latent TB in pregnant women

- **TBTC STUDY 35 (CDC & Sanofi) PI: Anneke Hesseling**

Dose Finding study of Rifapentine for Treatment of Latent TB in children 0-12

- **TBM KIDS (NICHD R01) PI: Kelly Dooley**

Tuberculosis Meningitis – Optimized Pediatric Dosing

- **MDR KIDS 2 (NICHD R01) PI: Tony Garcia-Prats & Rada Savic**

Optimized dosing of Moxifloxacine, Levofloxacin and Linezolid

# Adult Study and Prior PK and Safety data

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D.,
Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackm
Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D
Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsbu
for the TB Trials Consortium PREVENT T

Rifapentine Pharmacokinetics and Tolerability in Children and Adults Treated Once Weekly With Rifapentine and Isoniazid for Latent Tuberculosis Infection

Marc Weiner,[1,2,a] Radojka M. Savic,[3,a] William R. MacKenzie,[4] Diane Wing,[1] Charles A. Peloquin,[5] Melissa Engle,[1] Erin Bliven,[4] Thomas J. Prihoda,[6] Jonathan A. L. Gelfond,[7] Nigel A. Scott,[4] Susan M. Abdel-Rahman,[8] Gregory L. Kearns,[8] William J. Burman,[9] Timothy R. Sterling,[10] and M. Elsa Villarino[4]; for the Tuberculosis Trials Consortium PREVENT TB Pharmacokinetic Group

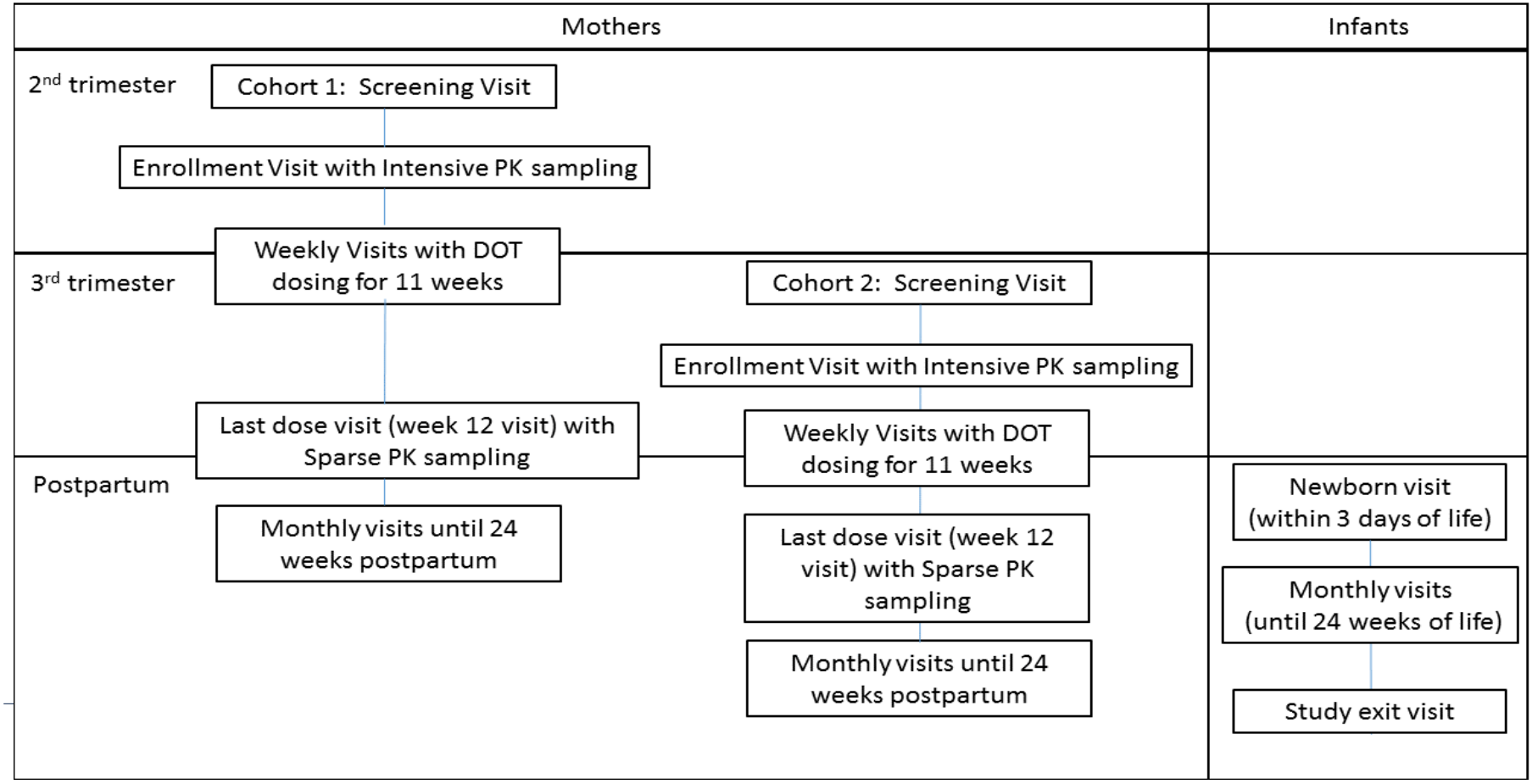
# IMPAACT 2001

- A Phase I/II Trial of the Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-infected and HIV-1-uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection
- Aim: To determine the optimal dose of RPT in the second and third trimesters of pregnancy and postpartum and to ensure enough safety data are collected at the targeted dose
- Study should provide guidance for extending treatment recommendations and drug label to this population

# Modeling Features

- Assessment of longitudinal changes in CL in pregnancy and postpartum (every women sampled twice)
  - Each women its own control – maximize power to detect pregnancy dependent change
- Interim analysis after 12 women in each cohort
- Early PK sampling (day 1) – interim analysis done as soon as feasible
- Dose adaptation planned after interim analysis
- Sparse sampling

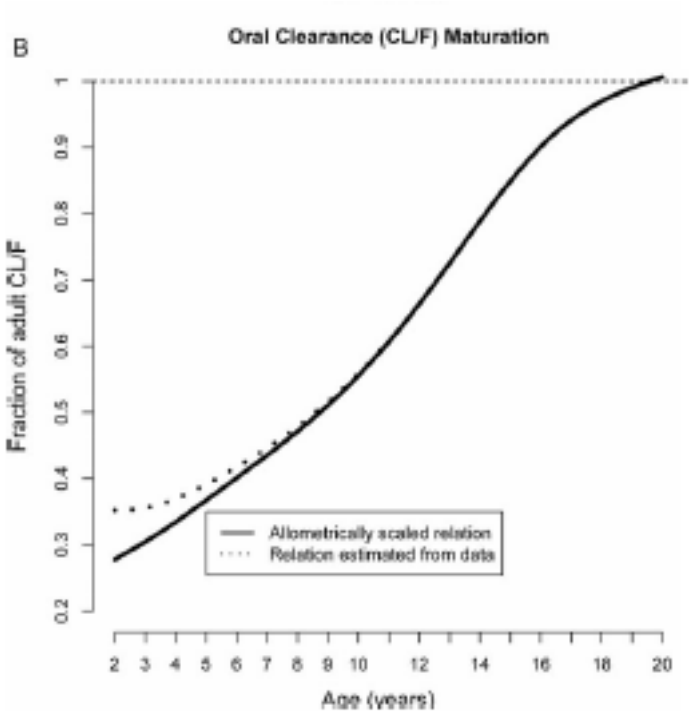
# Study schema

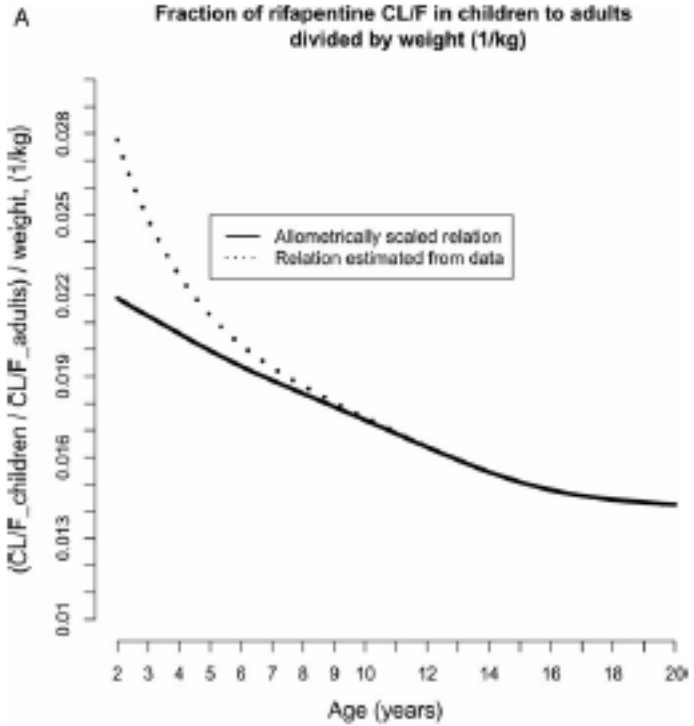


# Tuberculosis Trials Consortium (TBTC) Study 35 (S35):

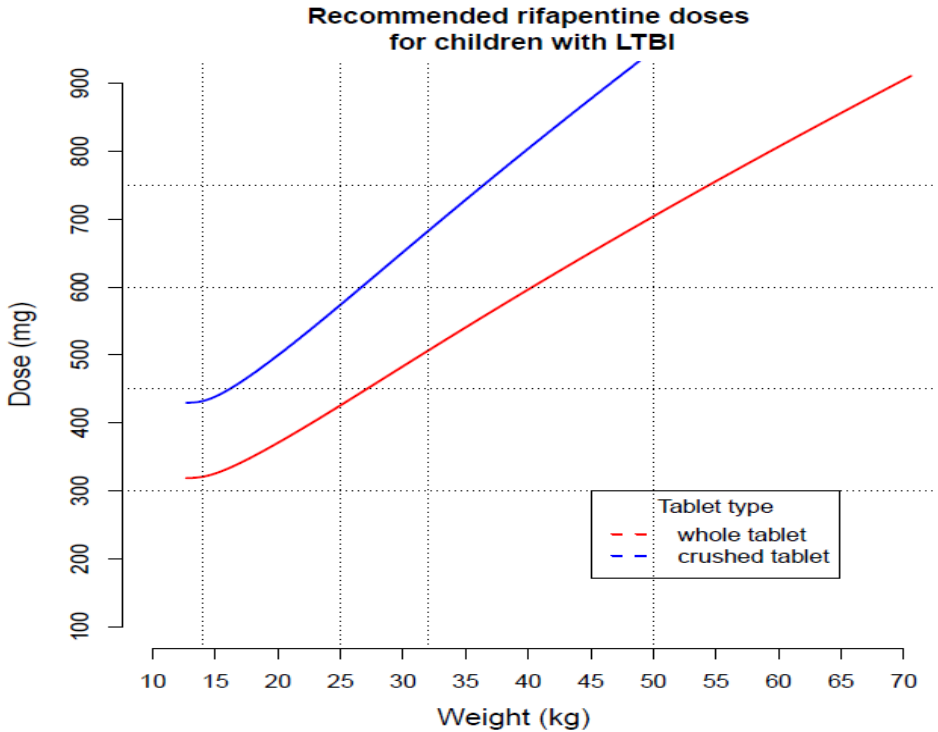
- Phase I/II Dose Finding And Safety Study Of Rifapentine in HIV-Infected And HIV-Uninfected Children With Latent Tuberculosis Infection
- a Phase I/II, open-label, single arm, exposure-controlled dose finding study using an adaptive design.

# Developmental Pharmacology



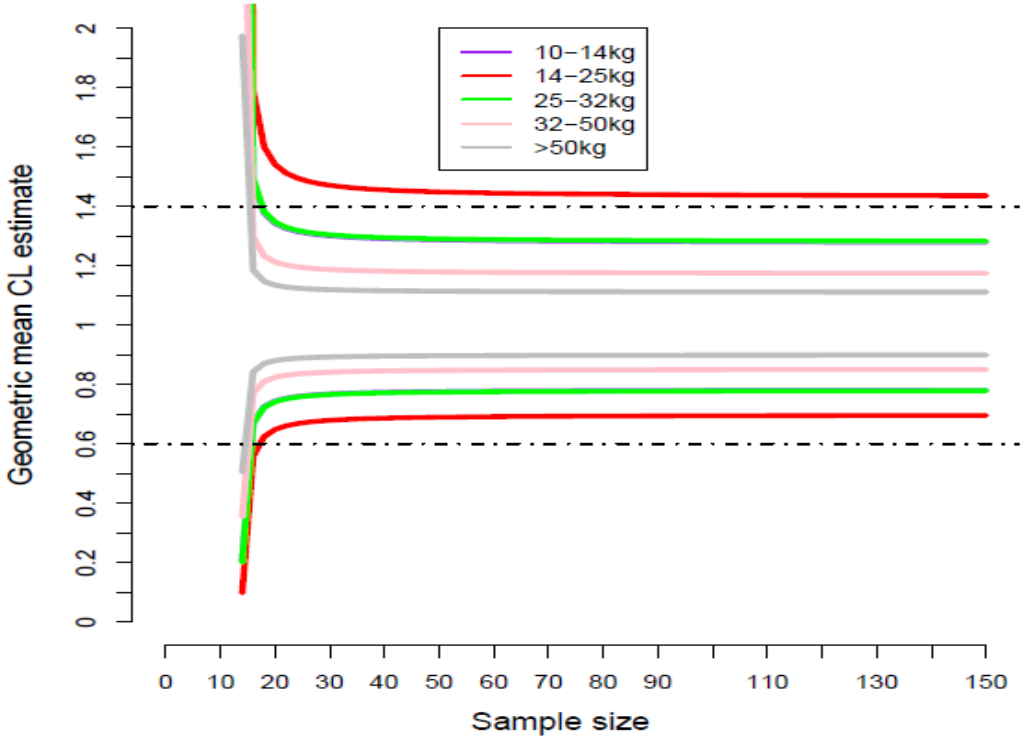



# Derive and Justify Dose Selection



# Justify the sample size:

## How certain we are about the estimates given the sample size of children in each WT group?




The FDA target

**Table 7B.** The Modeled Algorithm Estimates for Whole Tablet Administration of Rifapentine Dose (mg) by Age and Percentile Weight[a]

| Age (y) | Whole Tablet Dose (mg) of Rifapentine by Percentile Weight (Table 7A) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | p3 | p5 | p10 | p25 | p50 | p75 | p90 | p95 | p97 |
| 2 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |
| 2.5 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |
| 3 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 450 |
| 3.5 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 450 | 450 |
| 4 | 300 | 300 | 300 | 300 | 300 | 300 | 450 | 450 | 450 |
| 4.5 | 300 | 300 | 300 | 300 | 300 | 300 | 450 | 450 | 450 |
| 5 | 300 | 300 | 300 | 300 | 300 | 450 | 450 | 450 | 450 |
| 5.5 | 300 | 300 | 300 | 300 | 300 | 450 | 450 | 450 | 450 |
| 6 | 300 | 300 | 300 | 300 | 300 | 450 | 450 | 450 | 450 |
| 6.5 | 300 | 300 | 300 | 300 | 450 | 450 | 450 | 450 | 450 |
| 7 | 300 | 300 | 300 | 300 | 450 | 450 | 450 | 450 | 600 |
| 7.5 | 300 | 300 | 300 | 450 | 450 | 450 | 450 | 600 | 600 |
| 8 | 300 | 300 | 300 | 450 | 450 | 450 | 600 | 600 | 600 |
| 8.5 | 300 | 300 | 450 | 450 | 450 | 450 | 600 | 600 | 600 |
| 9 | 450 | 450 | 450 | 450 | 450 | 450 | 600 | 600 | 600 |
| 9.5 | 450 | 450 | 450 | 450 | 450 | 600 | 600 | 600 | 750 |
| 10 | 450 | 450 | 450 | 450 | 450 | 600 | 600 | 750 | 750 |
| 10.5 | 450 | 450 | 450 | 450 | 600 | 600 | 600 | 750 | 750 |
| 11 | 450 | 450 | 450 | 450 | 600 | 600 | 750 | 750 | 750 |
| 11.5 | 450 | 450 | 450 | 600 | 600 | 600 | 750 | 750 | 900 |

Abbreviations: p3, 3rd percentile; p5, 5th percentile; pN, Nth percentile.
[a]The percentile weight is identified in Table 7A by age (y) and weight (kg).

**Table 7C.** The Modeled Algorithm Estimates for Crushed Tablet Administration of the Rifapentine Dose (mg) by Age and Percentile Weight[a]

| Age (y) | Crushed Tablet Dose (mg) of Rifapentine by Percentile Weight (Table 7A) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | p3 | p5 | p10 | p25 | p50 | p75 | p90 | p95 | p97 |
| 2 | 300 | 300 | 450 | 450 | 450 | 450 | 450 | 450 | 450 |
| 2.5 | 300 | 300 | 450 | 450 | 450 | 450 | 450 | 450 | 450 |
| 3 | 300 | 300 | 450 | 450 | 450 | 450 | 450 | 450 | 450 |
| 3.5 | 300 | 450 | 450 | 450 | 450 | 450 | 450 | 450 | 600 |
| 4 | 450 | 450 | 450 | 450 | 450 | 450 | 450 | 600 | 600 |
| 4.5 | 450 | 450 | 450 | 450 | 450 | 450 | 600 | 600 | 600 |
| 5 | 450 | 450 | 450 | 450 | 450 | 450 | 600 | 600 | 600 |
| 5.5 | 450 | 450 | 450 | 450 | 450 | 600 | 600 | 600 | 600 |
| 6 | 450 | 450 | 450 | 450 | 450 | 600 | 600 | 600 | 600 |
| 6.5 | 450 | 450 | 450 | 450 | 450 | 600 | 600 | 600 | 750 |
| 7 | 450 | 450 | 450 | 450 | 600 | 600 | 600 | 750 | 750 |
| 7.5 | 450 | 450 | 450 | 450 | 600 | 600 | 750 | 750 | 750 |
| 8 | 450 | 450 | 450 | 600 | 600 | 600 | 750 | 750 | 750 |
| 8.5 | 450 | 450 | 450 | 600 | 600 | 600 | 750 | 750 | 900 |
| 9 | 450 | 450 | 600 | 600 | 600 | 750 | 750 | 900 | 900 |
| 9.5 | 600 | 600 | 600 | 600 | 600 | 750 | 750 | 900 | 900 |
| 10 | 600 | 600 | 600 | 600 | 750 | 750 | 900 | 900 | 900 |
| 10.5 | 600 | 600 | 600 | 600 | 750 | 750 | 900 | 900 | 1050 |
| 11 | 600 | 600 | 600 | 750 | 750 | 900 | 900 | 1050 | 1050 |
| 11.5 | 600 | 600 | 600 | 750 | 750 | 900 | 1050 | 1050 | 1050 |

Abbreviations: p3, 3rd percentile; p5, 5th percentile; pN, Nth percentile.
[a]The percentile weight is identified in Table 7A by age (y) and weight (kg).

# Study 35: Cohorts

| Table 1. Minimum evaluable number of participants per age group and by HIV status | | | | |
|---|---|---|---|---|
| **Cohort** | **Age** | **Total number** | **Number HIV-infected** | **Number HIV-uninfected** |
| 1 | ≥ 6 to ≤ 12 years | 18 | 6 | 12 |
| 2 | ≥ 24 months to < 6 years | 18 | 6 | 12 |
| 3 | ≥ 12 to < 24 months | 12 | - | 12 |
| 4 | 0 to < 12 months | 12 | - | 12 |
| | Total | 60 | 12 | 48 |

# Design

- The study utilizes a modified age de-escalation approach given the extensive PK and safety data already available in children older than 2 years of age.
- The protocol allows for parallel enrolment of children into cohorts 1 and 2, simultaneously, using a predetermined modeled initial dose for each cohort, separately.

# Modeling Features

- Powered to asses developmental changes in CL
- Initial doses should be “optimal”  based on all prior knowledge
- Cohort enrichment for the < 2 yrs (24 kids)
- Interim analysis after 6 children in first two cohorts (n=12)
- Early PK sampling (day 1) – interim analysis done as soon as feasible
- Dose adaptation planned after interim analysis
- Sparse sampling
- HIV children (12 kids > 3 yrs)
- Utilization of prior knowledge

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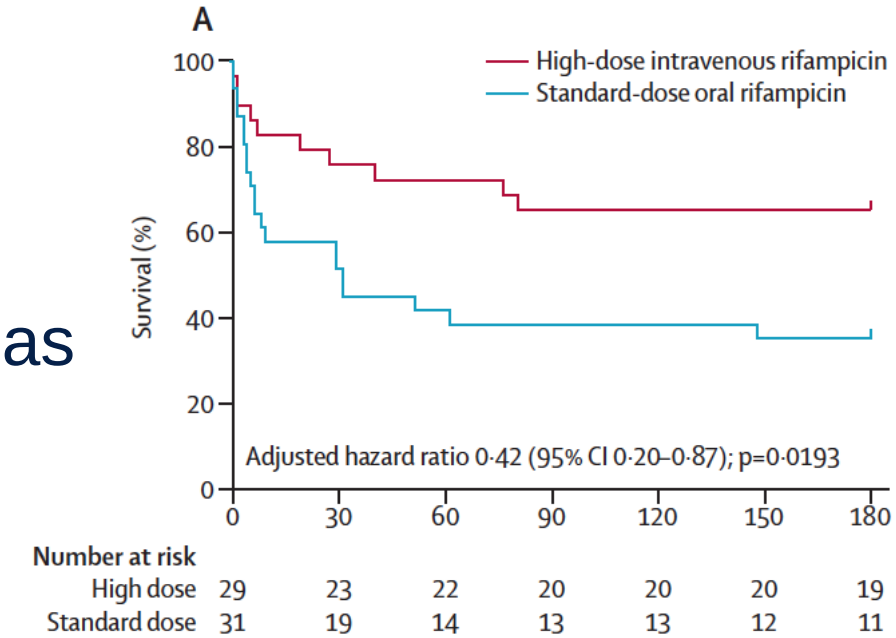
# TBM KIDS

## *Dose optimization of Rifampin and Levofloxacin in children for treatment of TB Meningitis*

6/22/2016

# TB Meningitis (TBM)

- 1% of all TB cases
- High morbidity & mortality
- Peak 0-4 y in endemic areas




*High dose IV Rifampin Improves Survival*

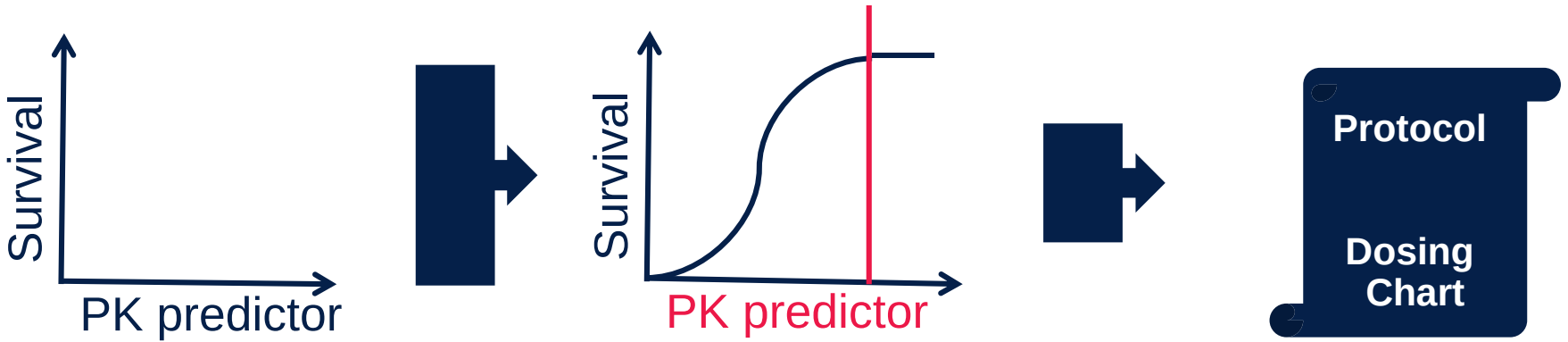
Ruslami *et al*. Lancet, Jan 2013

# Modeling methodology

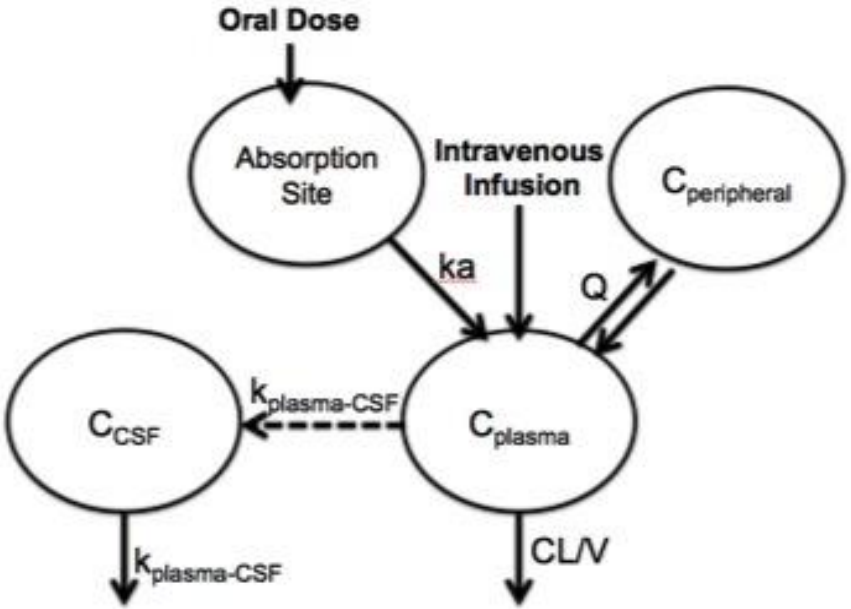
**Pharmacokinetic & Outcome Data**

**Target 99% of Maximum Response**

**Translate to Pediatric Population**



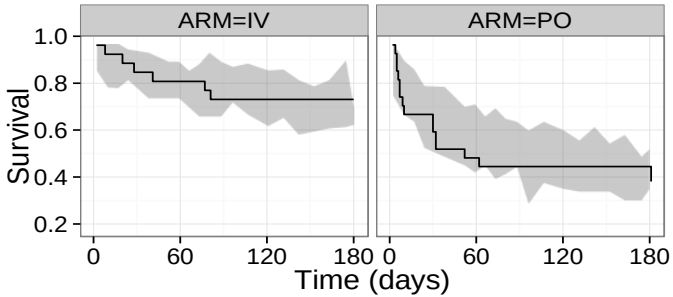
# 1. Pharmacokinetic Model



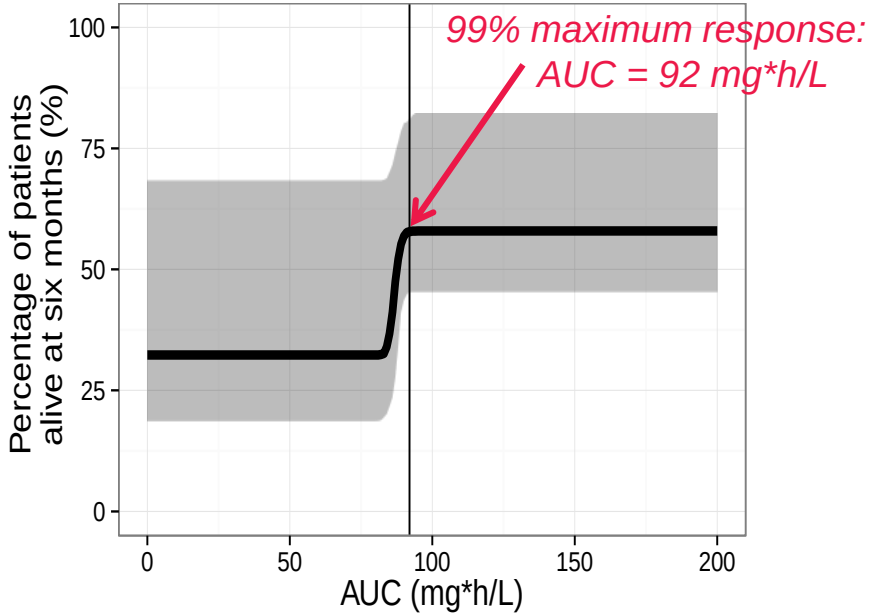
# 3. Exposure - response

| Covariate | -2Log Likelihood | P Value |
|---|---|---|
| ARM | 295.7 | 0.076 |
| $AUC_p$ | 291.6 | 0.010 |
| $Cmax_p$ | 293.1 | 0.020 |
| $AUC_{CSF}$ | 294.3 | 0.037 |
| $Cmax_{CSF}$ | 294.0 | 0.033 |

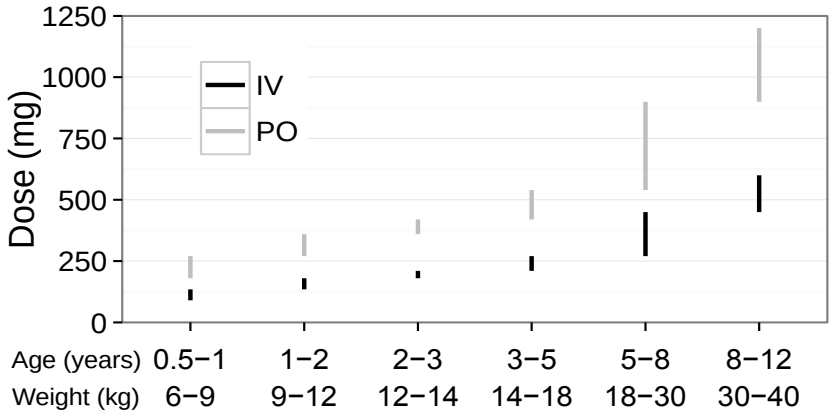
## Visual Predictive Check




## Exposure-Response Simulation



# Conclusion: Final Protocol Interventions

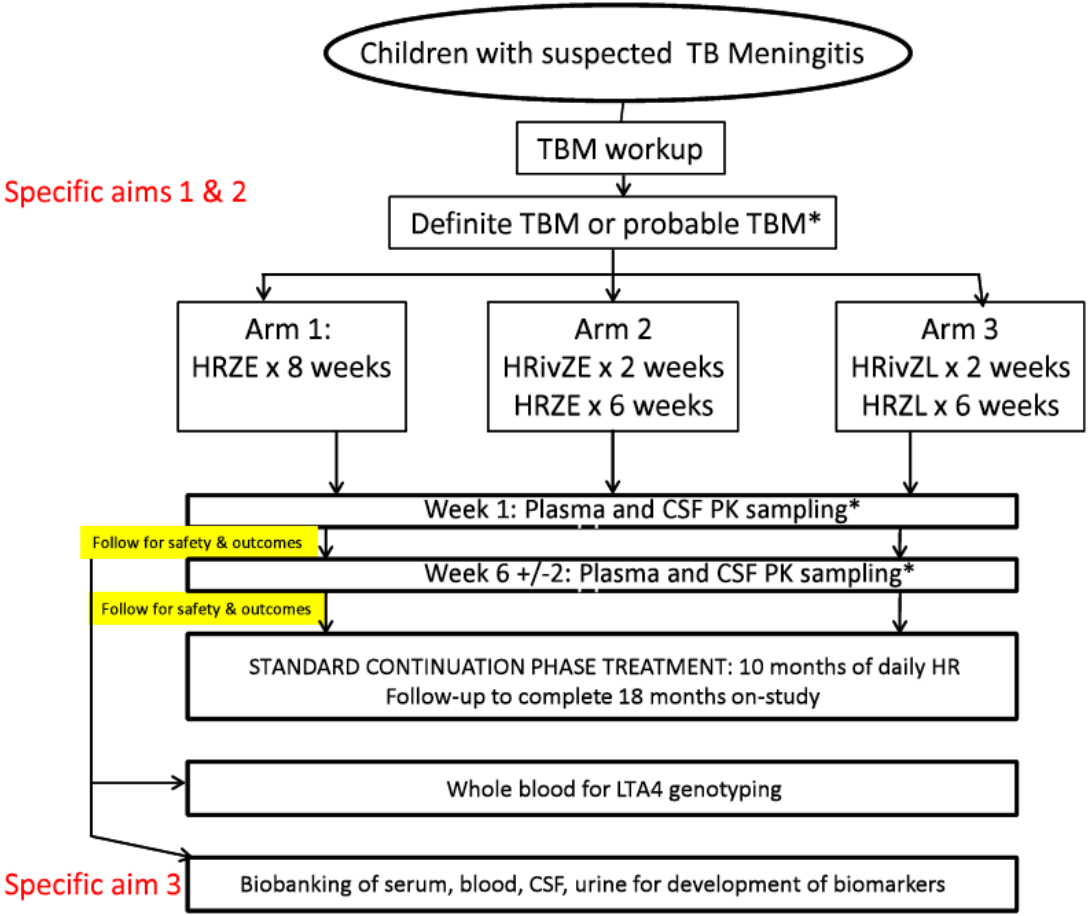



| | Week 0-2 | Week 3-8 |
|---|---|---|
| Intervention | 15 mg/kg iv | 30 mg/kg oral |
| Control | 15 mg/kg oral | 15 mg/kg oral |

*Modeling predicts 15 mg/kg IV or 30 mg/kg orally to attain target exposure in children*

# Study Schema

Specific aims 1 & 2



# Modeling Features

- Powered to asses efficacy using longitudinal scores (not survival) – “improvement in morbidity”
- Initial doses should be “optimal”  based on all prior knowledge
- Extensive modeling went into determining optimal doses
- Interim analysis with possible dose adaptation
- Early PK sampling (day 1) – interim analysis done as soon as feasible
- Sparse sampling

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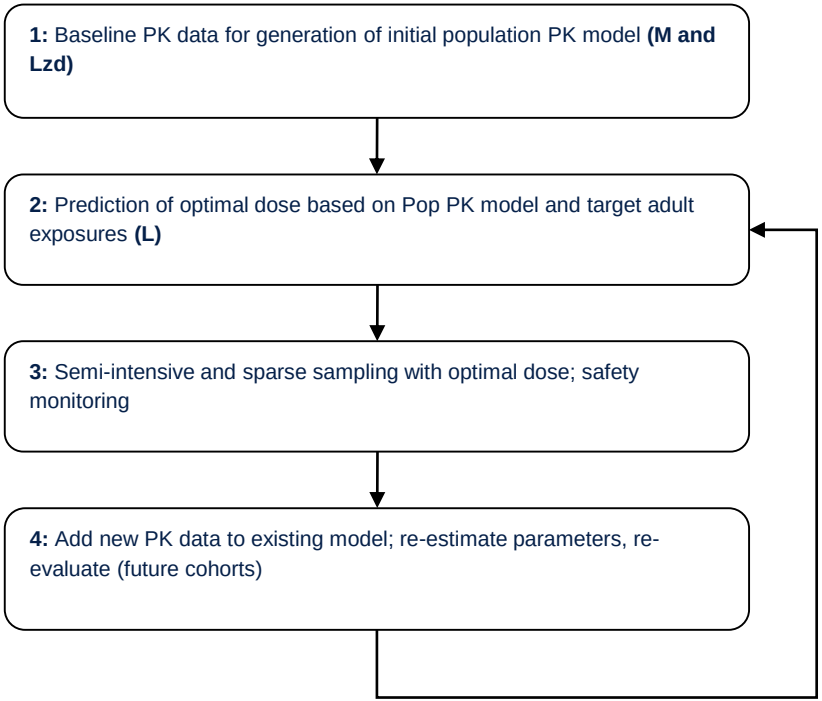
# MDR KIDS 2

## *Dose optimization of Moxifloxacin, Levofloxacin and Linezolid in children with MDR TB*

6/22/2016

# Conceptual framework for dose optimization



# Initial optimized doses of L, M and Lz based on adult targets

| Weight bands | | | Levofloxacin | | | Moxifloxacin | | | Linezolid | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| From | To | | Dose | Unit | Use | Dose | Unit | Use | Dose | Unit | Use |
| - | 3 | kg | 62.5 | mg | Broken pil 1/4 | 40 | mg | Susp. (2 mL) | 30 | mg | Susp. (2 mL) bid |
| 3 | 5 | kg | 62.5 | mg | Broken pil 1/4 | 60 | mg | Susp. (3 mL) | 40 | mg | Susp. (3 mL) bid |
| 5 | 10 | kg | 125 | mg | Broken pil 1/2 | 100 | mg | Susp. (5 mL) | 80 | mg | Susp. (4 mL) bid |
| 10 | 15 | kg | 250 | mg | Whole pill | 160 | mg | Susp. (8 mL) | 120 | mg | Susp. (6 mL) bid |
| 15 | 20 | kg | 500 | mg | Whole pills (2) | 200 | mg | Susp. (10 mL) | 180 | mg | Susp.(9 mL) bid |
| 20 | 30 | kg | 500 | mg | Whole pills (2) | 250 | mg | Susp. (12.5 mL) | 250 | mg | Susp. (12.5 mL) bid |
| 30 | 40 | kg | 750 | mg | Whole pills (3) | 350 | mg | Susp. (17.5 mL) | 300 | mg | Broken pill (1/2) qd |

# Modeling Features

- Powered to asses developmental pharmacology for L, M and Lz in target population
- Initial doses should be close to “optimal”  based on all prior knowledge
- Extensive modeling went into determining optimal doses
- Interim analysis with possible dose adaptation
- Early PK sampling (day 1) – interim analysis done as soon as feasible
- Sparse sampling
- Evaluation of a new formulation and safety and PK of M in younger
- Collection of efficacy data

# Conclusion

- Build Data Bases Ahead of Trials
- Confirmatory Trials in Children and Pregnant Women
- Modelling and Simulation shall be used throughout the development program:
  - To design the study (power, sampling scheme)
  - To chose the studied dose in children/pregnant women
  - To understand developmental and pregnancy-related changes of Drug X
  - To modify the dose if necessary
  - To Analyze the results
  - To File
- Minimize/avoid standard of care arm in children & pregnant women

# Acknowledgments


- IMPAACT 2001: Jyoti Mathad
- S35: Anneke Hesseling, Deron Burton
- TBM KIDS Kelly Dooley
- MDR KIDS: Tony Garcia-Prats
- Amita Gupta
- UCSF team (Jenn Hibma, Ron Keizer)
- IMPAACT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