

FDA Perspective: Exposure-Response Assessments and Application to Pediatric Regulatory Review

Kevin M. Krudys, Ph.D.

Team Leader

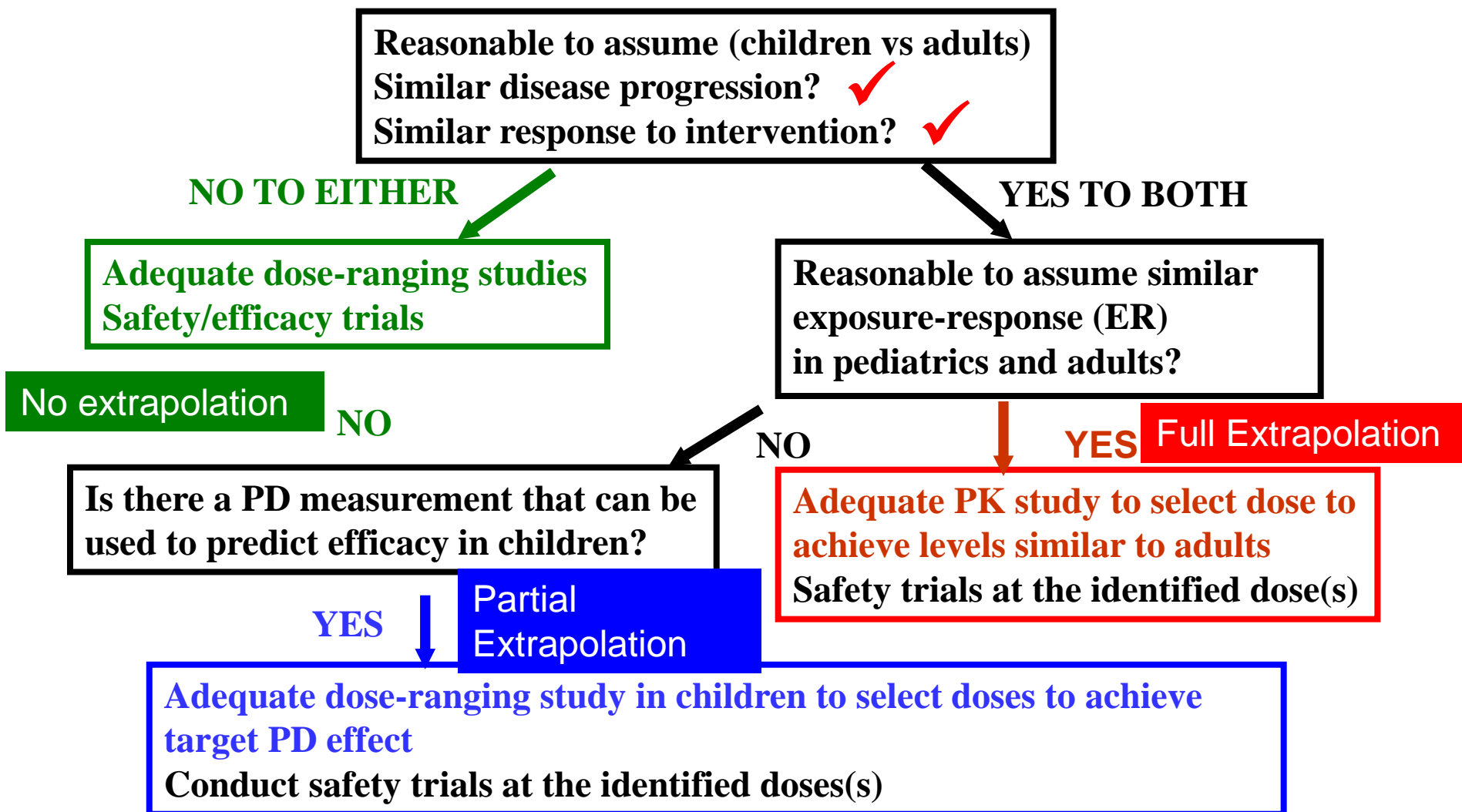
Division of Pharmacometrics

Office of Clinical Pharmacology

Disclosures

- The views expressed in this presentation are that of the author and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.
- The data presented is publicly available
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Quantitative Framework for Extrapolation



Exposure-Response Analysis for Extrapolation in Pediatric Drug Development

- Maximize the use of existing information to increase efficiency
- When extrapolation is used, 61% of drug products obtained indication (34% when no extrapolation)



Dunne et. al., Pediatrics 2001;128;e1242

Value of Exposure-Response Analysis

- “Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs^{*}”
 - Concentrations of drugs drive the effect (in general)
 - Contributes to evidence of effectiveness
 - Allows for deriving optimal doses in general and in special populations

Challenges Facing Use of Extrapolation

- Logistical
 - Sharing data between Sponsors
 - Data quality
 - Quantitative expertise
 - Availability of PK/PD data
- Trial characteristics
 - Different endpoints (pediatric vs. adult)
 - Different trial designs
 - Different placebo responses
- Evidence generation
 - How to assess similarity in exposure-response relationships?
 - Number of drugs, mechanisms of action

Case Study #1

Derivation of darunavir doses in HIV-infected treatment experienced pediatric patients ages 6 to 17 years

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf>

Study Design (Part 1)

- 44 pediatric patients randomized to two dose arms for 2 weeks

Weight (kg)	Darunavir Dose (Group A)	Darunavir Dose (Group B)
20-30	300 mg	375 mg
30-40	375 mg	450 mg
40-50	450 mg	600 mg

* Adult dose is 600 mg

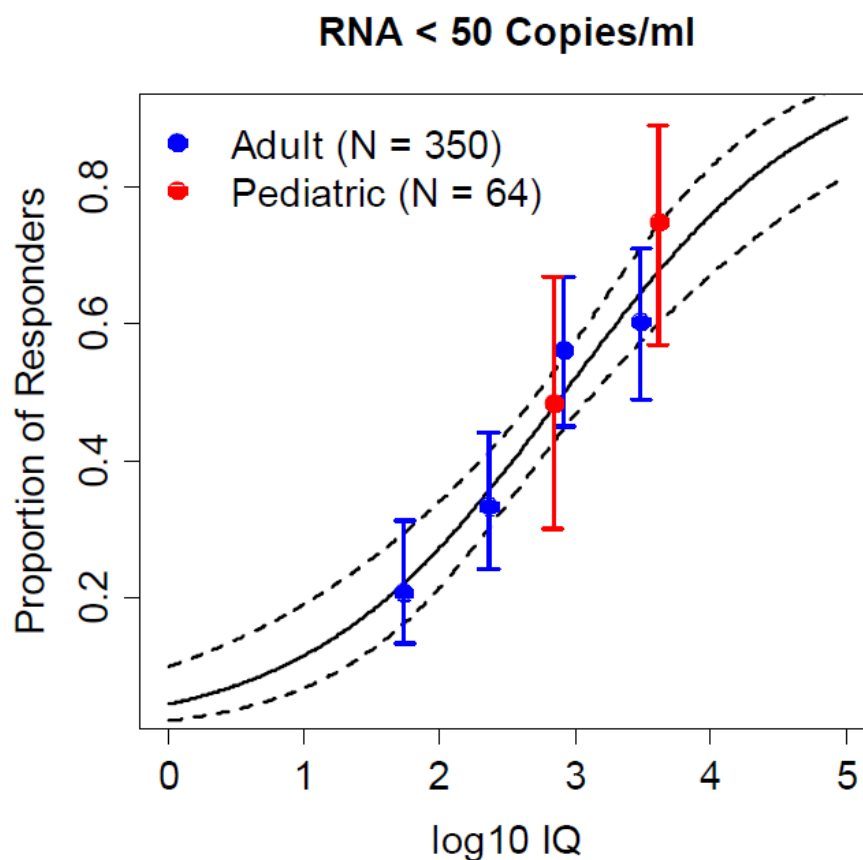
$$\text{Dose}_{\text{child}} = \text{Dose}_{\text{adult}} * (\text{Body Weight}_{\text{child}})^{0.75}$$

Study Design (Part 2)

- Week 2 interim PK data were analyzed
- Dose group B was chosen for Part 2
 - 22 patients in dose group A were switched to higher dose
 - 24 additional subjects were enrolled
- Safety and activity (viral load) measured through 48 weeks

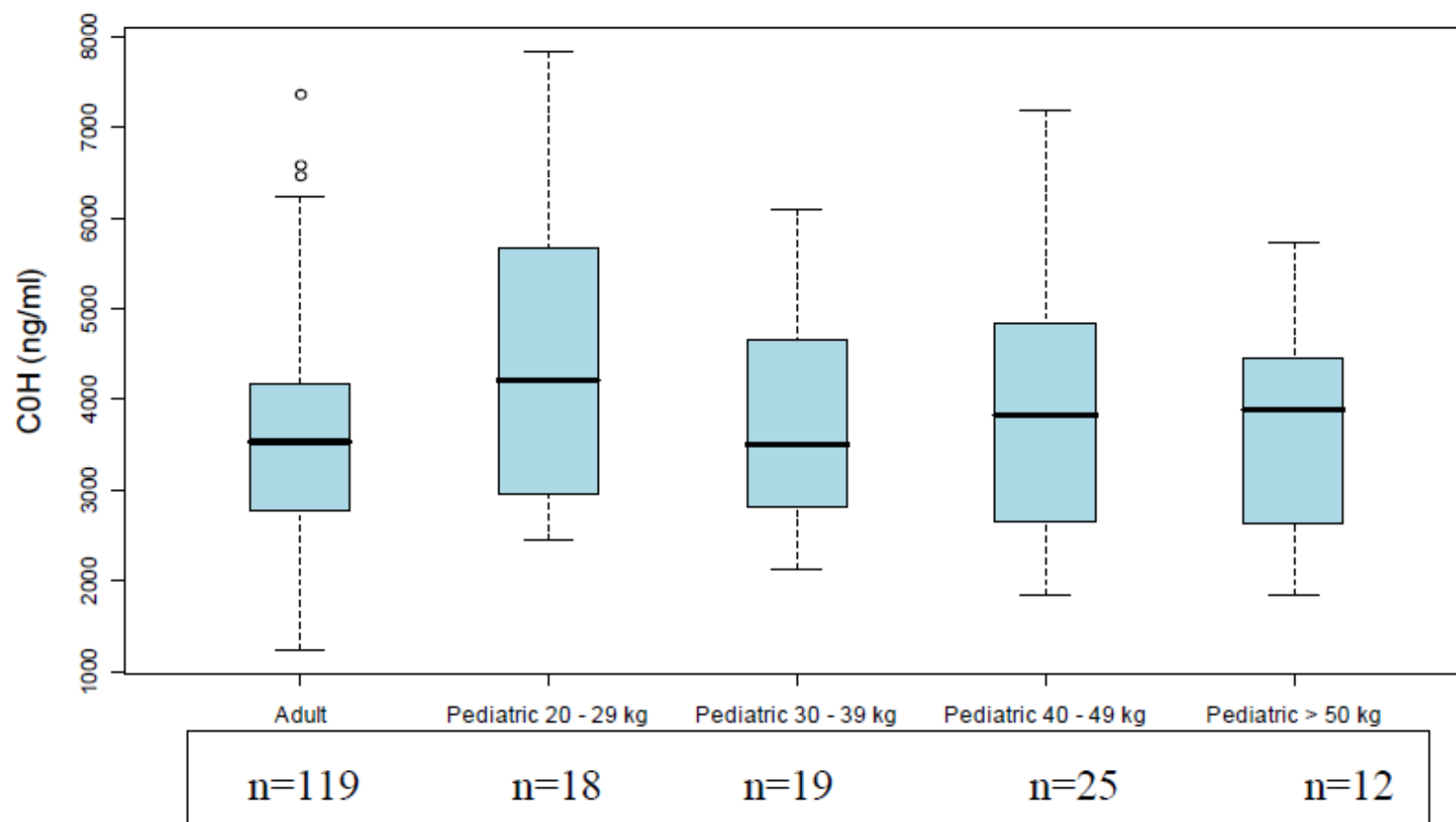
Is it reasonable to assume similar exposure-response relationship in adults and children?

YES



$$\text{Exposure} = \text{IQ} = C_{0h}/IC_{50}$$

Similar Exposure in Pediatric and Adult Patients



Case Study #2

Vigabatrin for refractory complex partial seizures (rCPS) in children 10 years of age and older

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM374644.pdf>

Use of Exposure-Response Modeling to Support Pediatric Approval

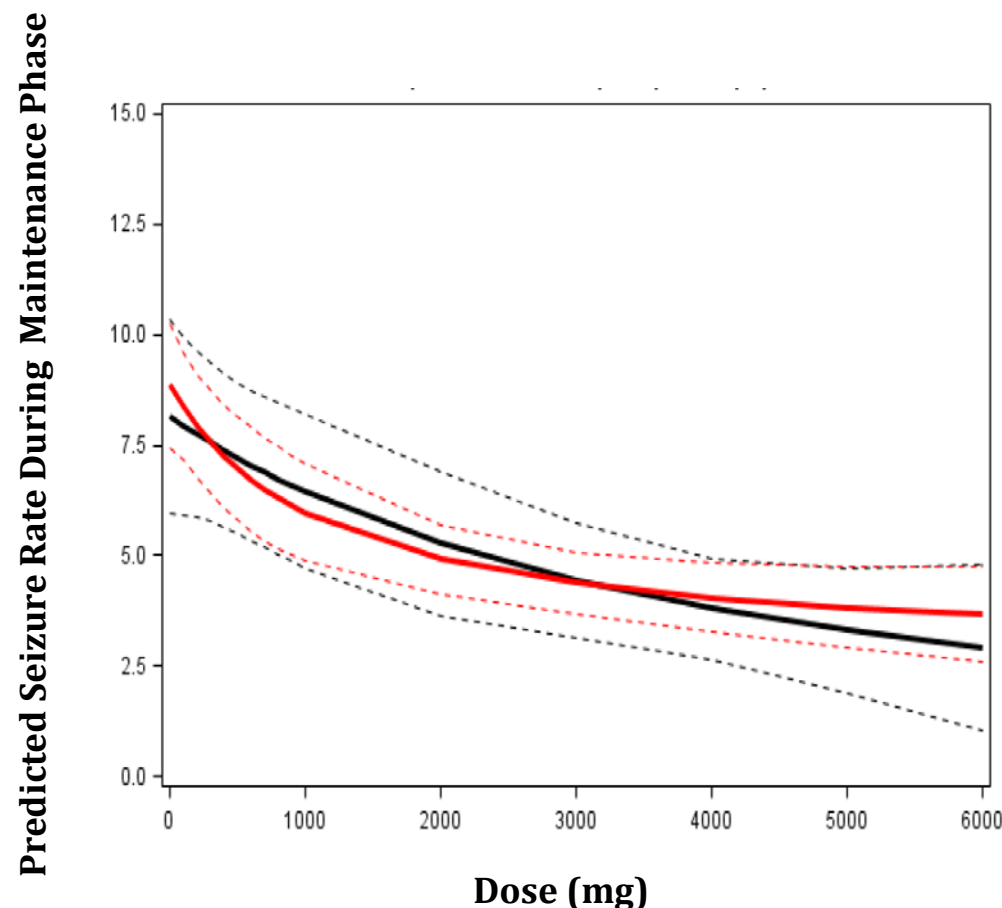
- Vigabatrin for refractory complex partial seizures (rCPS) in children 10 years of age and older
- Approved for rCPS in adults and infantile spasms (1 month to 2 years of age)
- In WR, the Sponsor was requested to conduct randomized efficacy study comparing two doses to placebo
 - Vigabatrin was previously studied in 3 controlled pediatric trials
 - No individual study was adequate to demonstrate efficacy in pediatric patients above 10 years of age

Exposure-Response Data Included in Analysis

Population	Study	Treatment	# of Patients	# of Daily Seizure Counts Recorded
Adults with Complex Partial Seizures	Study 24	Placebo	90	17821
		Vigabatrin 3g/day	92	17927
	Study 25	Placebo	45	9360
		Vigabatrin 1g/day	45	9186
		Vigabatrin 3 g/day	43	8638
		Vigabatrin 6 g/day	41	7954
Children with Complex Partial Seizures	Study 118	Placebo	31	5169
		Vigabatrin 20 mg/kg/day	30	4771
		Vigabatrin 60 mg/kg/day	32	5098
		Vigabatrin 100 mg/kg/day	32	5046
	Study 192	Placebo	27	4292
		Vigabatrin 0.5-4 g/day	28	4155
	Study 221	Placebo	44	6664
		Vigabatrin 0.5-4 g/day	41	6087

Extrapolation Supported by E-R Relationship

- Data analyzed separately for adults and pediatrics
- Endpoint: Seizure rate
- Sensitivity analyses were performed (C_{avg} , linear, e_{max} , separate drug effect)



Value and Impact

- Existing data was used to maximize efficiency
- WR was amended to remove the efficacy study
- Approval and dosing recommendations provided for pediatric patients in a timely manner

Table 1. Pediatric CPS Dosing Recommendations

Body Weight [kg]	Total Daily* Starting Dose [mg/day]	Total Daily* Maintenance Dose [†] [mg/day]
25 to 60 ^{††}	500	2000

*Administered in two divided doses.

[†]Maintenance dose is based on 3000 mg/day adult-equivalent dose

^{††}Patients weighing more than 60 kg should be dosed according to adult recommendations

Case Study #3

Infliximab for pediatric ulcerative colitis (UC)

Extrapolation in a Pediatric Rare Disease

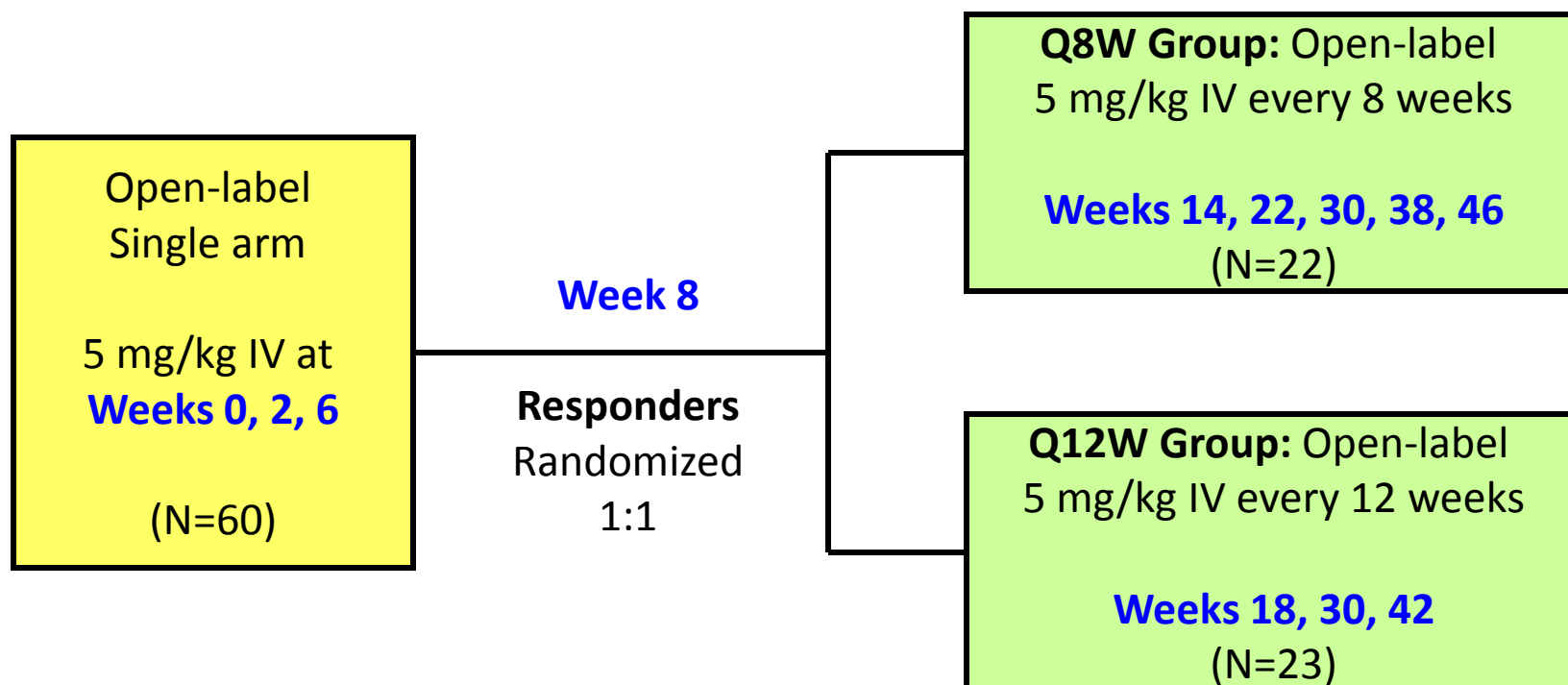
- Infliximab for pediatric ulcerative colitis (UC)
- Approved for adult Crohn's disease (CD), adult ulcerative colitis and pediatric CD

Dosing Regimen	Crohn's Disease	Ulcerative Colitis
Adult	5 mg/kg 0, 2, 6 weeks and then every 8 weeks	5 mg/kg 0, 2, 6 weeks and then every 8 weeks
Pediatrics	5 mg/kg 0, 2, 6 weeks and then every 8 weeks	

Pediatric UC (T72) Study

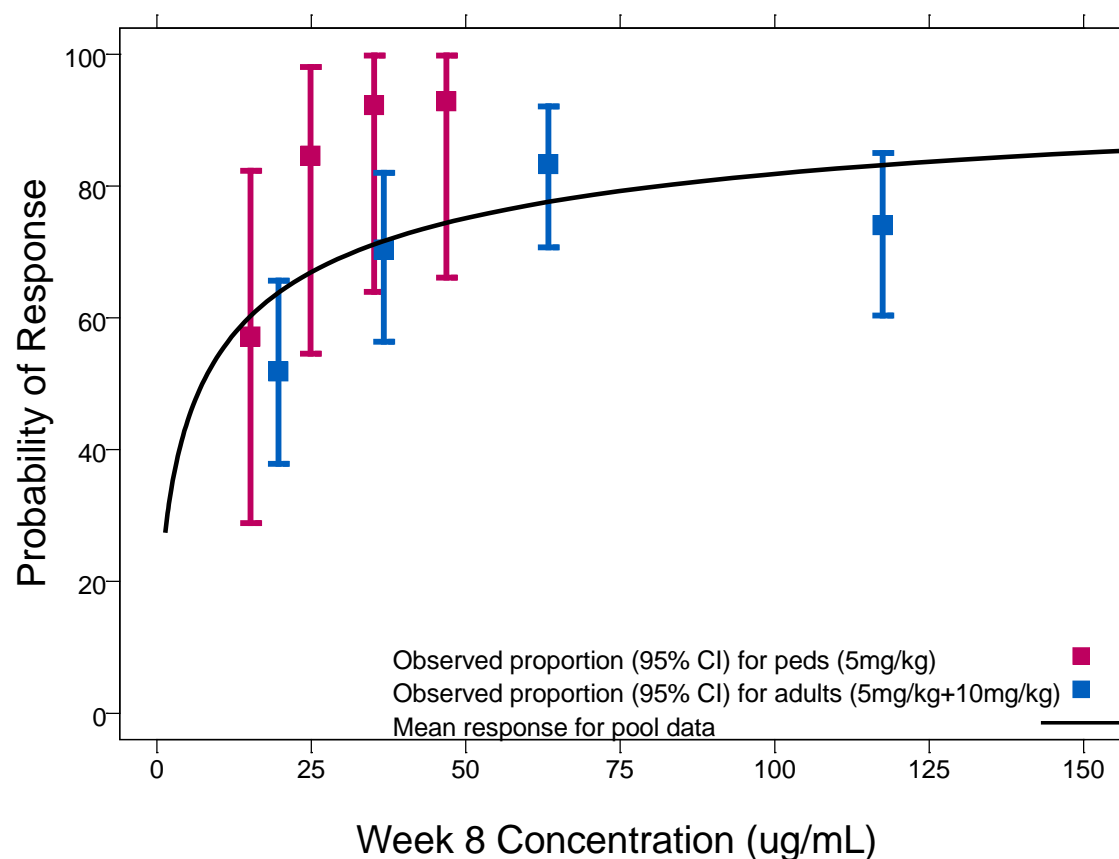
INDUCTION PHASE

MAINTENANCE PHASE



Responder: decrease from baseline in Mayo by $\geq 30\%$ and ≥ 3 points, with a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1

Pediatric Exposure-Response Relationship for Induction Does Not Appear Different from Adults



Value and Impact

- Pediatric approval based on open-label single arm study

Dosing Regimen	Crohn's Disease	Ulcerative Colitis
Adult	5 mg/kg 0, 2, 6 weeks and then every 8 weeks	5 mg/kg 0, 2, 6 weeks and then every 8 weeks
Pediatrics	5 mg/kg 0, 2, 6 weeks and then every 8 weeks	5 mg/kg 0, 2, 6 weeks and then every 8 weeks

Future Directions

- Reactive → Proactive
 - Identify disease areas where it is thought that exposure-response relationship might be similar in adults and children
 - Construct PK/PD database across development programs
 - Bring together disease specialists, pharmacometricians, clinical pharmacologists, drug developers, regulators
 - Explore exposure-response relationships
- Partial extrapolation → Complete extrapolation
 - Where appropriate, can reduce drug development time and increase probability of success