Case Example: Exposure Response to Support Extrapolation of Efficacy in Pediatric Ulcerative Colitis

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Remicade® (infliximab)

A chimeric (human/murine) IgG 1 monoclonal antibody specific for human tumor necrosis factor α (TNFα)

- **Neutralizes biological TNFα activity by binding to TNFα and inhibiting its ability to bind to receptors**

Approved Indications

•**Dermatology**:	**Plaque Psoriasis**
•**Rheumatology**:	**Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis**
•**Gastroenterology**:	**Adult Crohn's disease, Adult Ulcerative Colitis, Pediatric Crohn's disease, Pediatric Ulcerative Colitis(≥ 6 y.o.)**

Remicade injection label last revised 1/02/2015; Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103772s5370lbl.pdf
Label approved 08/24/1998.

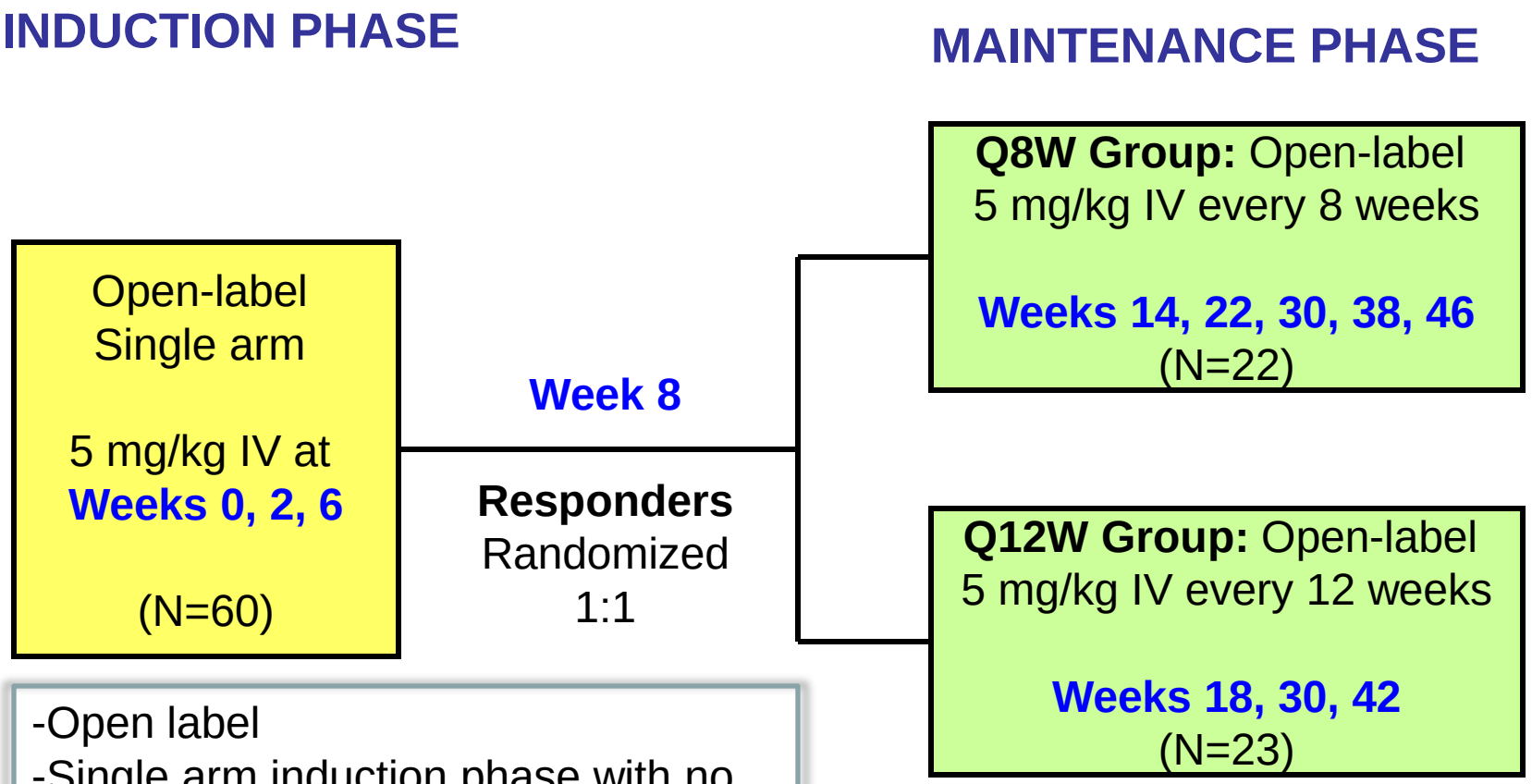
General Approach to Extrapolation of Efficacy in Pediatric UC

The course of the disease and response to treatment are expected to be sufficiently similar between adults and children with UC.

It was not clear whether a similar exposure-response relationship in children and adults could be assumed.

Explored support for partial extrapolation of efficacy through PK & exposure-response analyses

Pediatric UC (T72) Study



-Open label
-Single arm induction phase with no control/comparison group
-Small sample size

FDA slide presented at Advisory Committee Meeting dated 7/21/11

Pediatric Dose Selection

- In T72, the **dose** selected for study was based on data from adult and pediatric CD and adult UC studies/approved doses and indications:
  - Adult IBD doses
    - Crohn's Disease: IND: 5mg/kg IV 0, 2, 6 weeks; MAINT: 5mg/kg IV q8 weeks, *(may ↑ to 10mg/kg)*
    - Ulcerative Colitis: IND: 5 mg/kg IV 0, 2, 6 weeks, MAINT: 5mg/kg IV q8 weeks
  - Pediatric IBD doses
    - Crohn's Disease: IND: 5mg/kg IV 0, 2, 6 weeks; MAINT: 5mg/kg IV q8 weeks
    - Ulcerative Colitis: IND: 5 mg/kg 0, 2, 6 weeks; MAINT: 5mg IV q8 weeks

Adapted from FDA slide presented at Advisory Committee Meeting dated 7/21/11

Induction Phase: Week 8 Median Concentrations and Response Rates Similar Between Populations based on Primary Endpoint (Clinical Response)

	T72 Pediatric UC (5mg/kg)	**ACT1** Adult UC (5mg/kg)
Number of Treated	60	121
Responder*	44	83
Response Rate	**73%**	**69%**
Median (90% CI) Concentration at Week 8 (μg/mL)	**29 (12 ~ 48)**	**33 (7 ~ 64)**

*** A decrease from the baseline Mayo score of ≥ 30 percent and at least three points, with a decrease in the rectal bleeding subscore of at least 1 or a rectal bleeding subscore of 0 to 1.**

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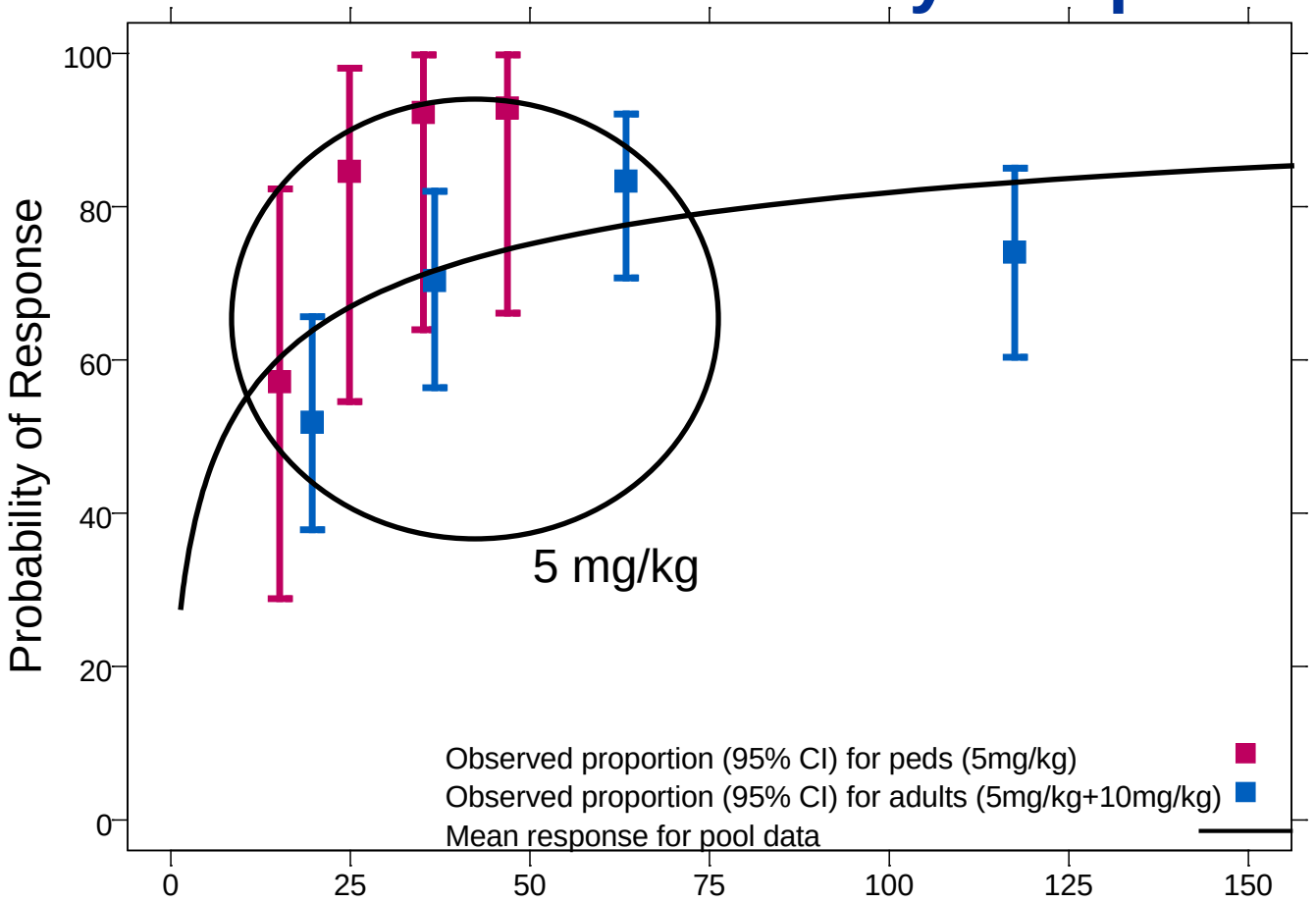
Induction phase: Exposure-Response Relationships between Adults and Pediatric Patients Appear Similar based on Primary Endpoint



Induction Phase

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Maintenance Phase: Limited Data to Support Exposure Response Evaluation

- PK exposure response data limitations
  - Few pediatric patients with both PK and clinical response (N=9) or clinical remission data (N=17) at Week 54
- Leveraged clinical observations to support the maintenance dose

Clinical Observations that Supported the Maintenance Dose (1)

Patients in Clinical Remission at Week 54

	T72	ACT 1	
	IFX 5 mg/kg	IFX 5 mg/kg	Placebo
Patients randomized	22	121	121
Patients with evaluable PUCAI (T72) or Mayo (ACT 1) at Week 54	21	121	121
Patients in clinical remission at Week 54	8/21 (**38%**)	42/121 (**35%**)	20/121 (**17%**)

T72: Pediatric UC trial; ACT1: Adult UC trial

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Clinical Observations that Supported the Maintenance Dose (2)

- Fewer pediatric patients required step-up therapy or discontinued treatment in the 5 mg/kg q8w group

Dose Group (N)	Step-up	Discontinued*
5 mg/kg q8w (22)	9	4
5 mg/kg q12w (23)	14	11

** Includes patients who discontinued regardless of step-up*

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Conclusions

- **Similar exposure-response relationships of response and remission between adults and pediatrics in the induction phase supported partial extrapolation of efficacy from adults that supported pediatric labeling for induction with Remicade.**

- **Demonstration of similar exposure-response relationships during induction phase, combined with clinical observations in the maintenance phase, supported dose selection in the maintenance phase.**

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