Use of extrapolation in small clinical trials:
Infliximab for pediatric ulcerative colitis

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Learning Objectives

1. Recognize when extrapolation is appropriate.
2. List advantages and limitations of extrapolation.
3. Understand how extrapolation was applied in a small pediatric trial through an example.

Legislation on Extrapolation of Efficacy

"Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another."

[21 CFR 314.55(a); 21 CFR 601.27(a)]

3

Extrapolation is based on three evidence-based assumptions.

1) The course of the disease is sufficiently similar between adults and children.
2) The response to treatment is sufficiently similar between adults and children.
3) Adults and children have a sufficiently similar exposure-response relationship.

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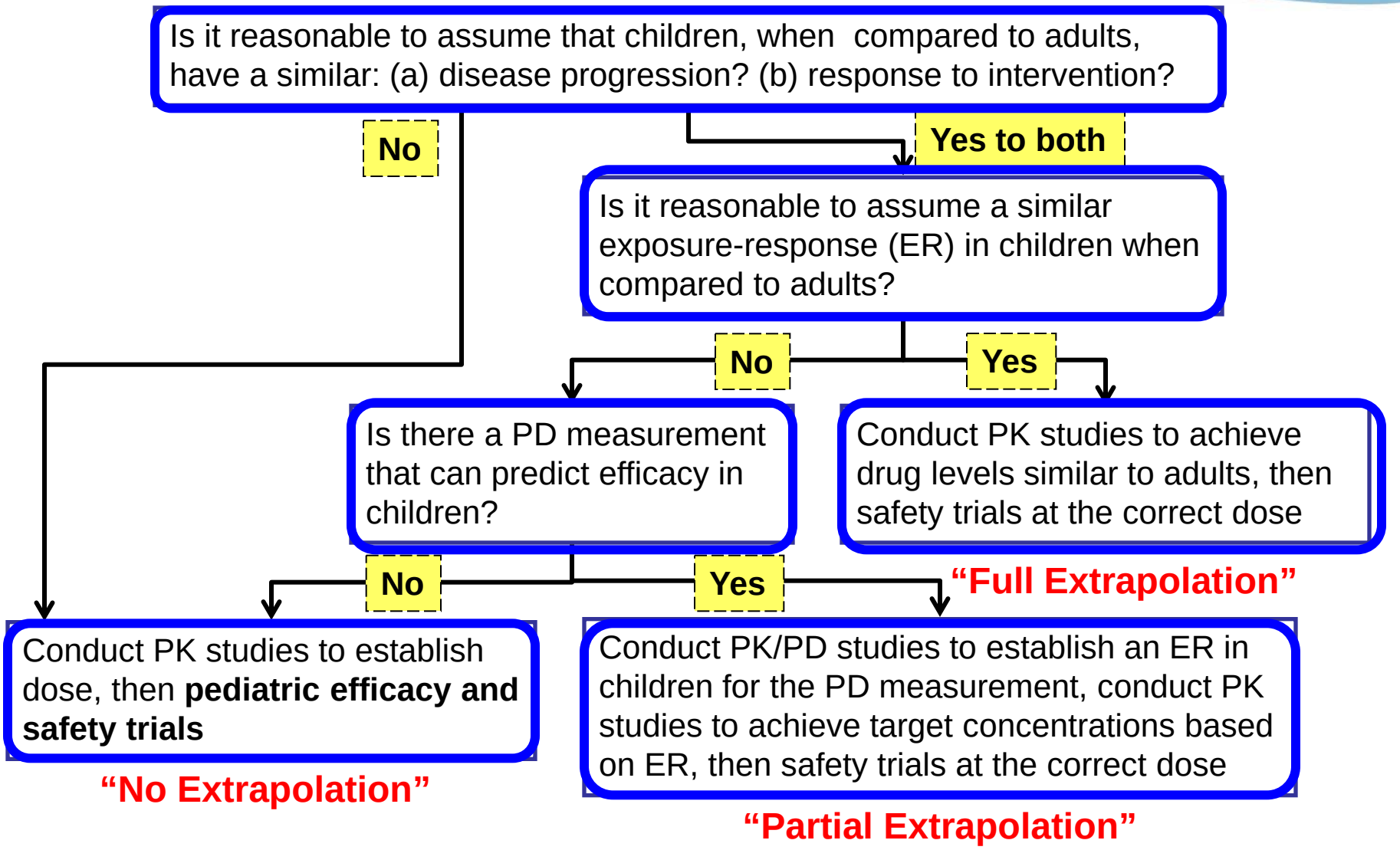
Pediatric Study Decision Algorithm



Advantages of Extrapolation

- Reduce the number and complexities of pediatric trials needed to achieve pediatric labeling.
- Obtain trial results more quickly to increase access to efficacious medications.
- Limit exposure of children to unnecessary studies.
- Better utilize limited resources.

Limitations of Extrapolation

- Extrapolation only applies to efficacy.
- Dose cannot be extrapolated.
  - Absorption, distribution, metabolism and elimination often differ in children based on developmental differences.
  - Need PK and exposure-response (ER) relationships.
- Safety cannot be extrapolated.
  - Adverse effects can be different in children.

An example of how extrapolation was applied in a pediatric registration trial:

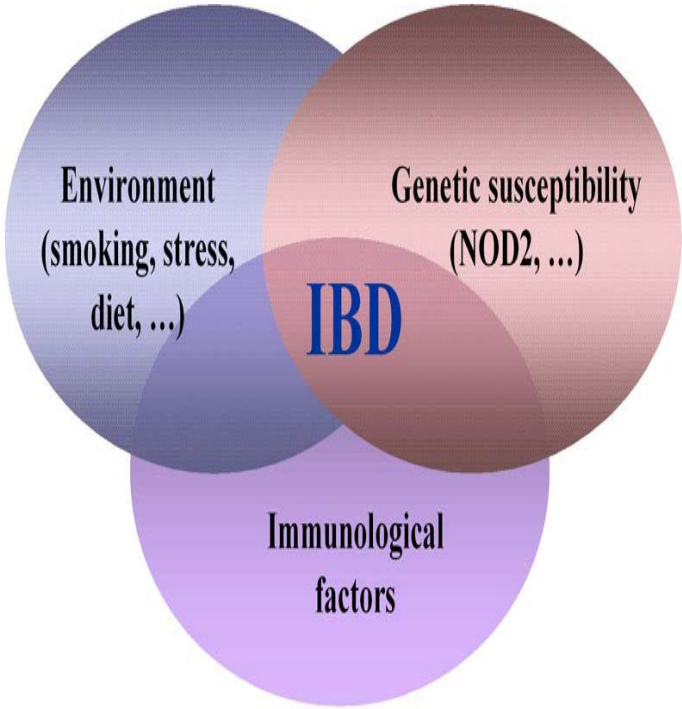
Infliximab Pediatric UC Trial

Infliximab (REMICADE)

- Chimeric IgG1κ monoclonal antibody to human tumor necrosis factor-alpha (TNF-α)
- Approved for adult Crohn's disease (CD) in 1998, adult ulcerative colitis (UC) in 2005, and pediatric CD in 2006.
- Also approved for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.
- Approved for pediatric UC in 2011.

Pathogenesis of inflammatory bowel disease (IBD) is thought to be similar between adults and children.

- Exposure of a **genetically predisposed** host to **environmentally modifying factor(s)**, resulting in **immunologically mediated damage** against the bowel.



- Major subtypes: Crohn's disease (CD) and ulcerative colitis (UC).
- Shared genetic risk variants between adults and children.

	Adult UC	Pediatric UC
Epidemiology	Male:female ratio 1:1 in adults & children	
Disease Location	Left-sided/proctitis predominant	Pancolitis in 80-90% at presentation
Disease phenotype	Colectomy rate @ 10 yrs: 20%	Colectomy rate @ 10 yrs: >40%
Clinical presentation	Similar presenting symptoms (e.g., rectal bleeding, diarrhea, abdominal pain) and extra-intestinal manifestations. Children tend to have higher disease severity and growth impairment only seen in children.	

	Adult UC	Pediatric UC
Treatment: Corticosteroids	1° induction agent	1° induction agent (taper over 2 mo)
5-ASA	High dose induction; mostly maintenance	Mostly maintenance for mild/mod disease
Immuno-modulators	Maintenance agent for mod/severe disease	
Biologics	Induction and maintenance, but currently reserved mostly for immunomodulator failures.	

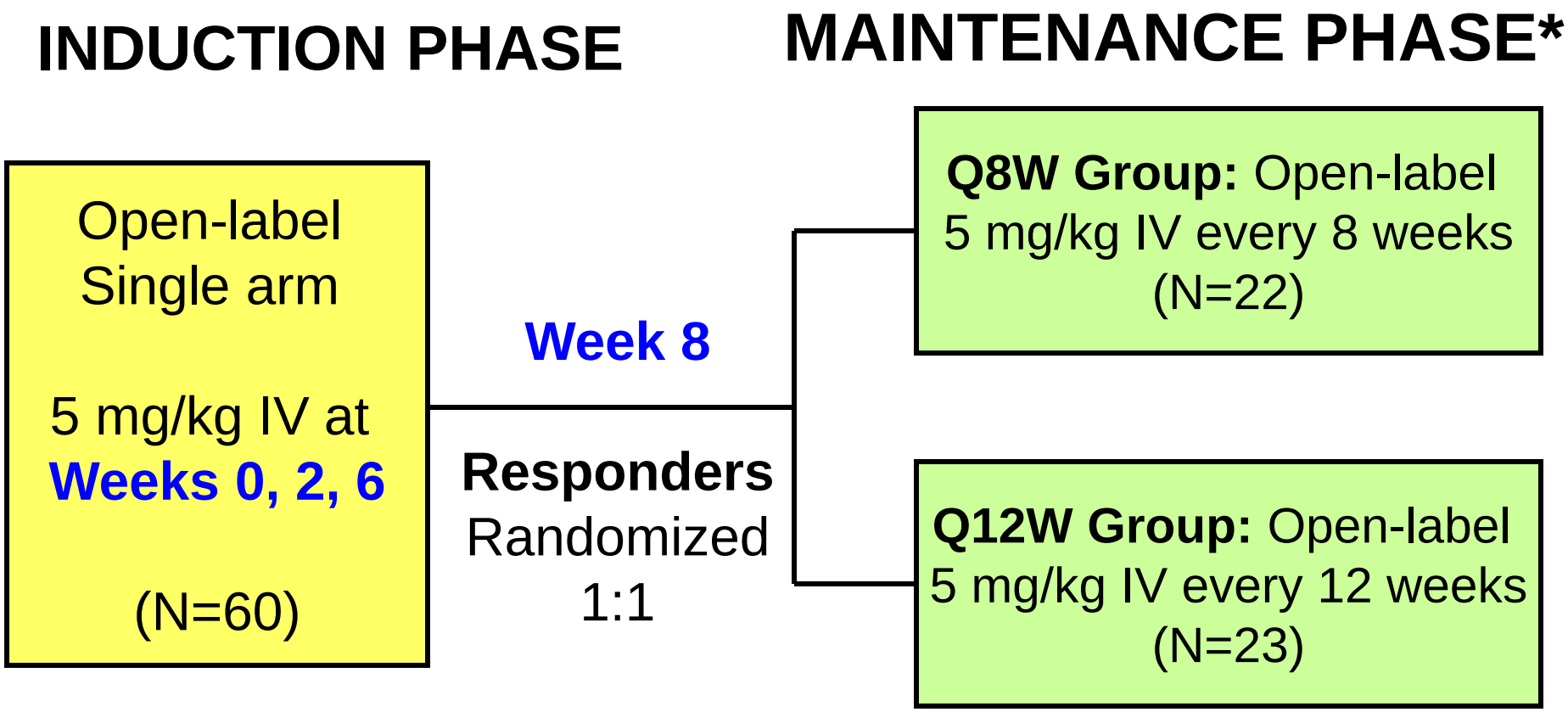
Assessment of extrapolation

- The review team and the Advisory Committee considered extrapolation of efficacy appropriate in pediatric UC.
- Hence, pediatric studies in UC did not need to be designed as adequate and well-controlled clinical efficacy trials.

Assessment of extrapolation

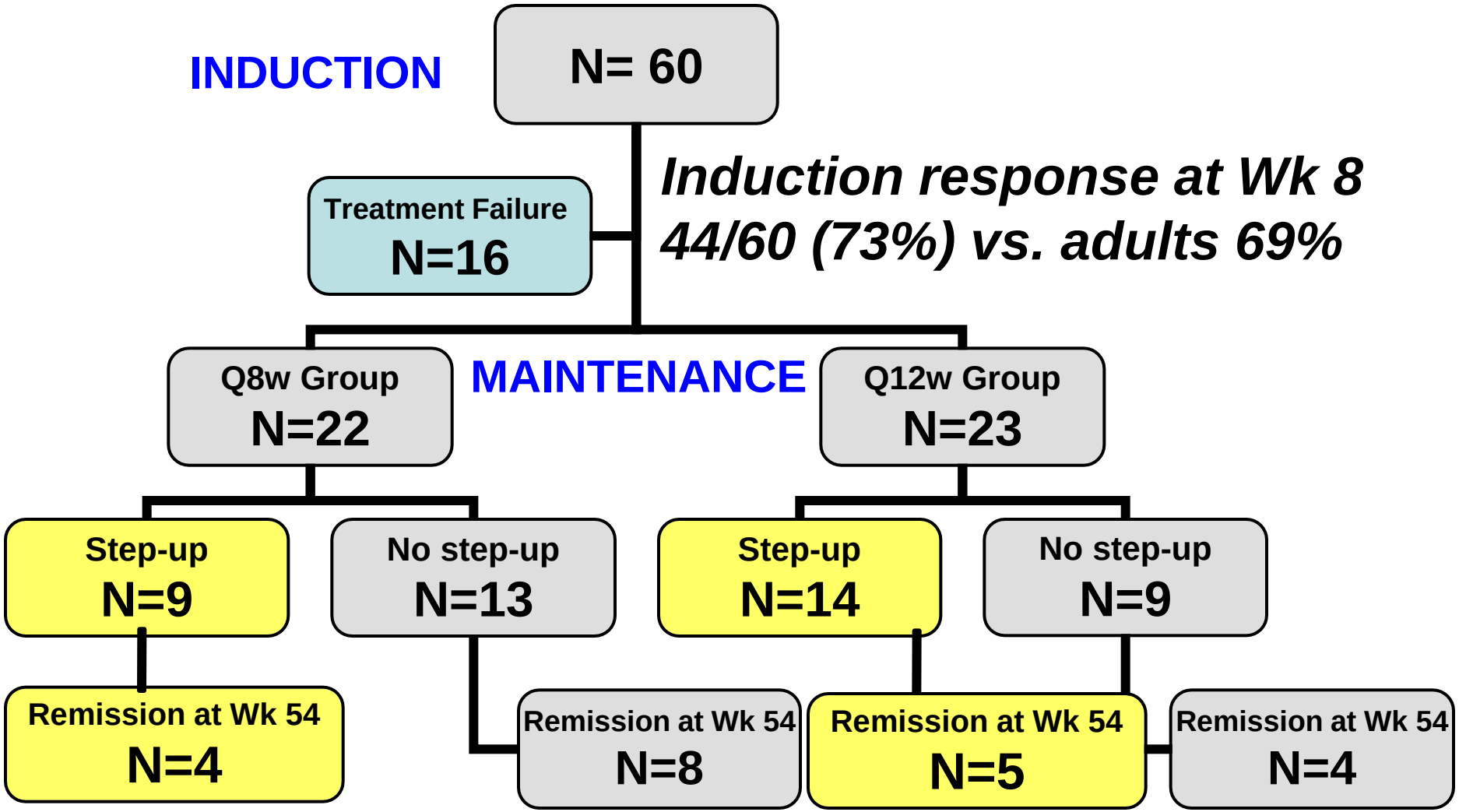
- It was not clear whether a similar exposure-response relationship in children and adults could be assumed.
- Determined that partial extrapolation was most appropriate based on available information.
- Dosing and safety still needed to be established.

Infliximab Pediatric UC Study Design

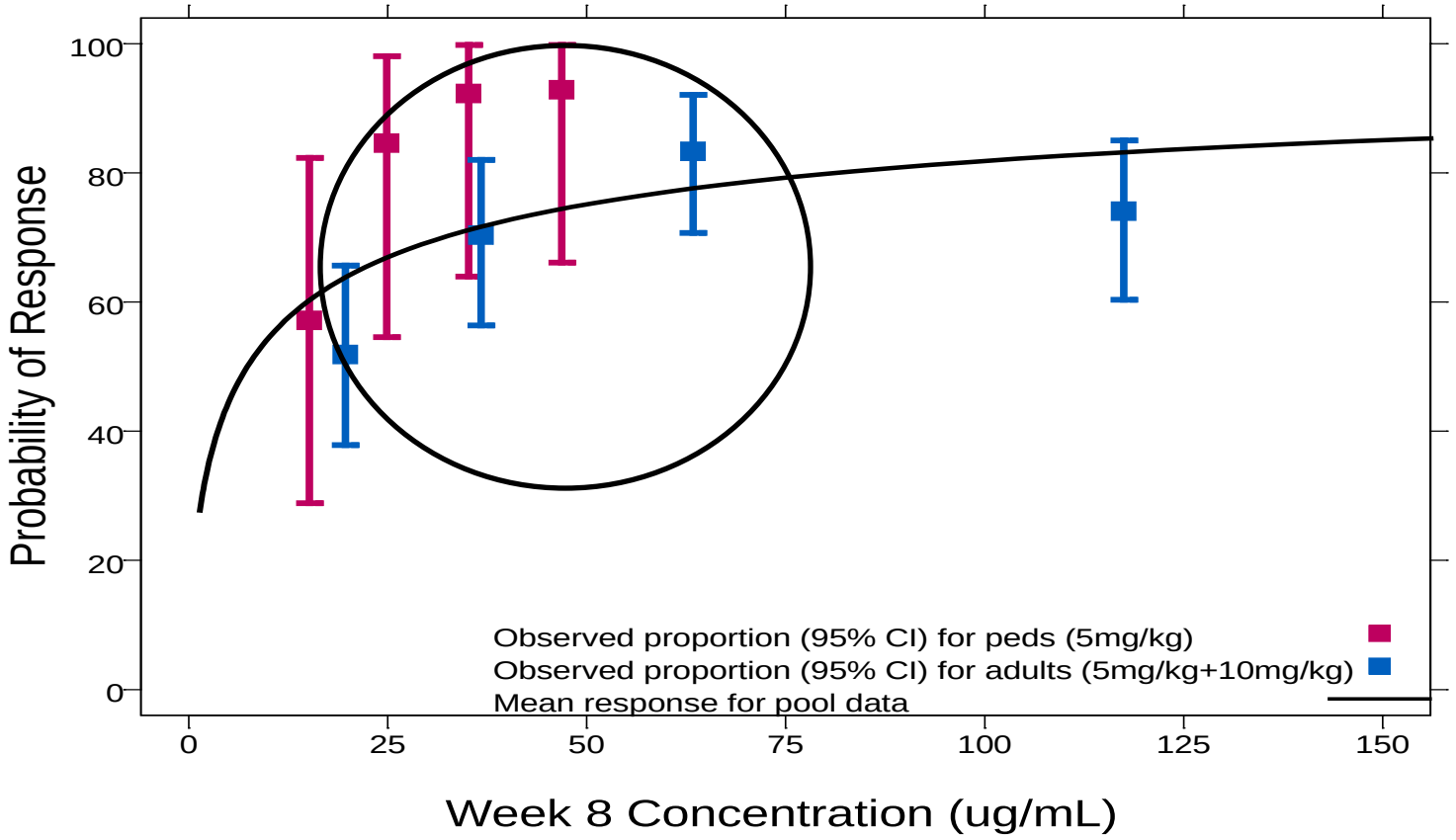


**Step-up therapy was allowed during maintenance phase in patients losing response.*

Patient Disposition



Post-hoc analysis revealed similar exposure-response relationship between adults and children during induction phase



Median concentration and clinical response rate at Week 8 (induction phase) were similar between adult and pediatric UC trials.

	Pediatric UC (5mg/kg)	**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)**

Limited data to evaluate the maintenance phase

- Few pediatric patients with both PK and clinical response (N=9) or clinical remission (N=17) data at week 54.
- Clinical observations that were supportive of the maintenance dose:
  - Fewer pediatric patients required step-up therapy or discontinued treatment in the 5 mg/kg q8w group.
  - At the 5 mg/kg q8w dose, the observed clinical remission rate at Wk 54 similar between adults (42/121, 35%) and pediatric patients (8/21, 38%).

Limited data to evaluate the maintenance phase

- AC meeting was convened to discuss the application.
  - 9 of 15 voted that there are adequate pediatric data to support the maintenance dose.
  - Committee members who voted “no” (6 of 15) stated that the proposed dose may not be high enough to maintain clinical remission.

Lessons learned

- Early and careful planning is particularly important when designing a small clinical trial.
- In the absence of a placebo or comparator arm, it is critical to determine early whether the exposure-response relationship is similar between adults and children.
- A dose-ranging study would have been helpful to better define appropriate induction and maintenance doses.

Conclusions (1)

- When the course of the disease and the response to therapy are sufficiently similar between adults and children, consider extrapolation of efficacy from adequate and well-controlled adult trials.

Conclusions (2)

- Dosing and safety cannot be extrapolated.
- Plan early and conduct PK studies to determine whether the exposure-response relationship is similar between adults and children to further guide study design.

Challenge Questions

1. All of the following are required to allow extrapolation of efficacy from adult data in pediatric drug development except:
   a) Disease pathogenesis is similar between adults and pediatric patients
   b) Duration of disease at the time of enrollment into the trials is similar between adults and pediatric patients
   c) Effects of the drug are similar between adults and pediatric patients
   d) All of the above are required to allow extrapolation

Challenge Questions

2. All of the following are potential advantages of using extrapolation in pediatric drug development except:
   a) Reduce the number and complexities of pediatric trials needed to achieve pediatric labeling
   b) Limit exposure of children to unnecessary studies
   c) Better utilize limited resources
   d) Eliminate the need to study dosing in pediatric patients

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