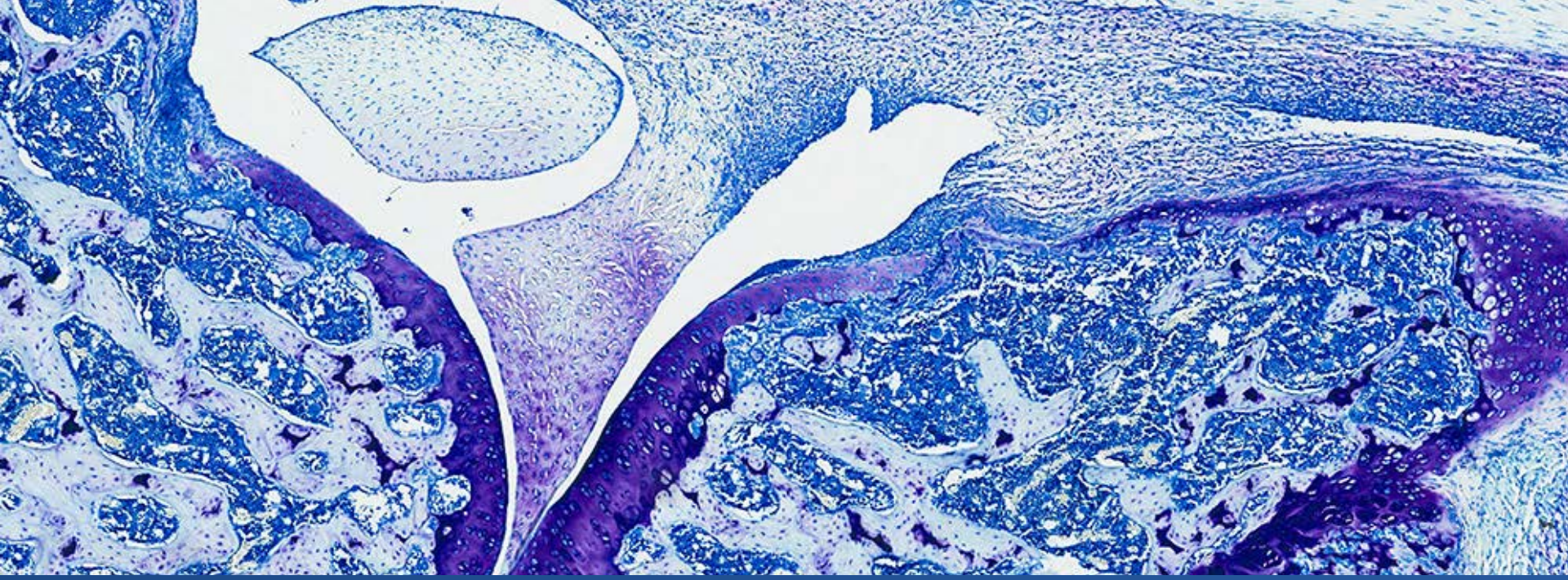

Extrapolation & Pediatric Development: A case study from pediatric Ulcerative Colitis

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janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Agenda

- Rationale for extrapolation in pediatric development
- Justification for extrapolation in pediatric UC
- Golimumab pediatric UC case study
- Key outstanding questions

Rationale for Extrapolation in Pediatric Development

- Timely access to approved treatments in Pediatric patients!
- Take advantage of development and approval process for adult indications
- Avoids limitations of pediatric efficacy studies
  - Difficulty of enrolling placebo-controlled trials
  - Limitations of small, underpowered studies
- Avoidance of unnecessary clinical studies in pediatrics

Justification for Extrapolation in Pediatric UC

Disease course is similar in children and adults

Treatment effects are similar in children and adults

Exposure-response relationship is comparable in children and adults

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Similarity of Disease

- Pathogenesis and genetics of UC similar in adults and children
- *"Although some differences in disease severity exist, the pathogenesis of UC in adults and children is the same, and the disease course in these two populations are similar enough to allow extrapolation of efficacy outcomes from adults to children*."*
- However, children tend to have more "severe disease" as evidenced by a higher incidence of pan-colonic disease

*Mulberg, JPGN 2014

Similarity of Treatment Effects

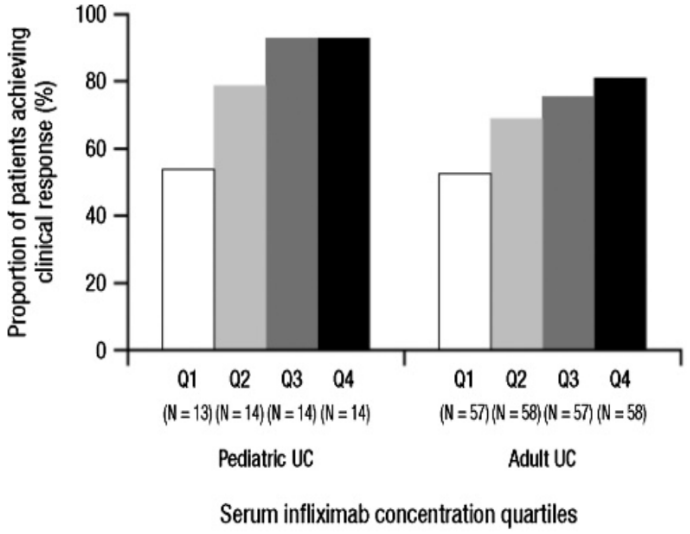
Across medications, treatment effects are generally similar between children and adults

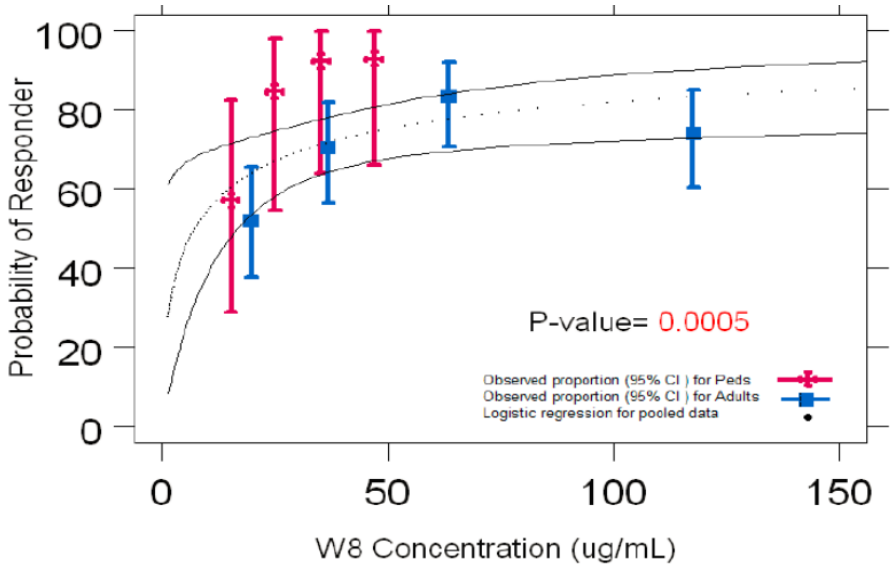
	Adults	Pediatric
5-ASAs	50%	59-70%
Corticosteroids	60%	58%
6-MP/AZA	49%	53%
TNFs (infliximab)	69%	73%

1. Zeisler B et al., JPGN 2013;56: 12–18.
2. Ford AC et al., AJG 2011; 106:601–616.
3. Hyams J et al., CGH 2006;4:1118–1123.
4. Ford AC et al., AJG 2011; 106:590–599.
5. Hyams J et al., AJG 2011; 106:981–987.
6. Ardizzone S et al., Gut 2006; 55:47-53.
7. Timmer A et al., Cochrane 2007: CD000478.
8. Hyams J et al., CGH 2012; 10(4):391–399.
9. Rutgeerts P et al., 2005; 353:2462-2476.

Similarity of Exposure-Response

- Similarity of Exposure Response in Pediatric and Adult UC has been previously demonstrated with anti-TNF therapy (ie. Infliximab)





Agenda

- Rationale for extrapolation in pediatric development
- Justification for extrapolation in pediatric UC
- Golimumab pediatric UC case study
- Key issues & group discussion

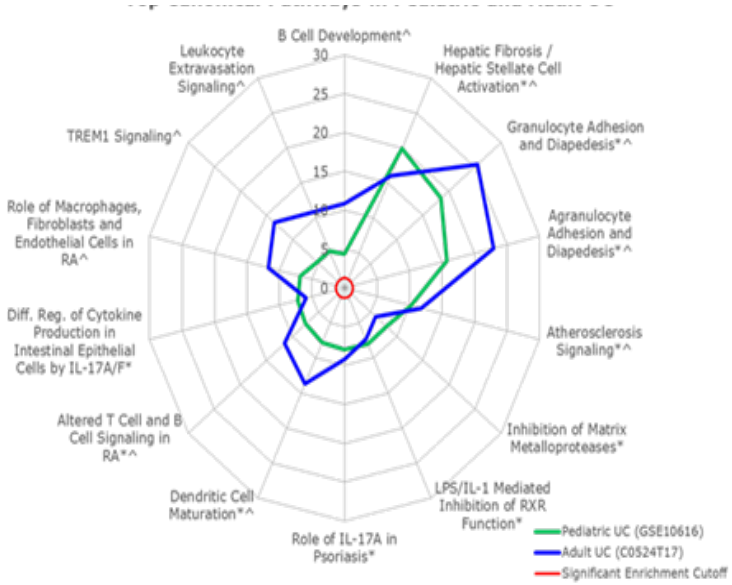
Golimumab Peds UC Case Study

- **Molecular analysis of Pediatric UC to confirm similarity**
- **Initial PK study across full pediatric age range**
  - Molecular analyses, PK, efficacy, E-R, Safety in children
  - Compare results to adult program to address “similarity” requirements
- **Modeling & Simulation analyses**
  - Further evaluate similarity of PK and E-R between children and adults

- **<u>Goal</u>: Find the right dose of golimumab to safely and effectively treat pediatric ulcerative colitis**

Molecular Analyses to Support Demonstration of Similarity of Disease

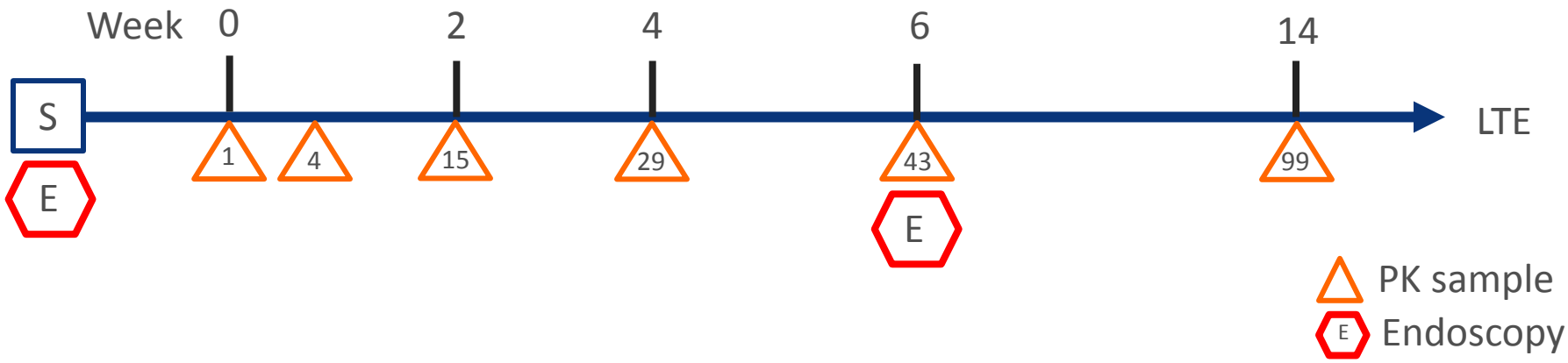
Upstream regulators	Activation z-score	
	Pediatric UC (GSE10616)	Adult UC (C0524T17)
lipopolysaccharide	11.27	12.84
IL1B	9.48	10.38
TNF	9.17	11.36
NFkB (complex)	8.15	9.21
IFNG	7.78	10.07
phorbol myristate acetate	7.76	8.62
CSF2	7.60	7.59
IL1A	7.59	8.09
SB203580	-7.39	-7.64
poly rI:rC-RNA	7.37	8.61
IL6	7.37	7.62



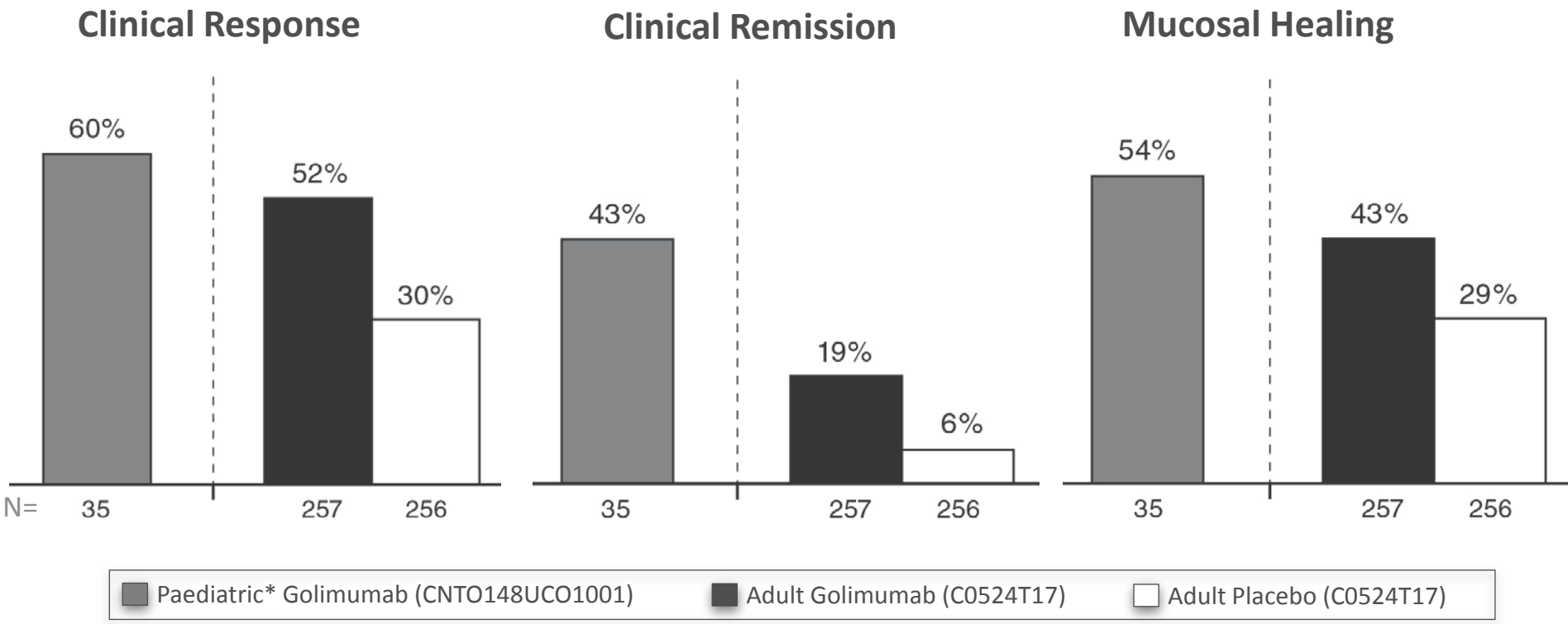
- Similarity in molecular response to golimumab in adults and children was also demonstrated
- Similarity in molecular profile of limited and extensive disease for both adult and pediatric UC was also demonstrated

CNTO148UCO1001 Study Overview

- Study consists of a PK portion (Week 0-14) and a study extension (Week 14-126); PK and E-R data through Week 14 are reported here
- Patients were dosed based on body weight at baseline:
  - **<45 kg:** 90 mg/m^2 at Week 0; 45 mg/m^2 at Week 2 and q4w in responders
  - **≥45 kg:** 200 mg at Week 0; 100 mg at Week 2 and q4w in responders
- Blood samples were collected through Week 14 to evaluate serum golimumab concentrations and immunogenicity
- Efficacy outcomes were assessed using the Mayo score and Pediatric Ulcerative Colitis Activity Index (PUCAI) at Week 6



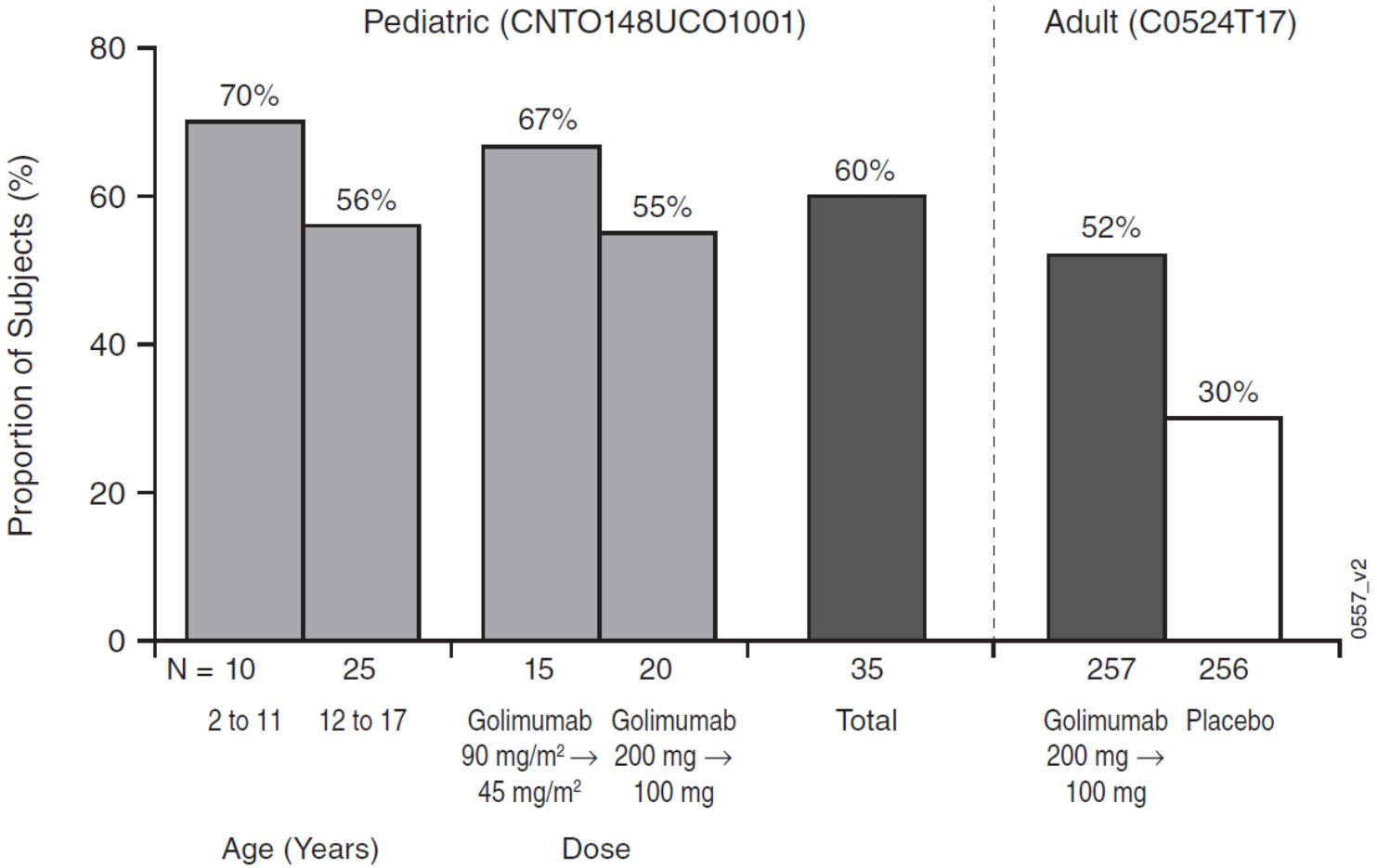
Rates of Clinical Response, Remission, and Mucosal Healing compared in adults and children



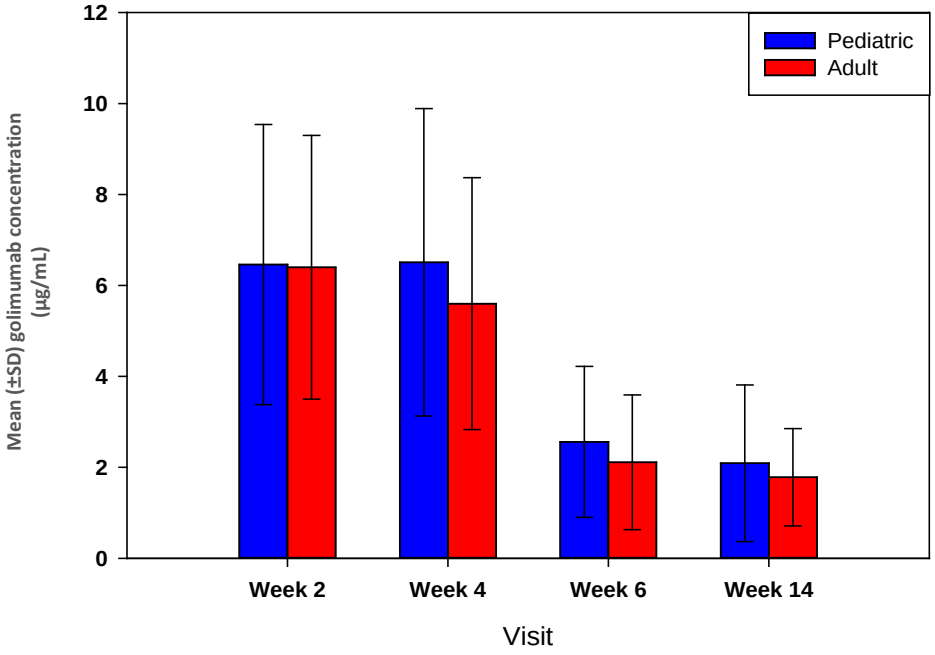
*Similar results by age and weight (dose regimen) subgroups in the paediatric study

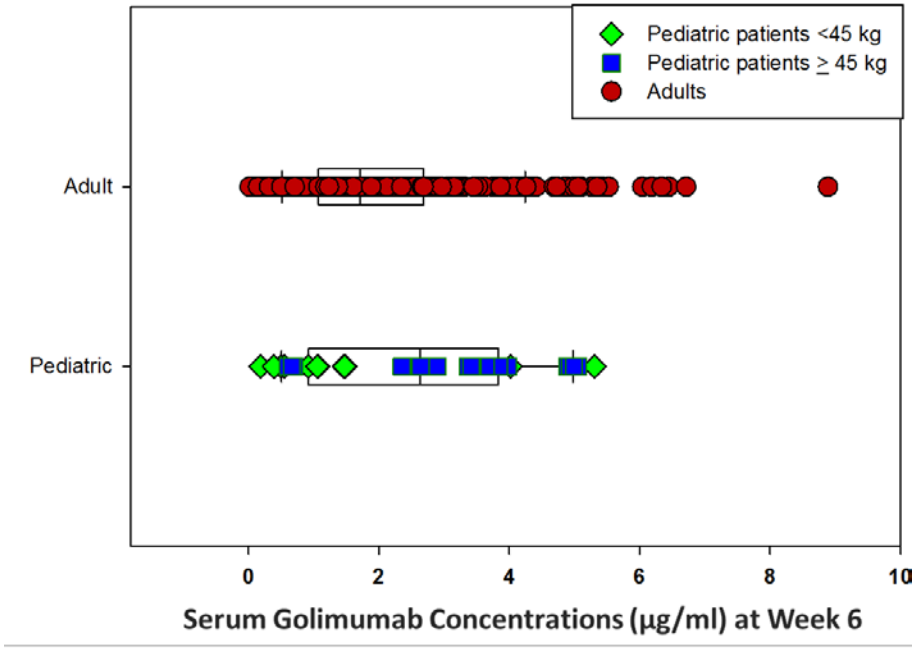
Consistent Outcomes by Pediatric Subgroups

Example shown: Mayo Clinical Response at Week 6



Similar PK (Descriptive Analyses)

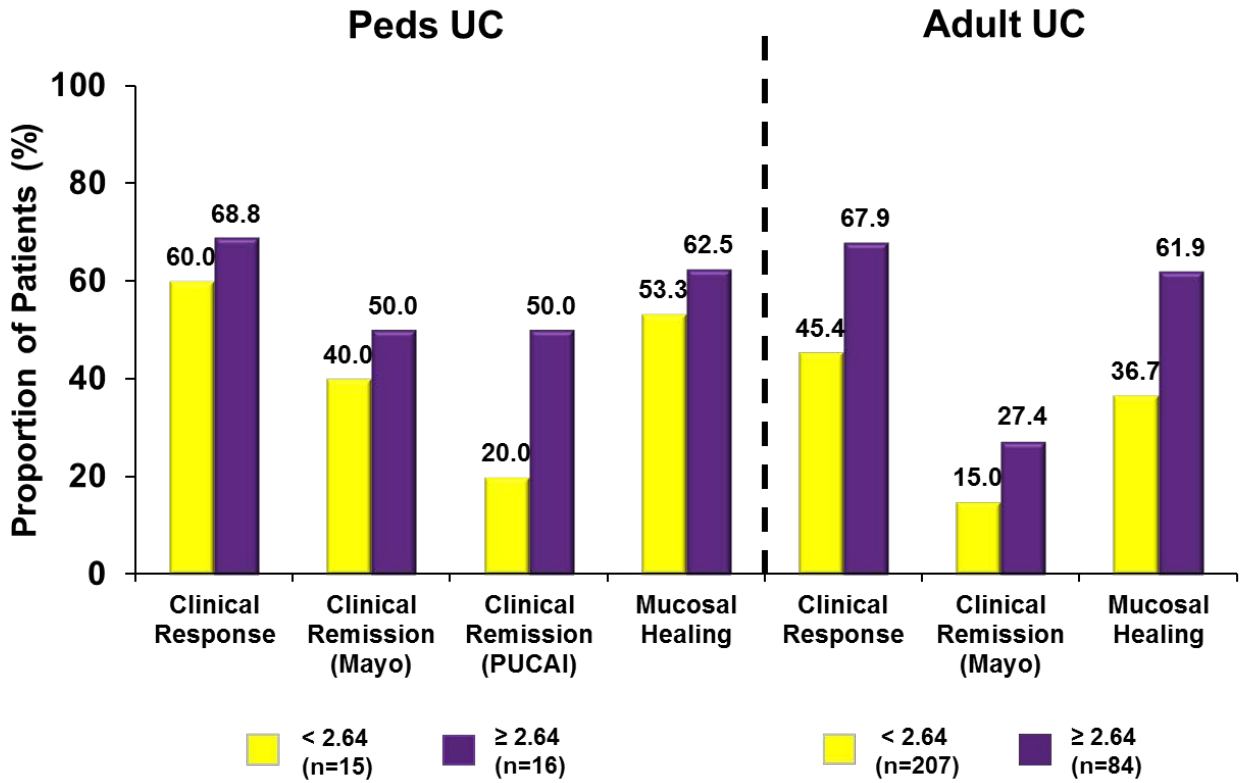




Adedokun O., et al. ECCO 2016. A-2543.

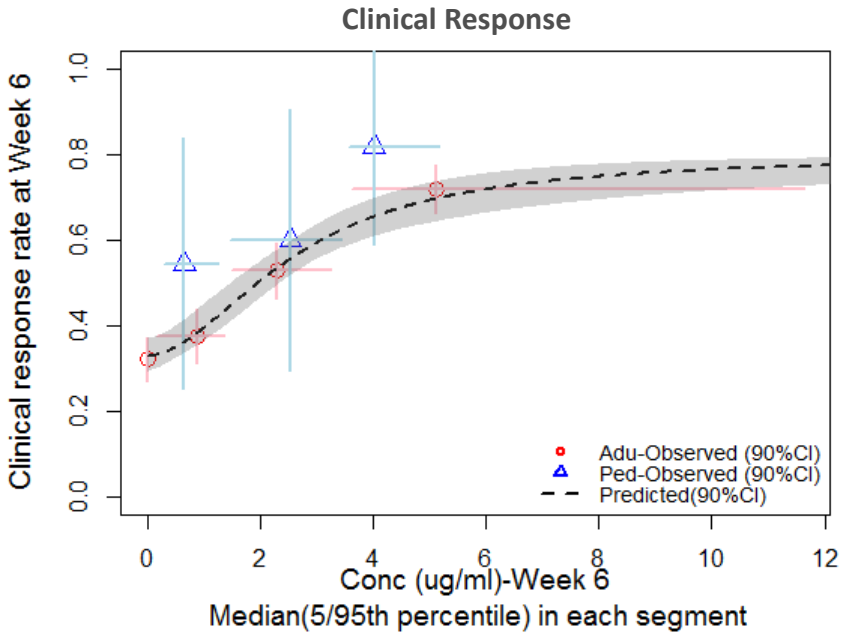
Exposure-Response (Descriptive Analyses)

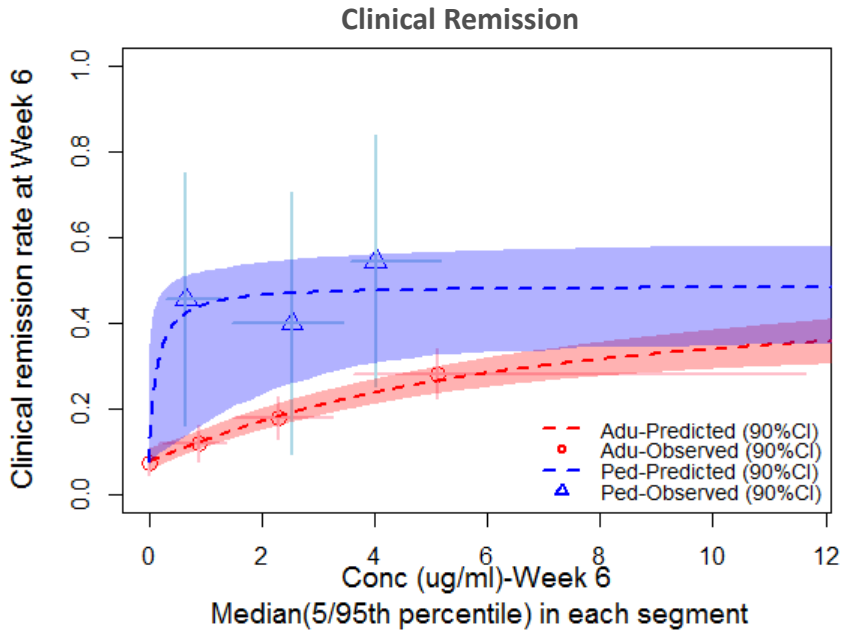
Serum golimumab concentrations were positively associated with efficacy outcomes; this relationship was generally comparable between pediatric and adult patients



Relationship Between Serum Golimumab Concentrations at Week 6 and Clinical Efficacy Outcomes at Week 6 in the Adult and Pediatric Ulcerative Colitis Populations

Exposure-Response (Modeled Analyses)

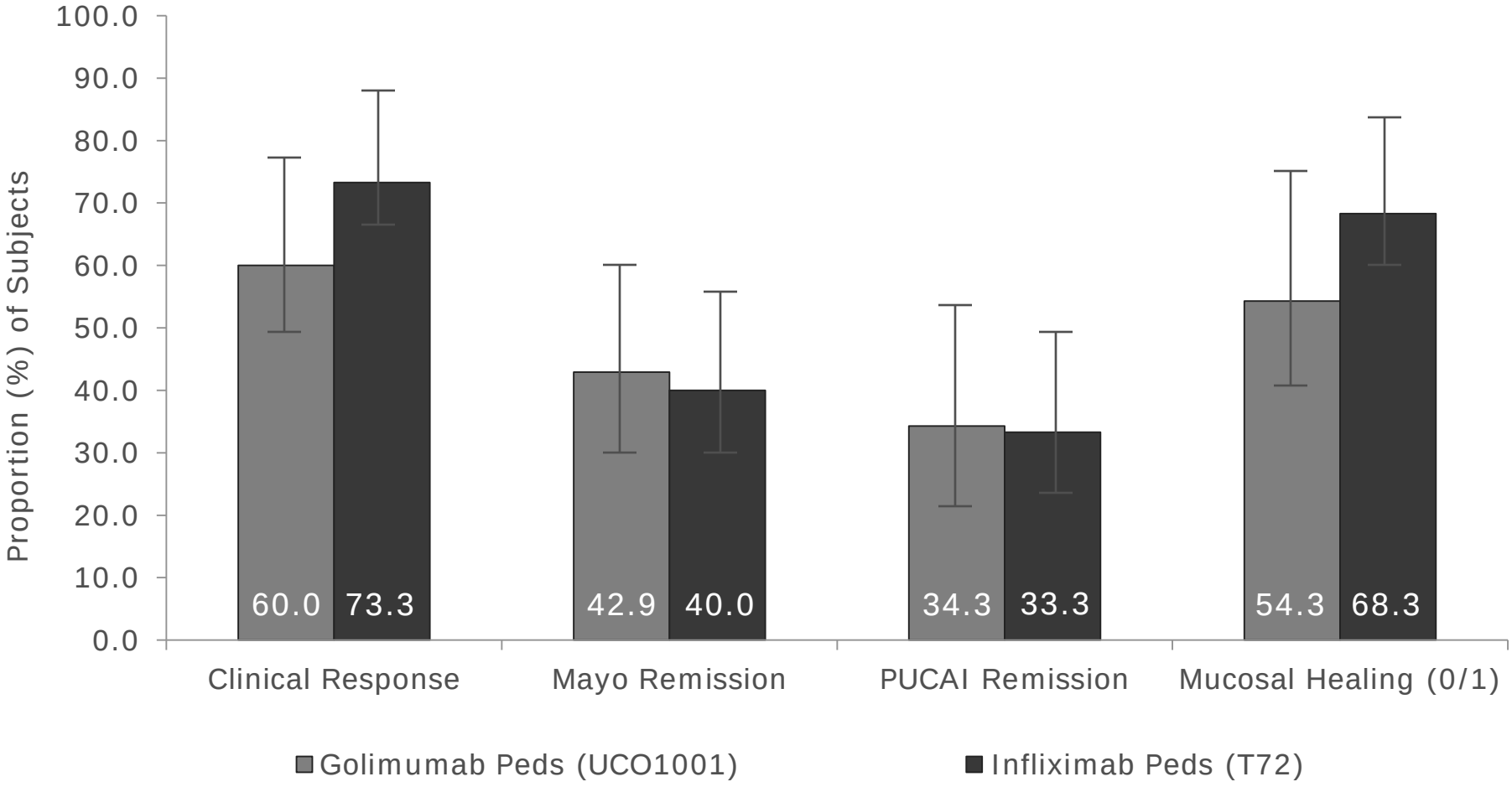




E-R for mucosal healing was similar to that for clinical response

A greater proportion of children achieved clinical remission than adults at the same concentrations

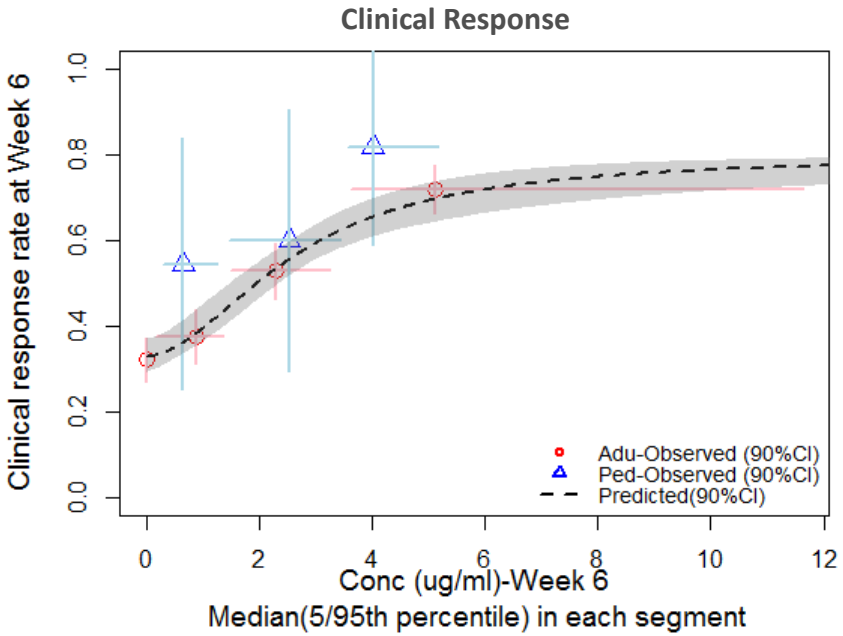
Overall study results were similar to that observed with Infliximab in Pediatric UC

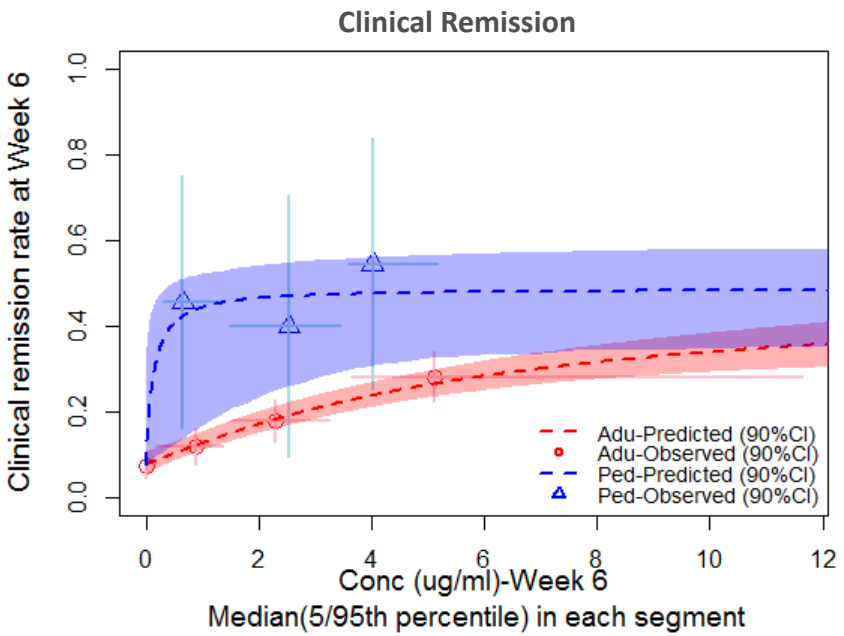


Turner D., et al. ECCO 2016. A-2216.
Hyams J., et al. CGH 2012. 391-9.

Key Outstanding Questions

How is Similarity Of E-R Relationships between children and adults defined?





Adedokun O., et al. ECCO 2016. A-2543.

- *What is the benchmark for defining "similar"? Is this descriptive? Or Statistical?*
- *Is the goal to match the adult exposures and adult response? Or to optimize response?*
  - *If the remission rates in children are higher than in adults, does that undermine the argument that E-R is "similar"?*

How should maintenance data be analyzed?

- Based upon adult data, approximately 50-60% of patients will achieve clinical response, of which 50-60% will maintain response over 1 year → 25-35% of original sample size

  - PK approach: PK data from GLM peds UC study demonstrates comparable steady state concentrations through week 14 in children are similar to adults, suggesting target maintenance exposures are achieved in children with UC
  - Descriptive approach: Show that maintenance data is consistent with the adult data. This was used for infliximab pediatric UC program
  - E-R approach: Demonstrate similar E-R in multiple phases of a disease. This approach will require identical design in maintenance (including additional endoscopies, similar discontinuation criteria, etc…).
  - Efficacy approach: Extremely large number of subjects (e.g. > 600) are needed to appropriately power a randomized withdrawal study

- *If similar exposure-response is demonstrated in induction, is the bar for maintenance different?*

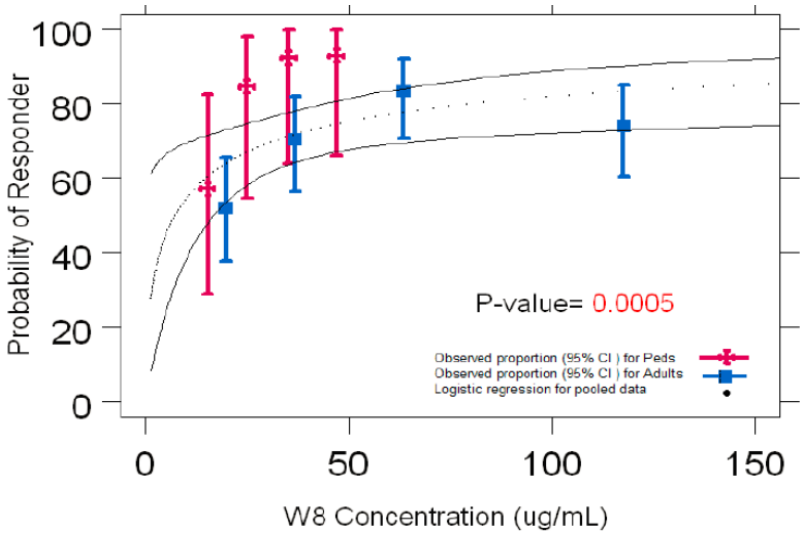
How much safety data is needed?

- 35 children were studied in the UCO1001 study
- Limited safety beyond 14 weeks (ie. 14 subjects beyond 1 year)
- However:
  - Data was supplemented with 173 children with JIA treated with golimumab
  - Large adult database show that the safety of golimumab is similar to other TNFs
  - Safety concerns of TNFs are characterized in children
  - The most serious events are rare and unlikely to be observed in a pediatric clinical trial.

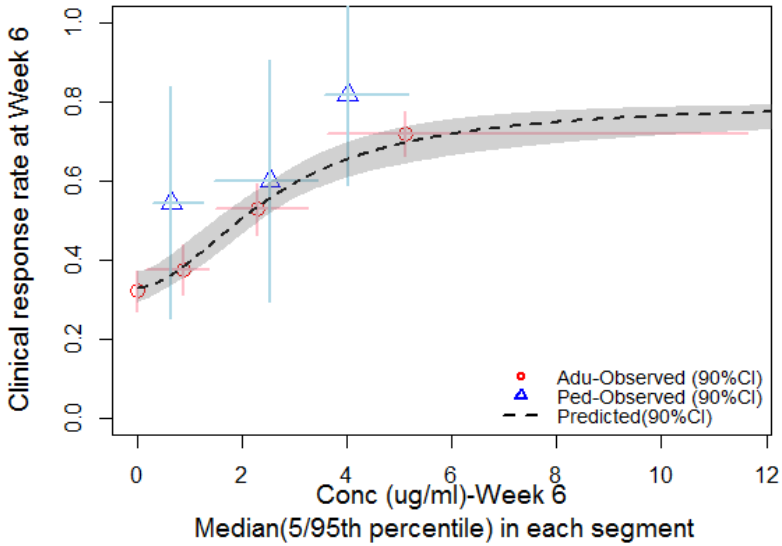
- *What is the size of safety database necessary for approval?*
  - *Is there a magic number?*
  - *Are the requirements the same for different diseases/ indications (e.g. UC vs JIA)?*
- *How should safety from children exposed to the same compound but different indication (e.g. JIA) be factored in?*
- *Are the safety requirements different for novel MOAs and known MOAs (e.g. anti-TNFs)?*

How do we extrapolate from one anti-TNF to another?

Infliximab E-R



Golimumab E-R



- *What are the criteria and conditions that need to be met?*
- *What is the right balance of benefit and risk?*

Adedokun O., et al. IBD 2012. 2753-62.
Adedokun O., et al. ECCO 2016. A-2543.

What is the burden of proof needed to meet the expectations of extrapolation?

Key Component	Approach
Rationale for extrapolation	Consensus that new ways to approach pediatric studies is essential
Similar Disease, Similar Response to Treatment	Built upon literature with molecular analysis
Characterize PK in children with Ulcerative Colitis	Conducted a rigorous phase 1 study across the age range and pop PK analysis
Characterize Exposure-Response	Leveraged experience with infliximab in pediatric UC and demonstrate consistent data with golimumab in UC
Characterize safety of golimumab in children	Large database of anti-TNF use in children and utilize data from golimumab from a different pediatric population
Identify uncertainties	Limitations of E-R model, limited maintenance data, low number of exposed patients with pediatric UC

This is a work in progress for industry, academics, and health authorities

Goal of Extrapolation: Close the gap between adult and pediatric approvals

Compound	Indication	Adult Approval	Pediatric Approval	Gap
Infliximab	Crohn's Disease	1998	2006	8 years
	Ulcerative Colitis	2005	2011	6 years
Adalimumab	Crohn's Disease	2007	2014	7 years
Pediatric Regulations				
	Ulcerative Colitis	2013	*	*
Golimumab	Ulcerative Colitis	2013	?	?
*Approximately 15% enrolled in 2 years				

Are we closing the gap with the current extrapolation framework?