

# **FDA Gastrointestinal Drugs Advisory Committee**

## **REMICADE® - Pediatric Ulcerative Colitis**

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**Stella S. Jones, PhD  
Vice President, Global Regulatory Affairs  
Centocor Ortho Biotech Inc.  
July 21, 2011**

# REMICADE® - Pediatric Ulcerative Colitis Indication

- **Orphan disease:**
  - FDA designated REMICADE orphan drug in pediatric UC on November 12, 2003
- **Pediatric Research Equity Act (PREA):**
  - Centocor entered into commitment on September 2, 2005 to conduct a pediatric UC study (T-72)
- **Adult UC indication:**
  - FDA approved REMICADE for adult UC on September 2005 and October 2006
- **REMICADE pediatric UC sBLA:**
  - Submitted to the FDA in December 2010

# **Pediatric Research Equity Act (PREA)**

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- **Reauthorized by Congress in 2007 under FDAAA**
- **General principle: to provide access to pediatric population for therapies proven safe and effective in adults**
- **Required pediatric assessment:**
  - **To assess safety and efficacy and**
  - **To support dosing and administration in children**
- **Extrapolation - if disease course and treatment effects are sufficiently similar in adults and pediatric patients:**
  - **Pediatric effectiveness can be extrapolated from adults**
- **Usually supplemented with other information obtained in pediatric patients, such as PK studies**

# REMICADE® - Rationale for Pediatric UC Program

- **Course of disease sufficiently similar in adults and pediatric UC patients, reasonable to assume:**
  - **Similar treatment effects of REMICADE in adult and pediatric UC**
  - **Similar concentration-response (CR) in adult and pediatric UC**
- **In accordance with PREA: pediatric UC efficacy can be extrapolated from adult UC**
- **Supplement with dosing, PK and safety data from pediatric UC study (T-72)**
  - **Additional pediatric efficacy data from T-72 confirm similar treatment effects and CR in adult and pediatric UC**

# REMICADE® - Pediatric UC Protocol T72

**Agreement reached with the FDA in 2006 to provide:**

- **PK in pediatric UC patients**
- **Supplemental pediatric efficacy to assess treatment effects and concentration-response (CR) to confirm pediatric dosing regimen**
  - **Induction of clinical response (Week 8)**
  - **Induction and maintenance of clinical remission (Week 8 and Week 54)**
  - **Induction and maintenance of mucosal healing (Week 8 and Week 54\*)**
  - **Elimination of corticosteroid use (Week 54\*\*)**
- **Safety data in children with UC**

\* Not pre-specified analyses or endpoint

\*\* Pre-specified analyses, but not designated primary or secondary endpoints

# REMICADE® - Data Supporting Pediatric UC Indication

- **PK:** Systemic exposure in pediatric UC patients generally comparable to adult UC in support of pediatric dosing regimen
- **Concentration-response (CR):** CR modeling confirms pediatric efficacy (response and remission) comparable or superior to adult UC at a given infliximab serum concentration
- **Efficacy:** Extrapolated from adult UC. Additionally, T72 efficacy confirms similar treatment effects (*response, remission, mucosal healing and steroid-sparing*) of REMICADE in adult and pediatric UC
- **Dosing regimen:** T72 confirms similar efficacy and concentration-response of REMICADE in adult and pediatric UC supporting recommended pediatric dosing regimen
- **Pediatric safety:** REMICADE safety characterized
  - T72 safety in children with UC
  - Post-marketing surveillance data from 1998 to 2011

# REMICADE® Pediatric UC – Proposed Indication and Recommended Dosing Regimen

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## Proposed Indication:

- REMICADE is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult **and pediatric** patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Recommended dose: 5 mg/kg at weeks 0, 2, 6, then q8 weeks
- Priority review

# REMICADE® - FDA Approved Indications

1998

## Crohn's Disease acute treatment

- Luminal Crohn's Disease
- Fistulizing Crohn's Disease

2000

## RA (MTX failures)

- Inhibiting progression of structural damage indication

9/2004

## RA (MTX-naïve)

- Reducing signs & Sx, inhibiting progression of structural damage & improving physical function

5/2005

## Psoriatic Arthritis

- Reducing signs & Sx of active arthritis indication

9/2006

## Plaque Psoriasis Indication

2/2002

## RA (MTX failures)

- Improving physical function indication

12/2004

## Ankylosing Spondylitis

- Reducing signs & Sx indication

8/2006

## Psoriatic Arthritis

- Inhibiting Progression of Structural Damage & Improving Physical Function

1999

## Rheumatoid Arthritis (MTX failures)

- Reducing signs & Sx

# REMICADE® - FDA Approved Indications

1998

## Crohn's Disease acute treatment

- Luminal Crohn's Disease
- Fistulizing Crohn's Disease

6/2002

## Crohn's Disease Maintenance indication

- Luminal Crohn's Disease

Pediatric Crohn's Disease

2003

## Crohn's Disease

- Maintenance indication of Fistulizing Crohn's Disease

Ulcerative Colitis

Ulcerative Colitis

# REMICADE® - FDA Approved Indications

**1998**  
**Crohn's Disease**  
**acute treatment**

- Luminal Crohn's Disease
- Fistulizing Crohn's Disease

**6/2002**  
**Crohn's Disease**  
**Maintenance indication**

- Luminal Crohn's Disease

**5/2005**  
**Psoriatic Arthritis**

- Reducing signs & Sx of active arthritis indication

**9/2006**  
**Plaque Psoriasis**  
**Indication**

**2000**  
**RA (MTX failures)**

- Inhibiting progression of structural damage indication

**9/2004**  
**RA (MTX-naïve)**

- Reducing signs & Sx, inhibiting progression of structural damage & improving physical function

**5/2006**  
**Pediatric Crohn's Disease**

- Reducing signs & Sx & inducing & maintaining clinical remission

**2/2002**  
**RA (MTX failures)**

- Improving physical function indication

**12/2004**  
**Ankylosing Spondylitis**

- Reducing signs & Sx indication

**8/2006**  
**Psoriatic Arthritis**

- Inhibiting Progression of Structural Damage & Improving Physical Function

**1999**  
**Rheumatoid Arthritis**  
**(MTX failures)**

- Reducing signs & Sx

**2003**  
**Crohn's Disease**

- Maintenance indication of Fistulizing Crohn's Disease

**9/2005**  
**Ulcerative Colitis**

- Reducing signs & Sx, achieving clinical remission & mucosal healing, and eliminating steroid use

**10/2006**  
**Ulcerative Colitis**

- Maintaining Clinical Remission & Mucosal Healing

# **REMICADE®: Post-Approval Experience**

## **August 24, 1998 – February 23, 2011**

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- **REMICADE approved in 103 countries for various immune-mediated diseases**
- **Cumulative worldwide exposure:**
  - **Adults (all indications): >1.5 million patients**
    - **IBD indications: >600,000 patients**
  - **Children (all indications): >23,000 patients**
    - **IBD indications: >19,000 patients**

# Attending Experts and Consultants

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- **Jeffrey S. Hyams, MD**

*Professor of Pediatrics (Gastroenterology)  
University of Connecticut, School of Medicine*

- **Robert Baldassano, MD**

*Professor of Pediatrics (Gastroenterology)  
University of Pennsylvania, School of Medicine*

- **Stephan A. Grupp, MD, PhD**

*Associate Professor of Pediatrics (Oncology)  
University of Pennsylvania, School of Medicine*

# Presentation Agenda

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**Stella S. Jones, PhD**

*Vice President,  
Global Regulatory Affairs, Centocor*

**Introduction**

**Jeffrey S. Hyams, MD**

*Professor of Pediatrics,  
University of Connecticut*

**Disease Overview  
and Clinical Efficacy**

**Joseph Adedokun, MS, RPh**

*Sr. Research Scientist,  
Pharmacometrics, Centocor*

**Overview of Clinical  
Pharmacology**

**Robert H. Diamond, MD**

*Lead Medical Director,  
Medical Affairs, Centocor*

**Safety & Conclusions**

# **Disease Overview and Clinical Efficacy**

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**Jeffrey S. Hyams, MD**  
**Head, Division of Digestive Diseases,  
Hepatology, and Nutrition**  
**Connecticut Children's Medical Center**  
**Professor of Pediatrics,**  
**University of Connecticut School of Medicine**

# REMICADE® in Pediatric Ulcerative Colitis

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- Disease overview
- Adult UC program overview
- Pediatric UC program overview
- T72 study results
  - Efficacy
  - Comparison to adult UC studies: ACT 1 and ACT 2

# Disease Overview

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# Ulcerative Colitis

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- **Chronic inflammatory disease of the colon**
  - TNF $\alpha$  is a cytokine mediator of UC
  - Targeting TNF $\alpha$  is an effective therapy for adult UC
- **50,000 to 100,000 children in United States with IBD**
  - 40% with UC
- **Clinical features: diarrhea, rectal bleeding, weight loss and fever**

# Similarity of Pediatric and Adult UC

- Pathogenesis and genetics of UC similar in adults and children
  - In GWAS studies, all risk variants present in both pediatric and adult UC<sup>1</sup>
- Response to treatment is comparable:

Treatment	Endpoint	Children	Adults
ASAs	Remission	50% <sup>2</sup>	59-70% <sup>3</sup>
Corticosteroids	Early CS responsiveness	60% <sup>4</sup>	58% <sup>5</sup>
Thiopurines	Corticosteroid-free inactive disease	49% <sup>6</sup>	53% <sup>6</sup>

- Disease phenotype is the same, except children have more extensive disease at diagnosis<sup>7</sup>

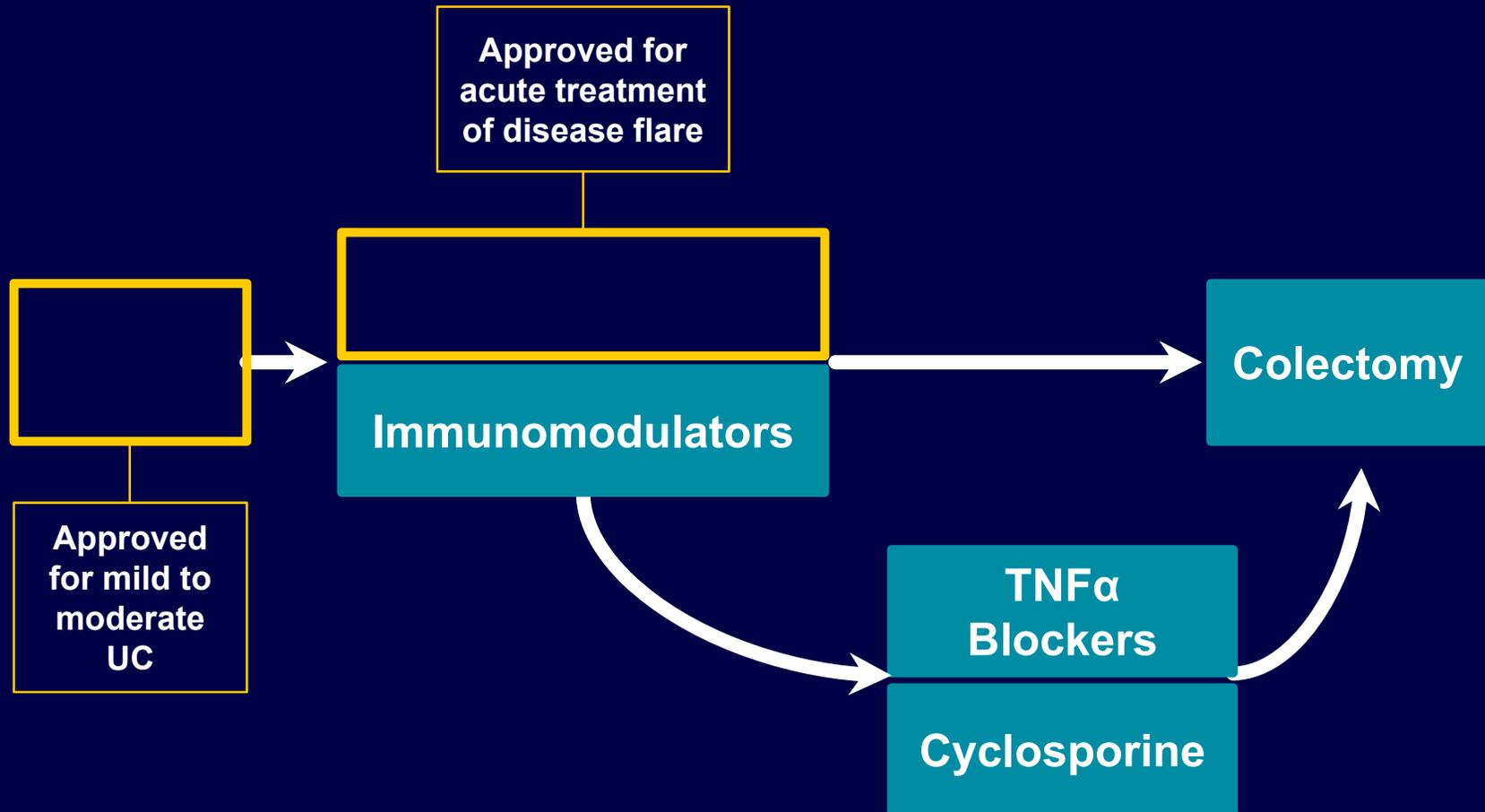
1. Sauer & Kugathasan, 2009 2. Zeisler et al, 2011 3. Hanauer et al, 1996 4. Hyams et al, 2006  
5. Faubion et al, 2001 6. Hyams et al, 2010 7. Van Limbergen et al, 2008

# Burden of Disease in Children

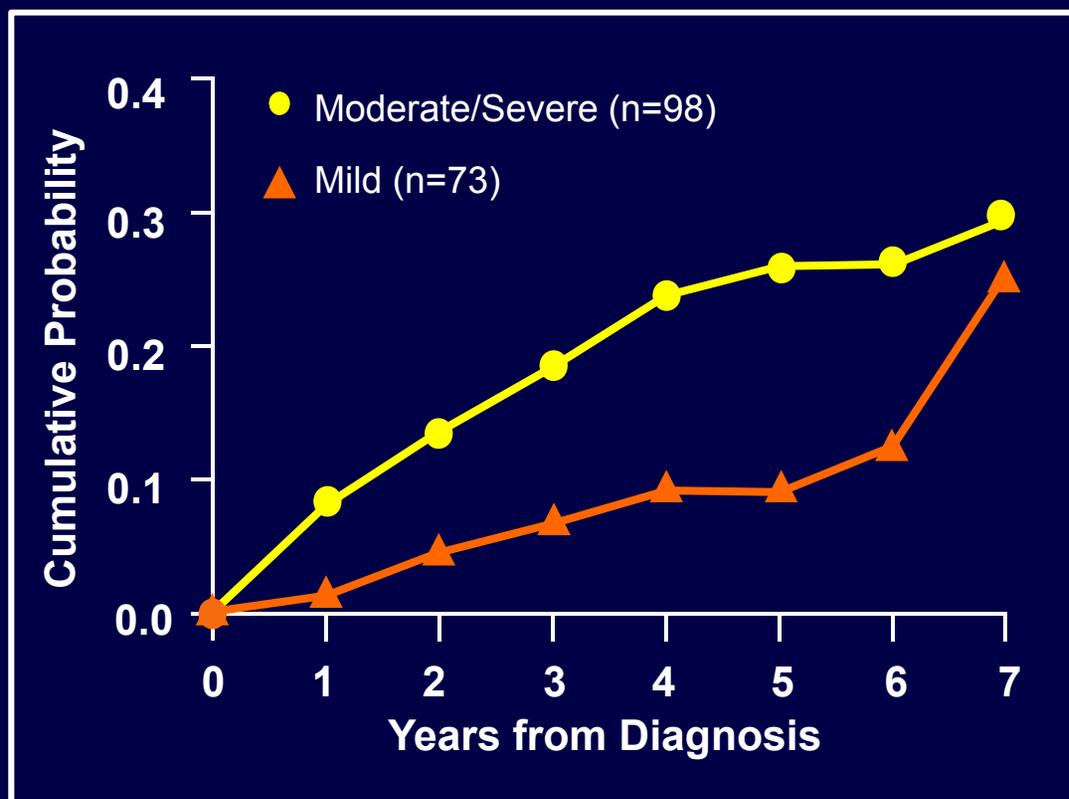
- 28% of children  $\leq 15$  years require  $\geq 1$  hospitalization over a three year period<sup>1</sup>
- 45% corticosteroid dependency<sup>2</sup>
- Up to 26% of pediatric patients with severe UC require colectomy within five years of diagnosis<sup>3</sup>
- Significant negative impact on quality of life:
  - Similar to children with cancer<sup>4</sup>
  - Psychiatric disturbances<sup>5</sup>
  - School absences increased<sup>6</sup>

1. Turner et al. 2008 2. Hyams et al. 2006 3. Hyams et al. 2005  
4. Marcus et al. 2009 5. Engstrom et al. 1991 6. Marri et al. 2005

# Current Treatment Paradigm in Pediatric UC



# Probability of Colectomy<sup>1</sup> and Adverse Consequences



- Frequent bowel movements (5-6/24 hrs)<sup>2</sup>
- Nocturnal stooling with soiling (up to 10%)<sup>3</sup>
- Small bowel obstruction (19%)<sup>4</sup>
- Wound infections (13%)<sup>4</sup>
- Pouchitis (30-40%)<sup>4</sup>
- Impaired fertility (48%)<sup>5</sup>
- Risk of mis-diagnosis (15%)<sup>6</sup>

1. Hyams et al. 1996 2. Hueting et al. 2005 3. Bremner et al. 2004  
4. Patton et al. 2010 5. Waljee et al. 2006 6. Alexander et al. 2003

# **Unmet Need: Approved Pediatric UC Medical Therapy**

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- **Moderate to severe population**
- **Spans both induction and maintenance**
- **Highly effective**
- **Established and acceptable safety profile in children**

# Adult UC Program Overview

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# REMICADE® Studies in Adult Ulcerative Colitis

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- Randomized, double-blind, placebo-controlled Phase 3
- Moderate to severe UC, failed conventional therapy
- ACT 1
  - 364 patients
  - 1 year
- ACT 2
  - 364 patients
  - 30 weeks

# REMICADE® in Adult Patients with UC

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REMICADE has shown clinically meaningful and statistically significant differences from placebo in the following endpoints:

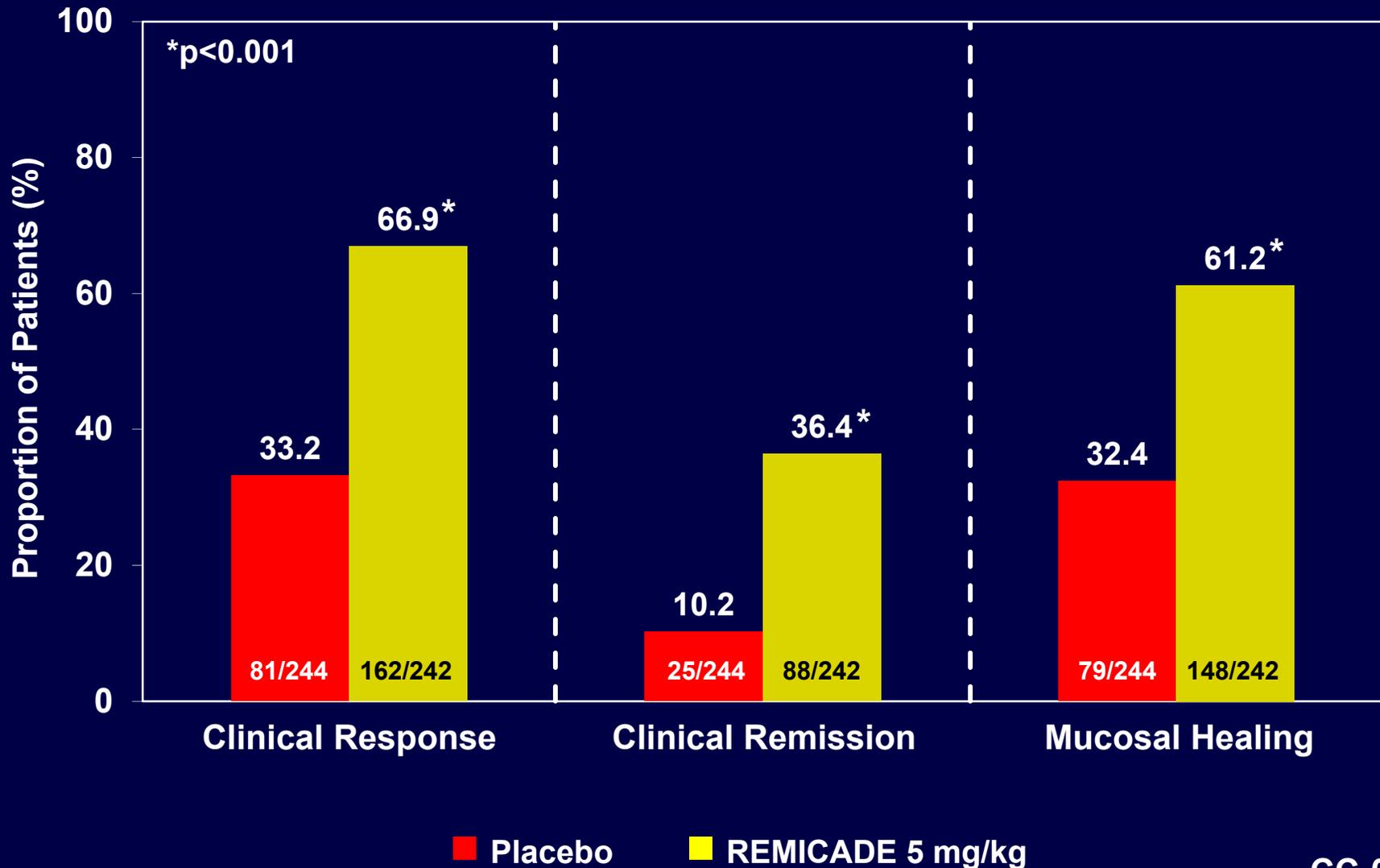
## Induction at Week 8

- Clinical response (primary endpoint)
- Clinical remission
- Mucosal healing

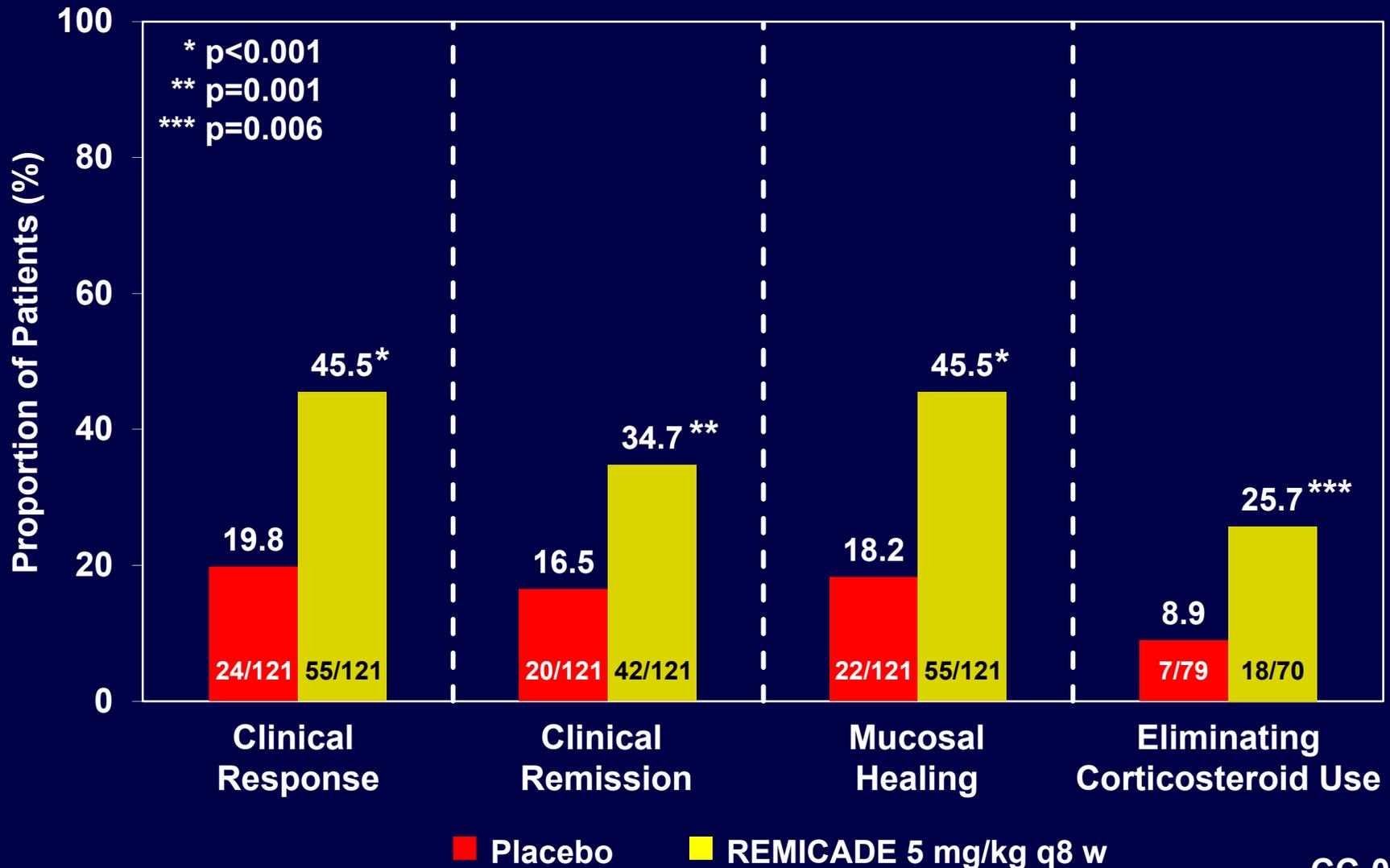
## Maintenance at Week 54

- Clinical response
- Clinical remission
- Mucosal healing
- Eliminating corticosteroid use

# ACT 1 and ACT 2: Induction Results at Week 8



# ACT 1: Maintenance Endpoints at Week 54



## **REMICADE® Indications in Adult UC**

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- **Reducing signs and symptoms**
- **Inducing clinical remission**
- **Inducing mucosal healing**
- **Maintaining clinical remission**
- **Maintaining mucosal healing**
- **Eliminating corticosteroid use**

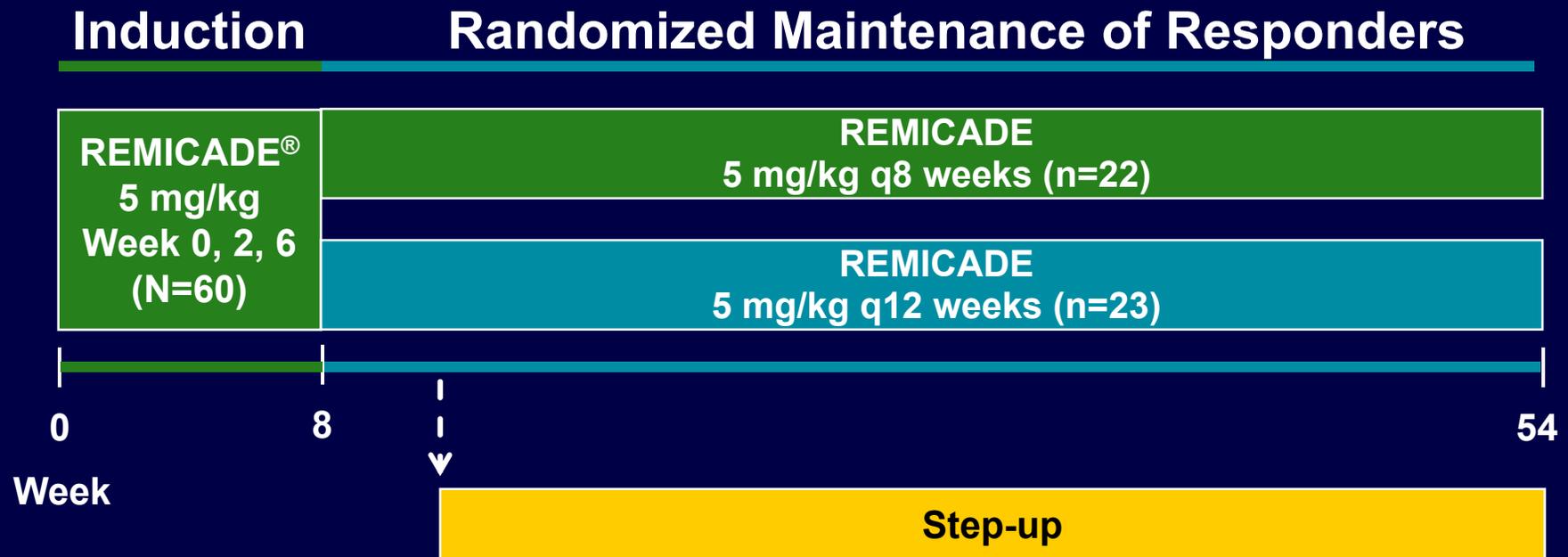
# Pediatric UC Program Overview

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## T72 and Supportive Studies

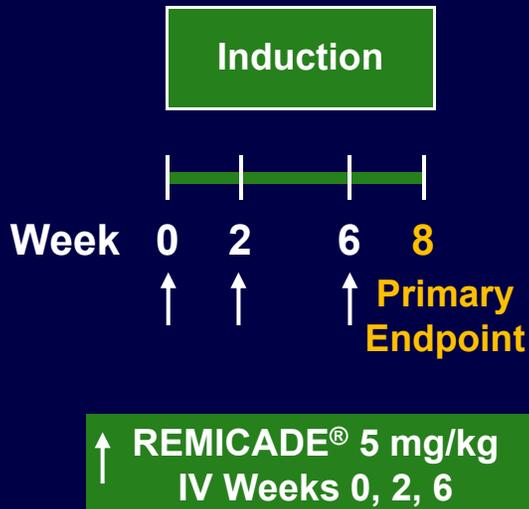
<b>T72</b>	<b>Pediatric UC</b>	<b>54 week induction/ maintenance study</b>	<b>N=60</b>
<b>ACT 1</b>	<b>Adult UC</b>	<b>54 week induction/ maintenance study</b>	<b>N=364</b>
<b>ACT 2</b>	<b>Adult UC</b>	<b>30 week induction/ maintenance study</b>	<b>N=364</b>
<b>REACH</b>	<b>Pediatric CD</b>	<b>54 week study</b>	<b>N=112</b>

# Phase 3 Pediatric UC Open-Label Study Design



- 27 Sites across US, Canada and Europe
- ~3 years to enroll

# Induction and Evaluation Instruments



- Mayo quantifies UC severity
  - 4 subscores
    - Stool frequency, rectal bleeding, PGA, endoscopy
  - Each subscore 0 to 3
  - Range: 0 to 12
- PUCAI assesses UC severity in children without the need for endoscopy
  - 6 subscores assessing symptoms and activity level
  - Total score is 0 to 85

# Pediatric Ulcerative Colitis Activity Index (PUCAI)

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- **6 subscores**
  - **Rectal bleeding (0 to 30 points)**
  - **Number of stools in a 24 hour period (0 to 15 points)**
  - **Stool consistency (0 to 10 points)**
  - **Abdominal pain (0 to 10 points)**
  - **Nocturnal bowel movement (0 to 10 points)**
  - **Activity level (0 to 10 points)**

# T72 Study Results

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# Baseline Characteristics

Characteristics	Total (N=60)
Age	
6 – 11 years	15 (25%)
12 – 17 years	45 (75%)
Median Disease Duration (years)	1.35
Extensive disease	77%
Median Mayo Score	8
Median PUCAI	55
<b>Baseline Medication</b>	
Corticosteroids	62%
Immunomodulators	53%
ASAs	53%

- **100% of patients were receiving baseline medications**
- **Baseline characteristics were generally comparable across the maintenance treatment groups**

# Prior Medication History

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	Total (N=60)
Any medications	100%
Corticosteroids	100%
Immunomodulators	70%
Aminosalicylates	90%

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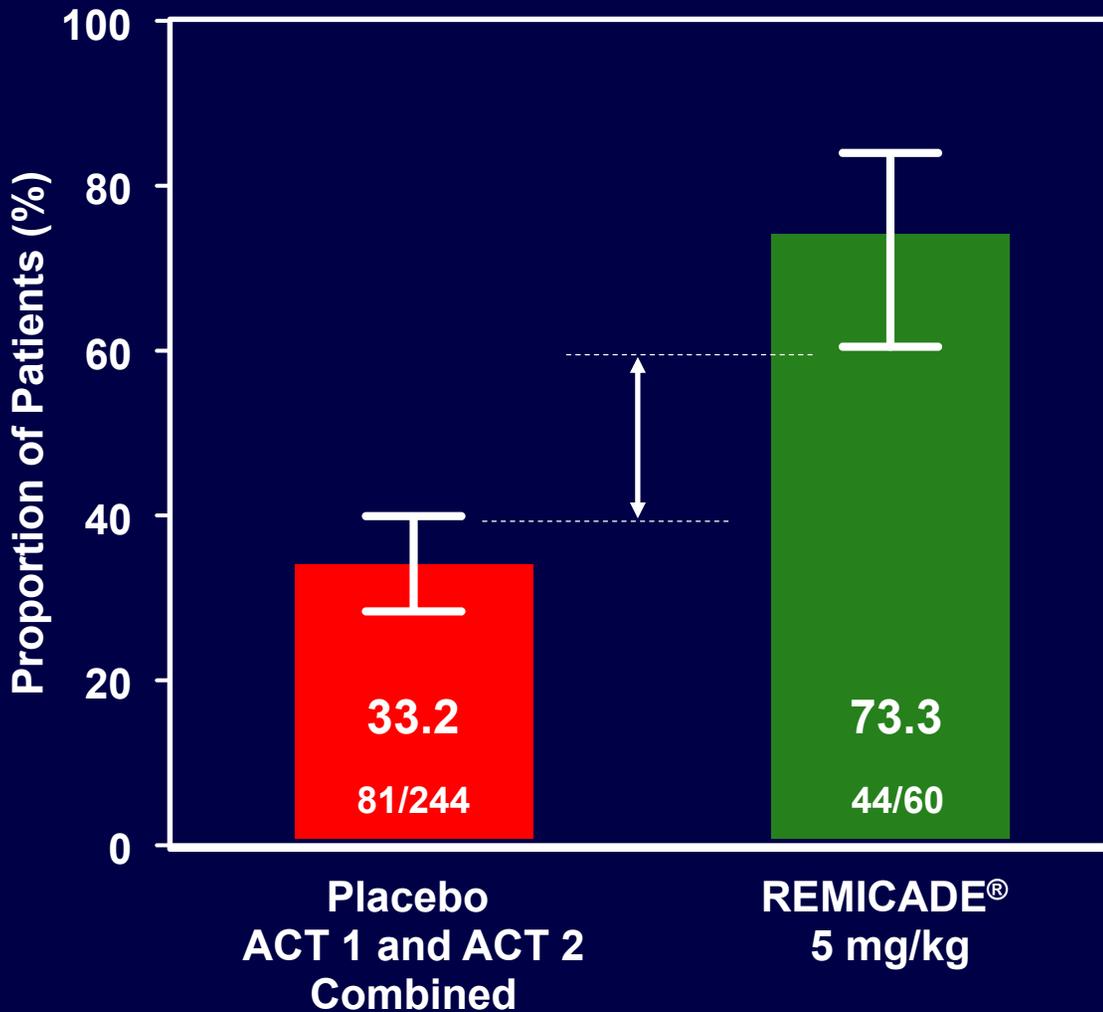
# T72: Primary Endpoint at Week 8

## Clinical Response:

- Decrease in Mayo score of  $\geq 30\%$  and  $\geq 3$  points, with
- A decrease in rectal bleeding subscore of  $\geq 1$  or
- A rectal bleeding subscore of 0 or 1

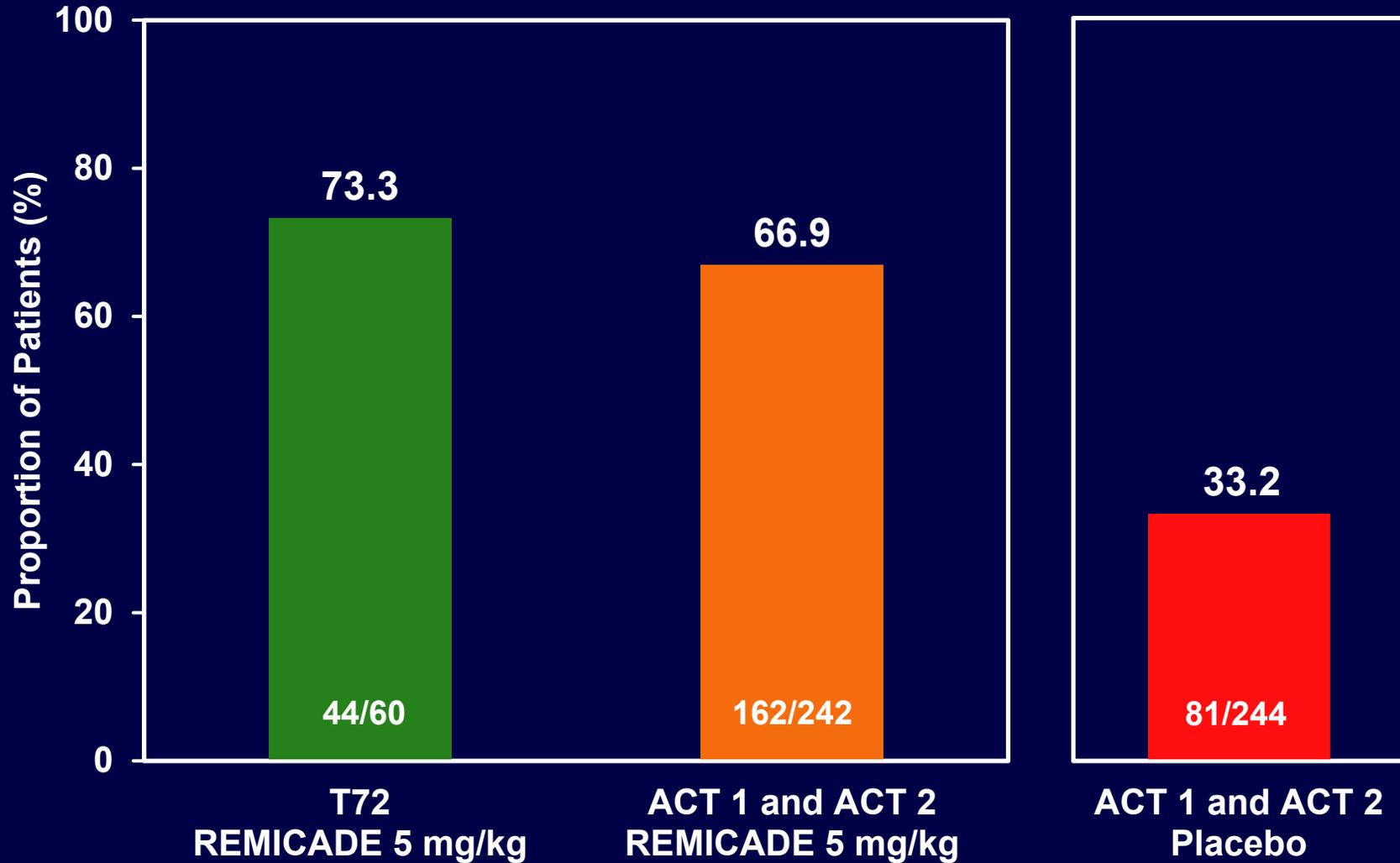
## Criteria for a Positive Study:

- Based on historical placebo control in ACT (27.3%, 39.1%)
- Lower limit of 95% CI for the proportion of patients in clinical response at Week 8 to be  $>40\%$



# Clinical Response at Week 8

## T72 Compared to ACT 1 and ACT 2



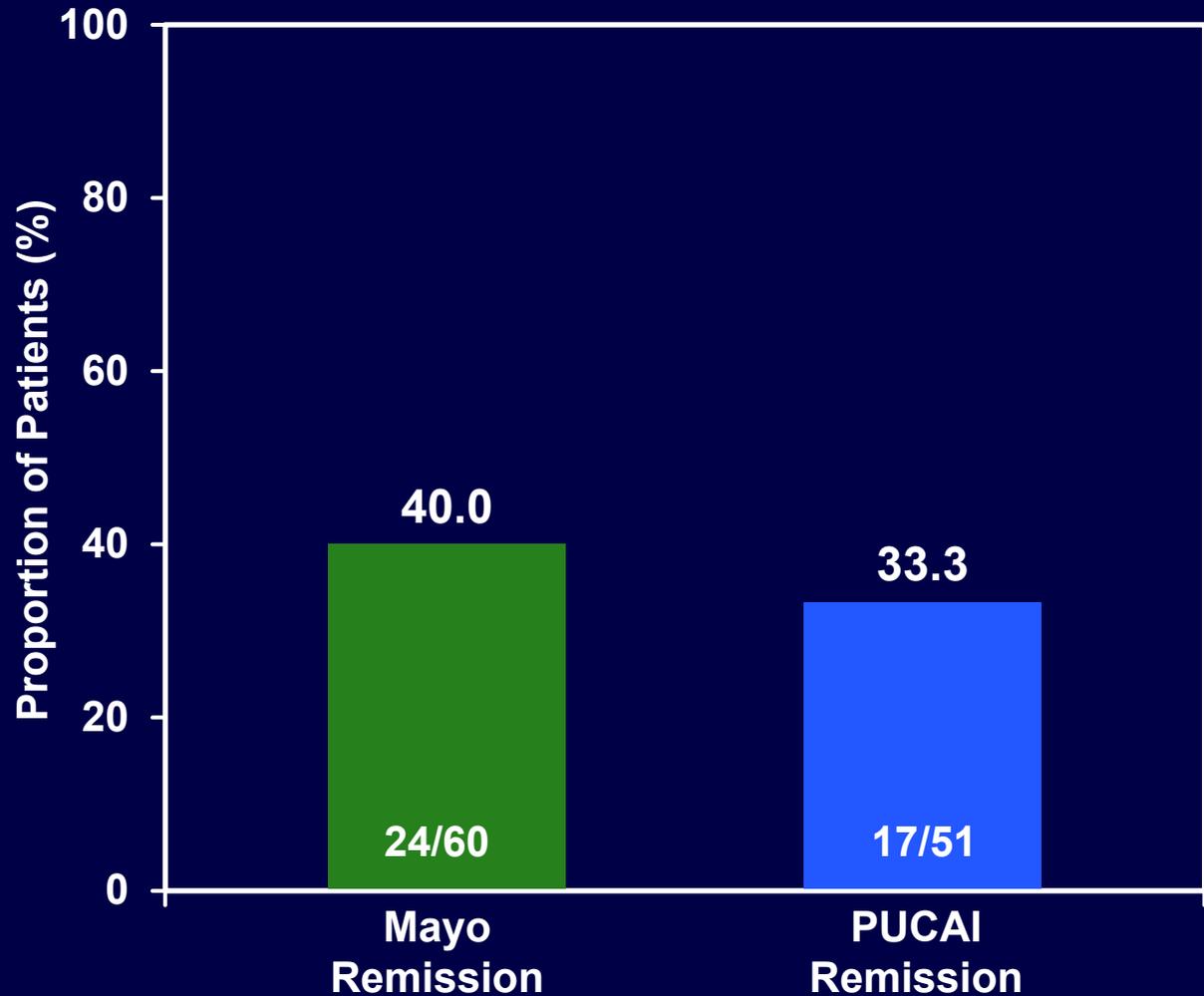
# T72: Remission at Week 8

## Mayo Remission:

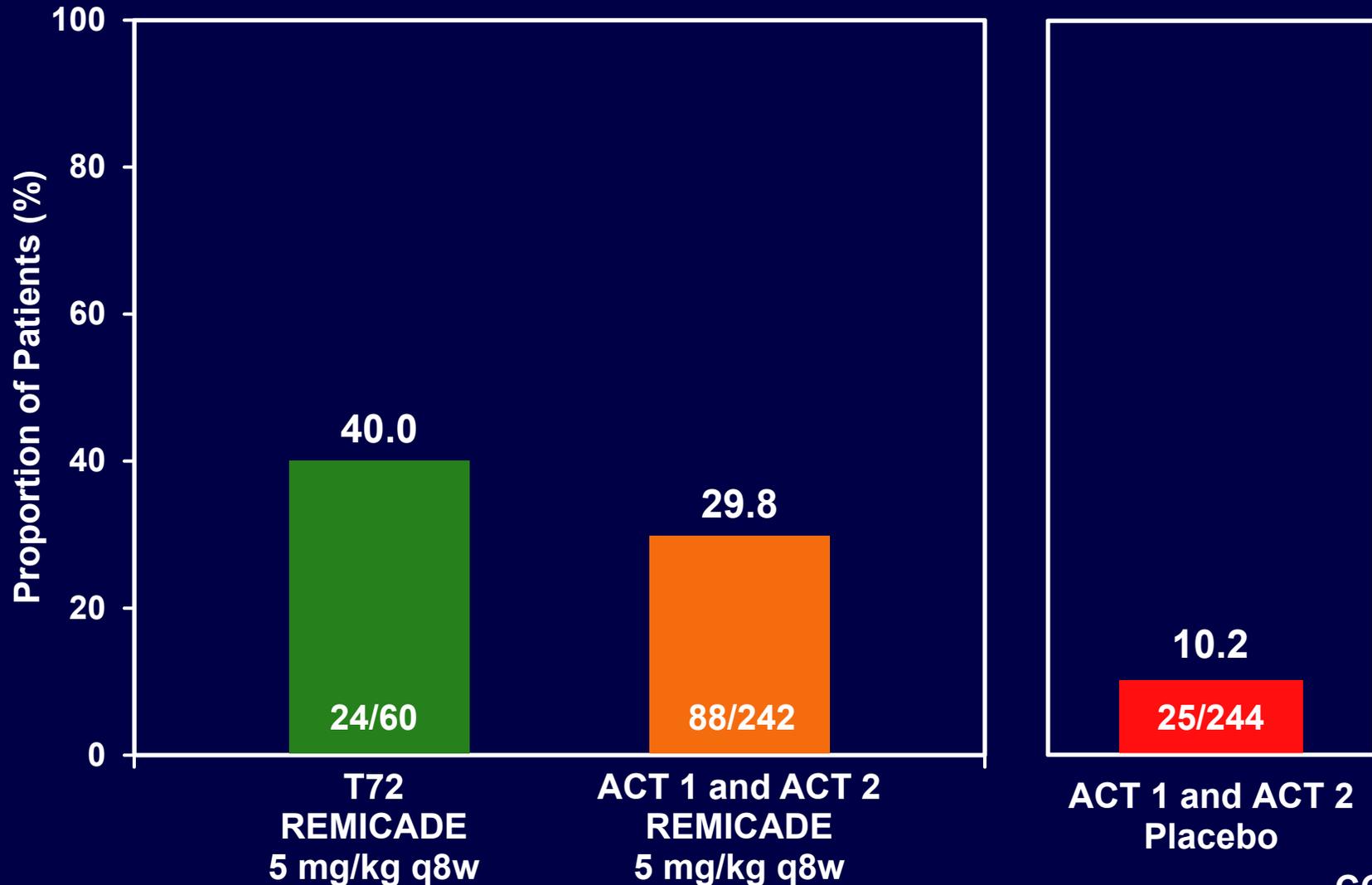
- Mayo score of  $\leq 2$  points, with
- No individual subscore  $> 1$

## PUCAI Remission:

- PUCAI  $< 10$



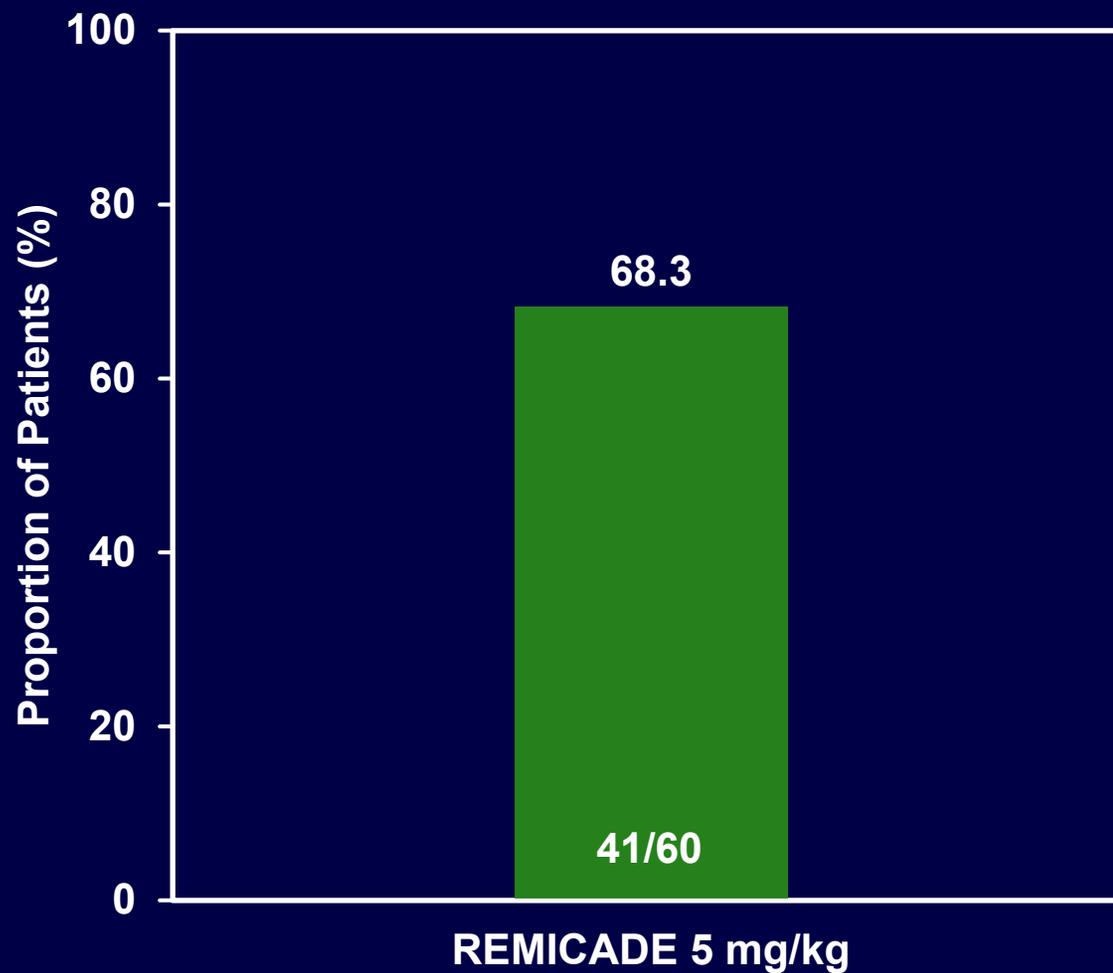
# Mayo Remission at Week 8 T72 Compared to ACT 1 and ACT 2



## T72: Mucosal Healing at Week 8

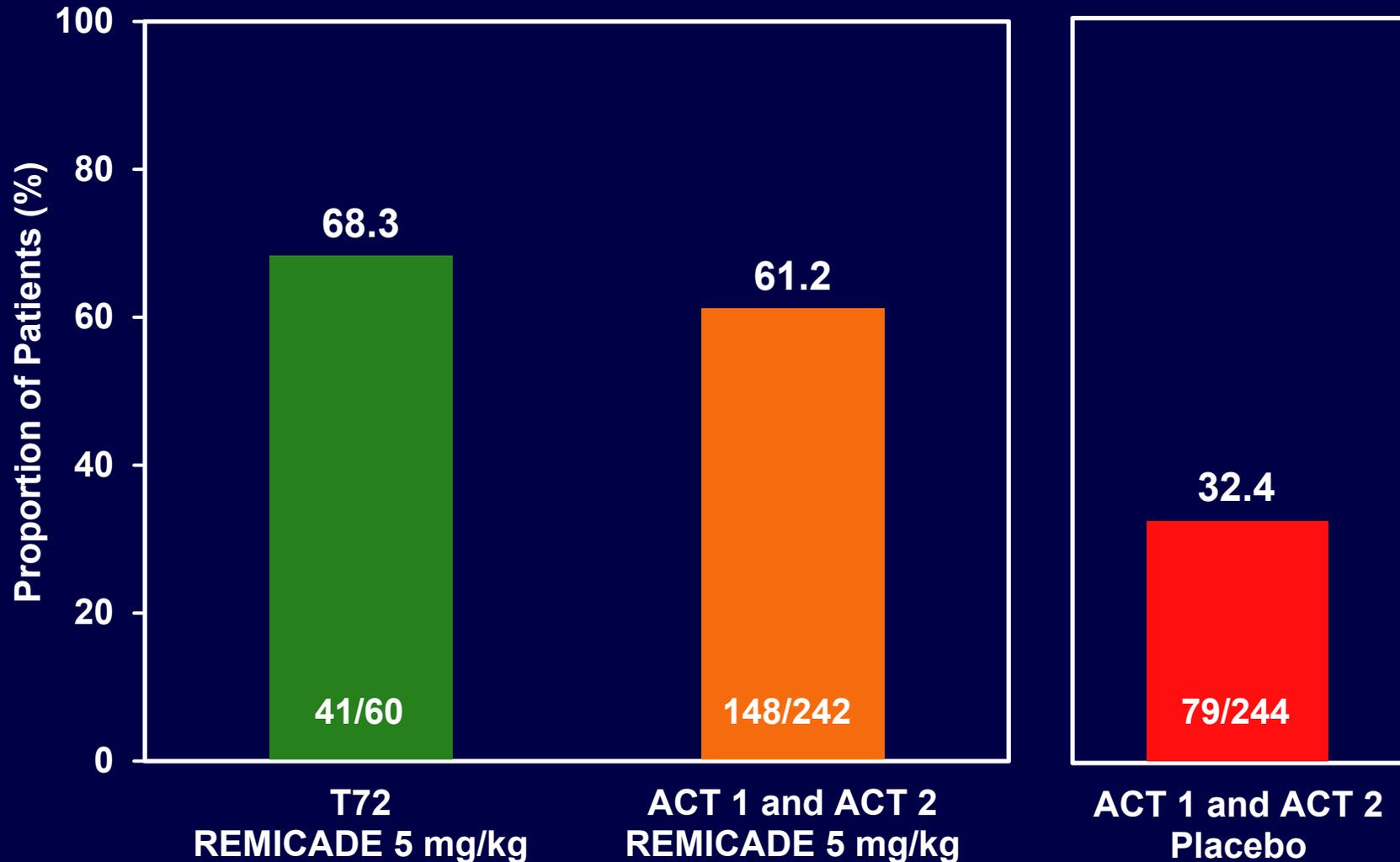
### Mucosal Healing:

- Endoscopic subscore of 0 or 1
- 100% of patients had a score of  $\geq 2$  at baseline



# Mucosal Healing at Week 8

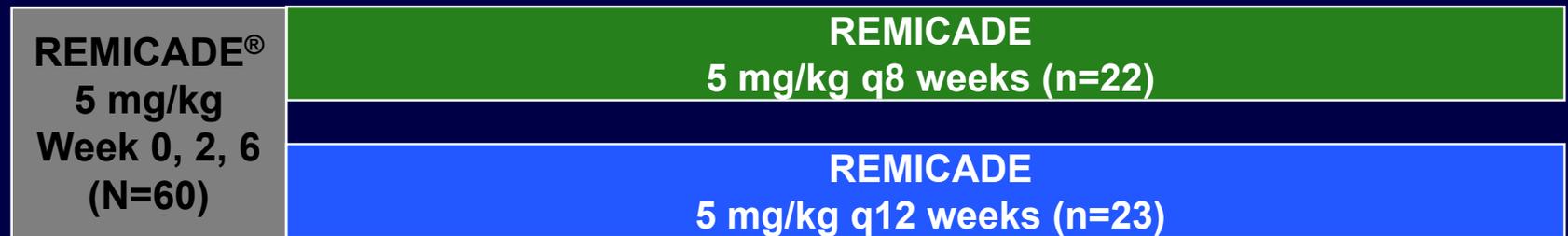
## T72 Compared to ACT 1 and ACT 2



# Phase 3 Pediatric Ulcerative Colitis Study Design

**Induction**

**Randomized Maintenance of Responders**



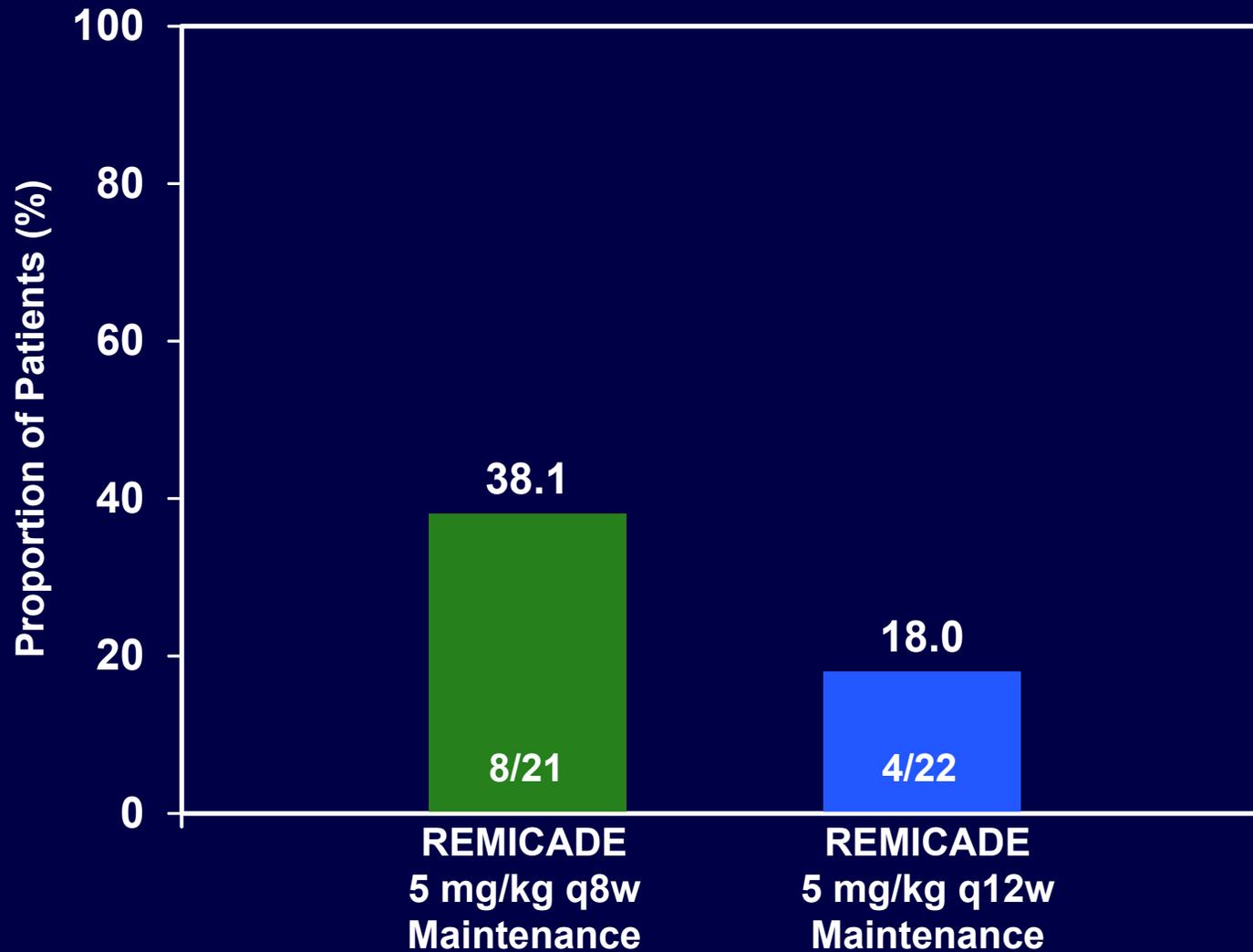
0

8

54

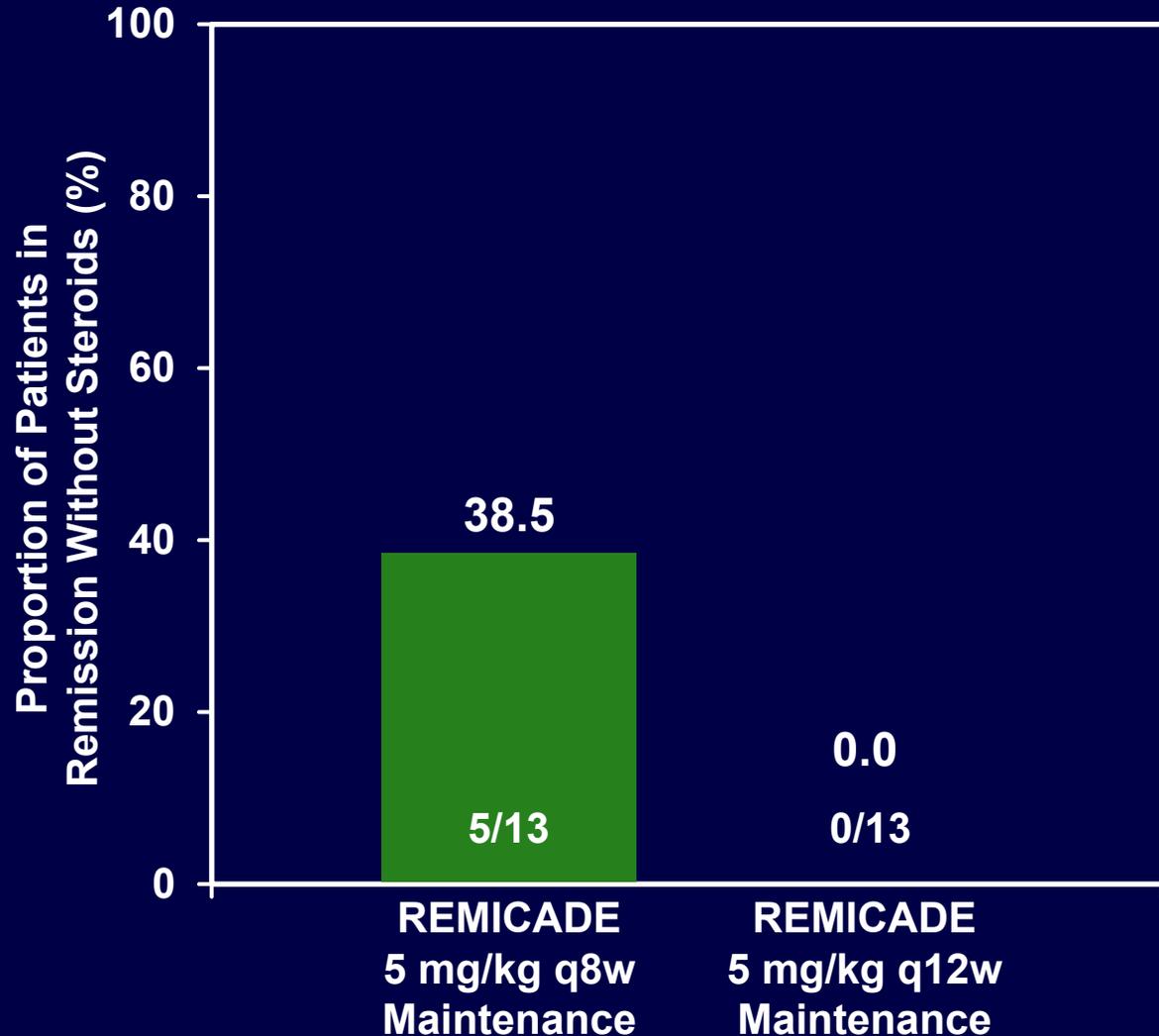
Week

# T72: PUCAI Remission at Week 54



# T72: Remission Without Corticosteroids at Week 54 for Patients on Corticosteroids at Baseline

- Taper permitted beginning at Week 0



## T72: Maintenance of Mucosal Healing

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- **Endoscopy at Week 54 in T72 optional due to challenges in pediatric population**
  - 8 of 9 patients with endoscopy at Week 54 maintained mucosal healing
- **Strong supportive data from ACT 1**
  - 45% maintained mucosal healing at Week 54 in REMICADE® 5 mg/kg q8w maintenance
- **Consistency of mucosal healing at Week 8 in T72 and ACT1 and ACT 2 as well as multiple other endpoints support maintenance of mucosal healing in T72**

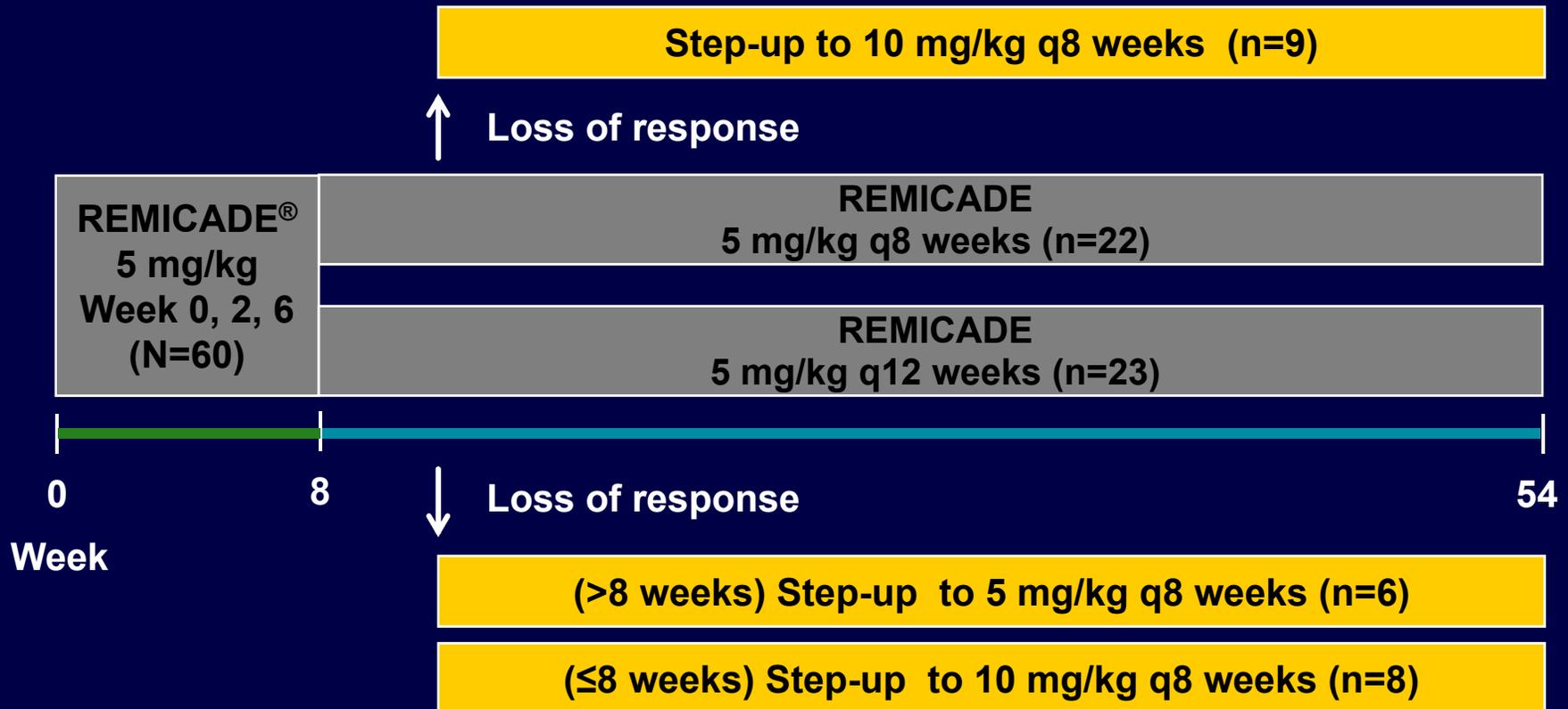
# Step Up

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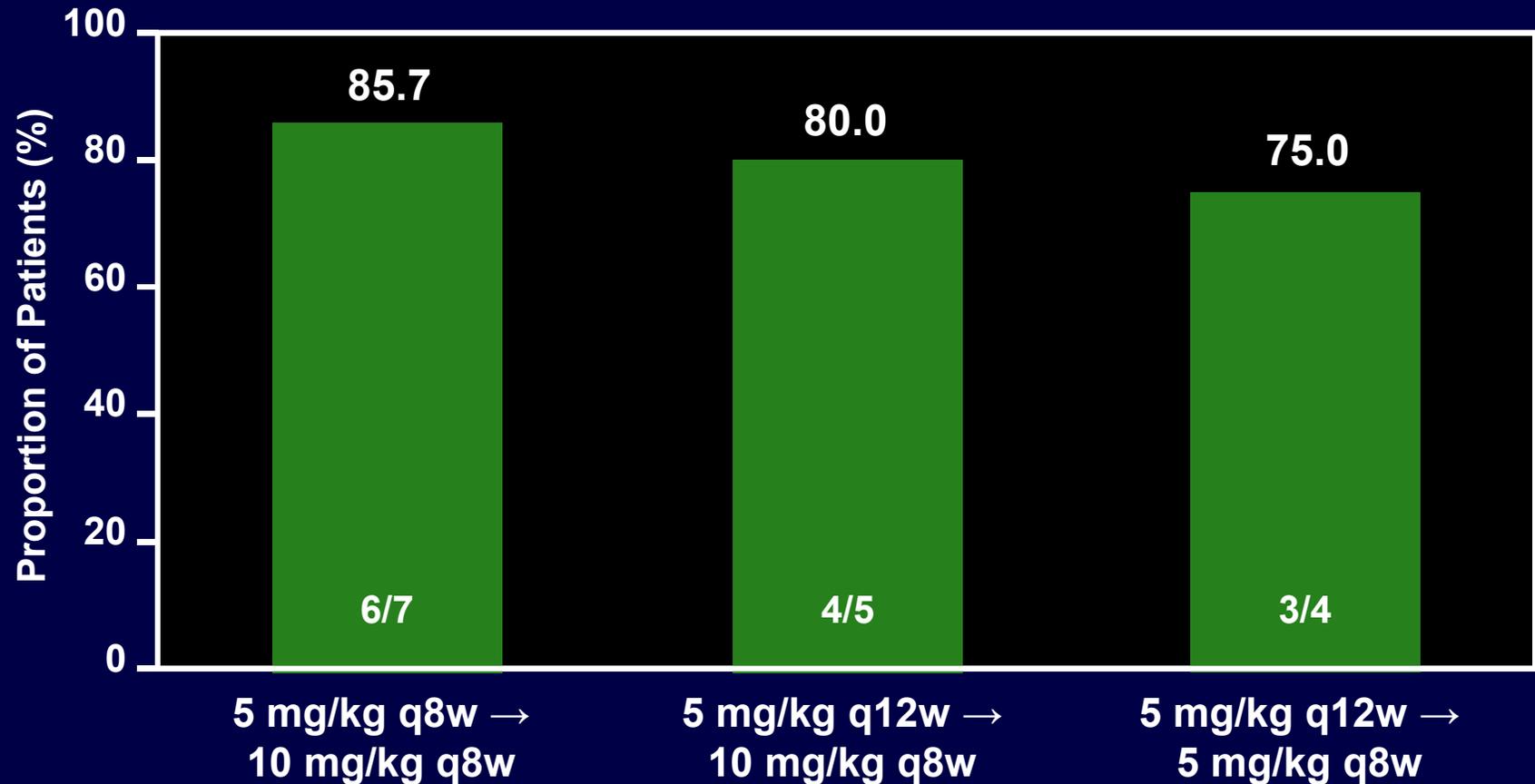
# T72: Step Up

**Induction**

**Randomized Maintenance of Responders**



# T72: Patients Who Stepped Up Regained Response\*



\* Decrease in the partial Mayo score of  $\geq 2$  points from first step up visit

# Conclusions

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- **Pediatric UC is a chronic, debilitating disease with high unmet need**
- **Pediatric and adult disease are similar**
- **REMICADE<sup>®</sup> was effective in children to:**
  - **Reduce signs and symptoms**
  - **Induce and maintain clinical remission and mucosal healing**
  - **Eliminate corticosteroid use in pediatric patients with moderately to severely active UC who have had an inadequate response to conventional therapy**
- **At Week 54, twice as many patients were in remission following q8 week vs q12 week therapy**
- **Results comparable to ACT Studies**

# Overview of Clinical Pharmacology

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**Joseph Adedokun, MS, RPh**  
**Senior Research Scientist**  
**Centocor Ortho Biotech Inc.**

# Overview

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- **General PK characteristics of infliximab**
- **Comparison of the PK of infliximab in pediatric UC with:**
  - **Pediatric CD**
  - **Adult UC**
- **Infliximab PK exposure-response relationship in pediatric and adult UC**
  - **Induction**
  - **Maintenance**
- **Conclusion**

# General PK Characteristics of Infliximab

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# General Infliximab PK Characteristics

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- **Linear PK relationship with dose**
- **Volume of distribution at steady state is indicative of primarily vascular distribution**
- **No systemic accumulation following repeated infusions at 8-week intervals**
- **$t_{1/2} = 7.7- 9.5$  days**
- **Factors known to affect PK include bodyweight, serum albumin and development of anti-drug antibodies**

# **Comparison of the PK of Infliximab in Pediatric UC with Pediatric CD and Adult UC**

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# T72 and Supportive Studies

**T72**  
**N=60**

**Pediatric UC**

**Primary Study**

**ACT 1**  
**N=364**

**Adult UC**

**PK Comparison**  
**Exposure-Response**

**ACT 2**  
**N=364**

**Adult UC**

**REACH**  
**N=112**

**Pediatric CD**

**PK Comparison**

# Comparable PK

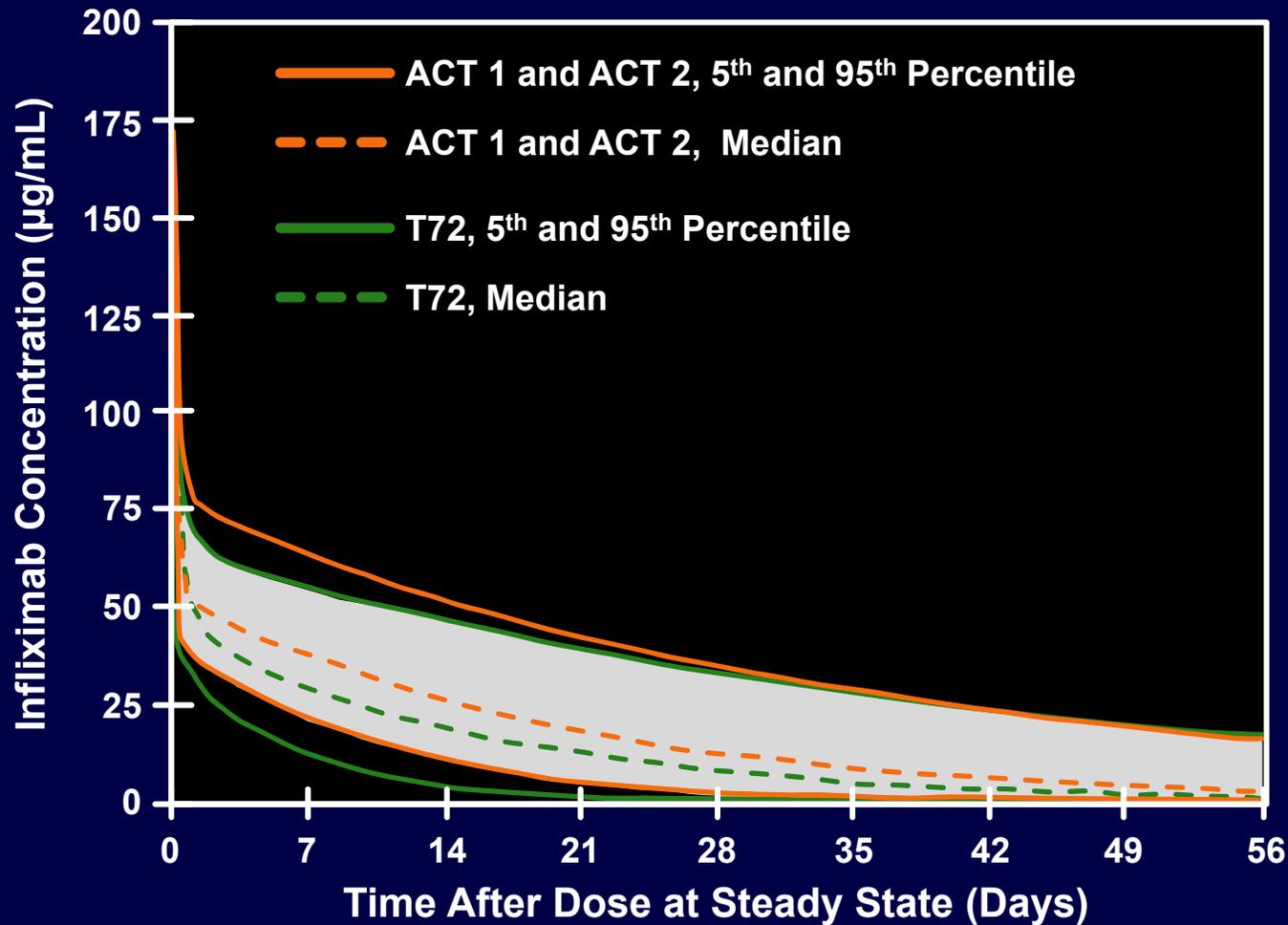
## T72 / REACH / ACT 1 and ACT 2

PK Parameter	T72	REACH	ACT 1 & ACT 2 Combined
Median $t_{1/2}$ (days)	10.8	10.7	11.7 <sup>†</sup>
Median infliximab serum concentration ( $\mu\text{g/mL}$ ) at Week 8	27.5*	NA	33.3*
Median peak serum infliximab concentration during induction ( $\mu\text{g/mL}$ ) at Week 2	115.1*	108.7*	131.6*
Median trough serum infliximab concentration during maintenance ( $\mu\text{g/mL}$ ) at Week 30	1.9*	1.8*	2.5*

\* Data presented for the 5 mg/kg q8w group

<sup>†</sup> Derived from data only in ACT 1

# Substantial Overlap in Simulated Steady State Infliximab Exposure: T72 / ACT 1 and ACT 2



Median AUC ~20% lower in pediatric patients with UC

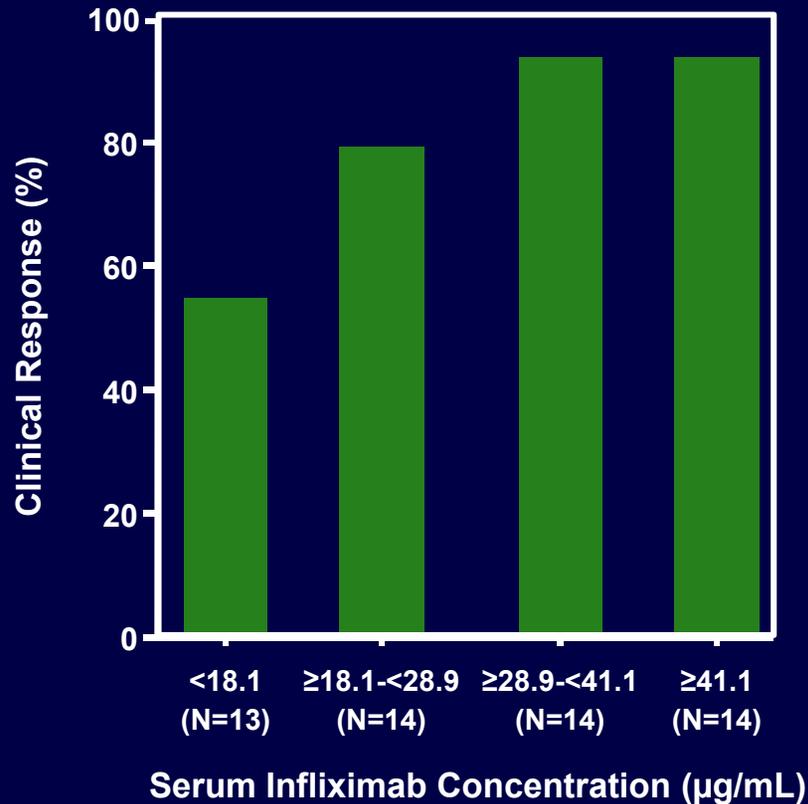
**Infliximab PK  
Exposure-Response Relationship  
in Pediatric and Adult UC**

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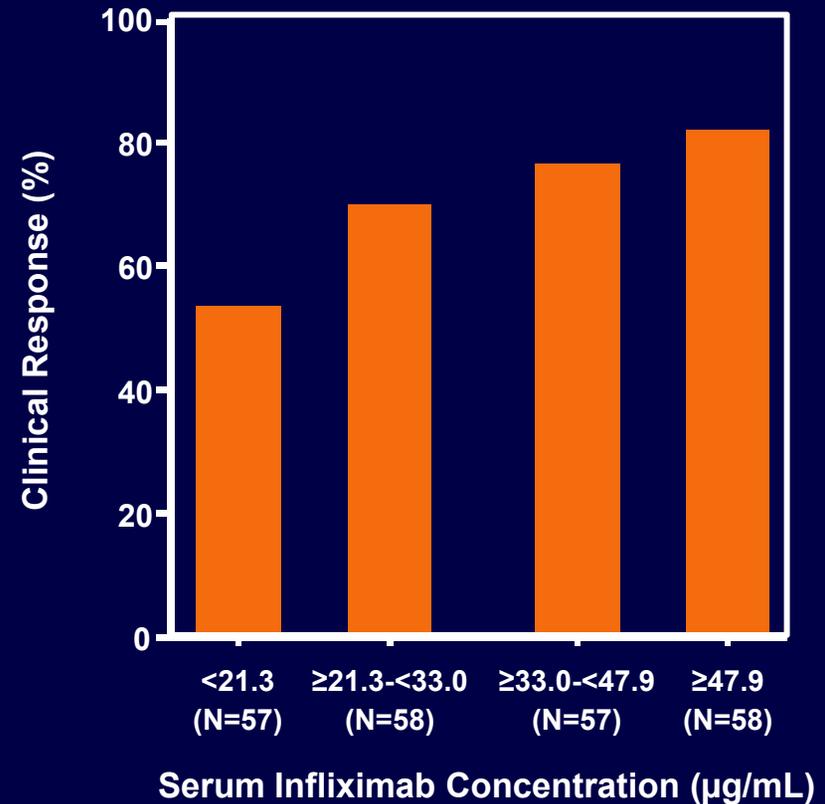
**Induction**

# Higher Serum Concentrations Associated with Higher Clinical Response Rates at Week 8

T72



ACT 1 and ACT 2 Combined\*

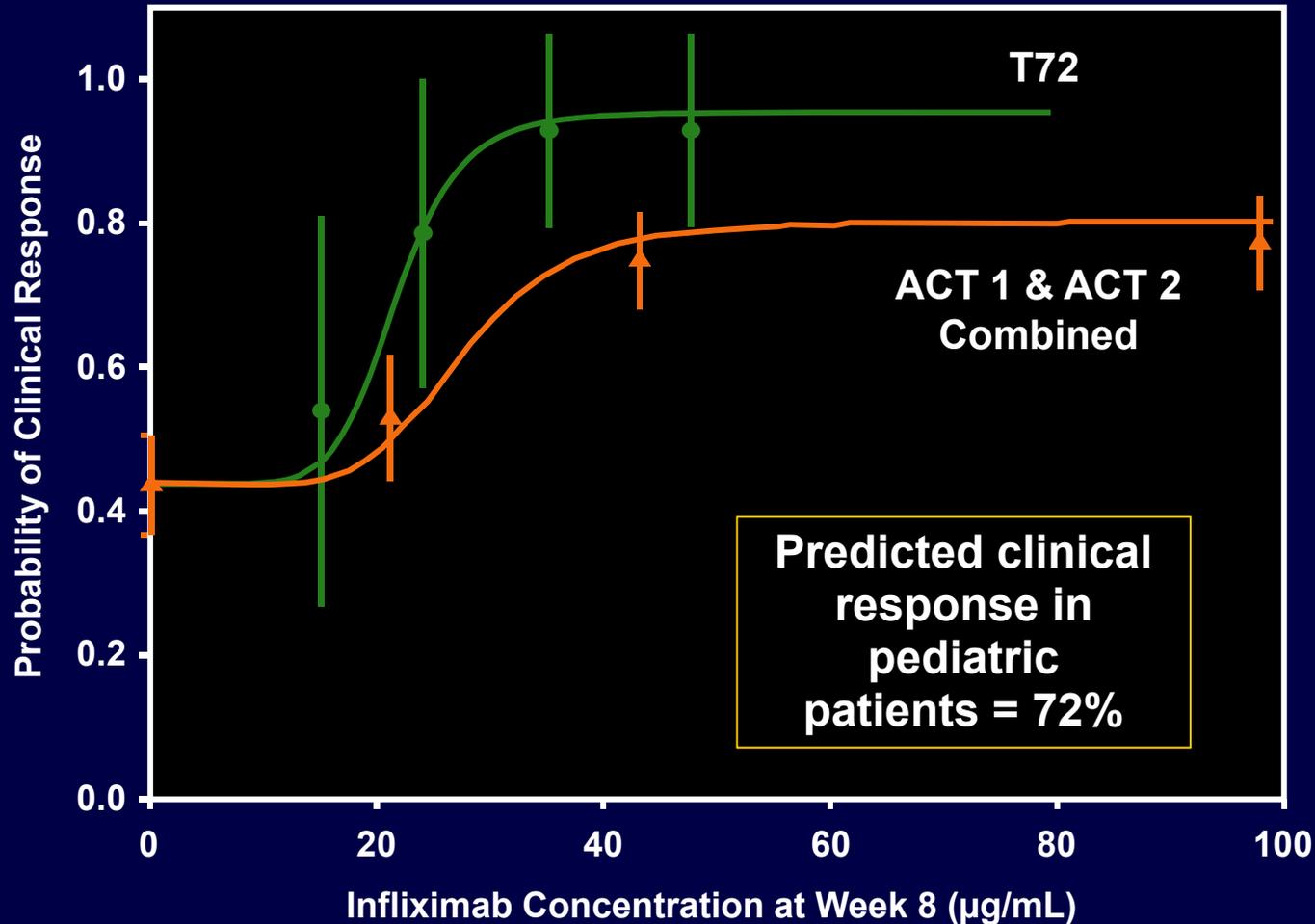


\* 5 mg/kg group in ACT 1 and ACT 2 combined

# Background for Exposure-Response Modeling

- **Exposure-Response (E-R) modeling was used to quantitatively describe the relationship between infliximab concentration and clinical efficacy measures**
- **Leveraged information from adult UC studies**
- **E-R models were used to predict response at a given level of infliximab exposure**
- **For maintenance we used Week 30 data**
  - **Steady state**
  - **Most data (ACT 1 and ACT 2)**
  - **PK and clinical endpoints are generally stable between Week 30 and Week 54**
- **E-R modeling confirmed the appropriateness of the dose studied for pediatric UC**

# Relationship Between Clinical Response and Infliximab Concentration at Week 8



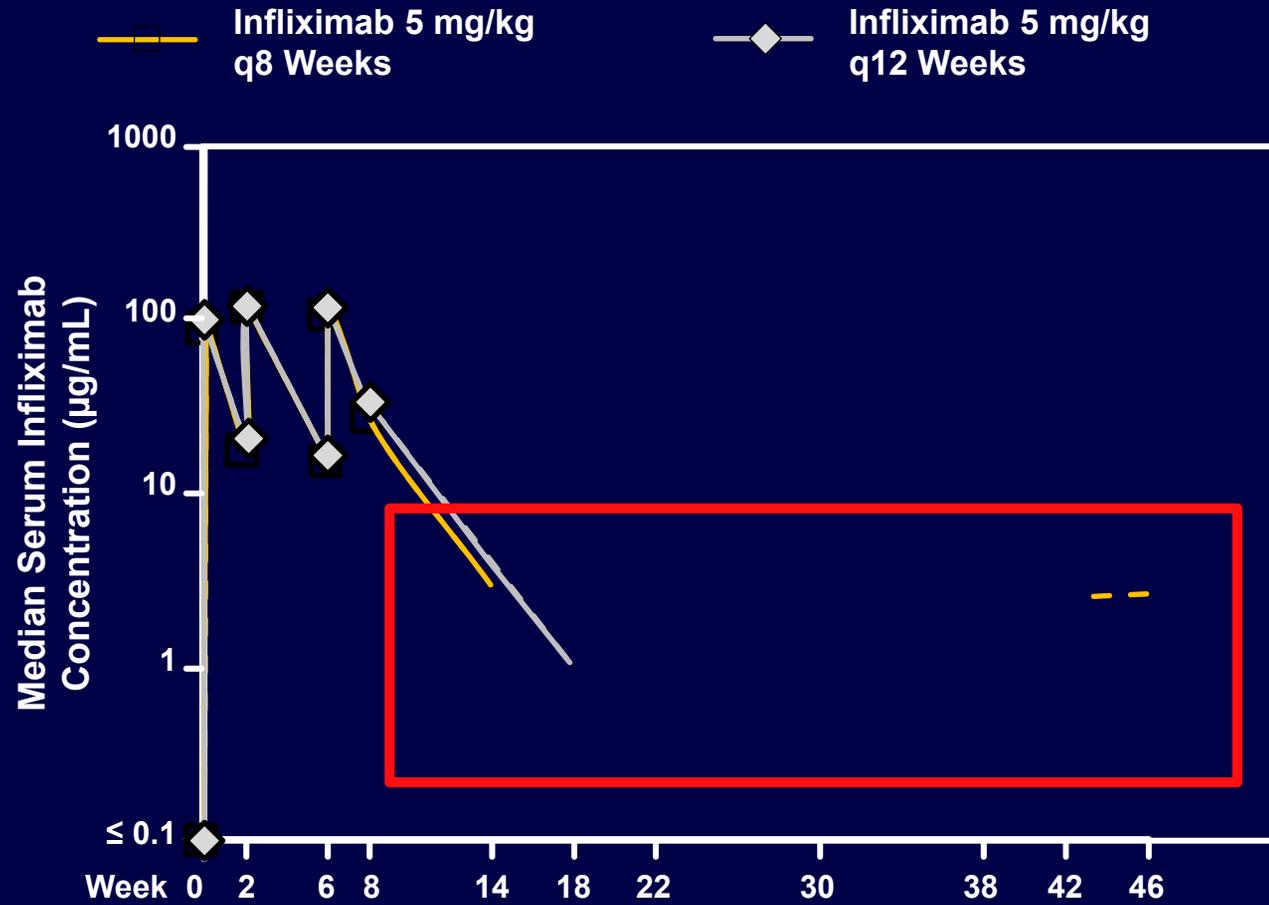
The response rates in each of the quartiles of the concentration at Week 8 for T72 (circles) and ACT 1\ACT 2 combined (triangles) are plotted at the mid-point of the values of the concentration at Week 8 quartile ranges

**Infliximab PK  
Exposure-Response Relationship  
in Pediatric and Adult UC**

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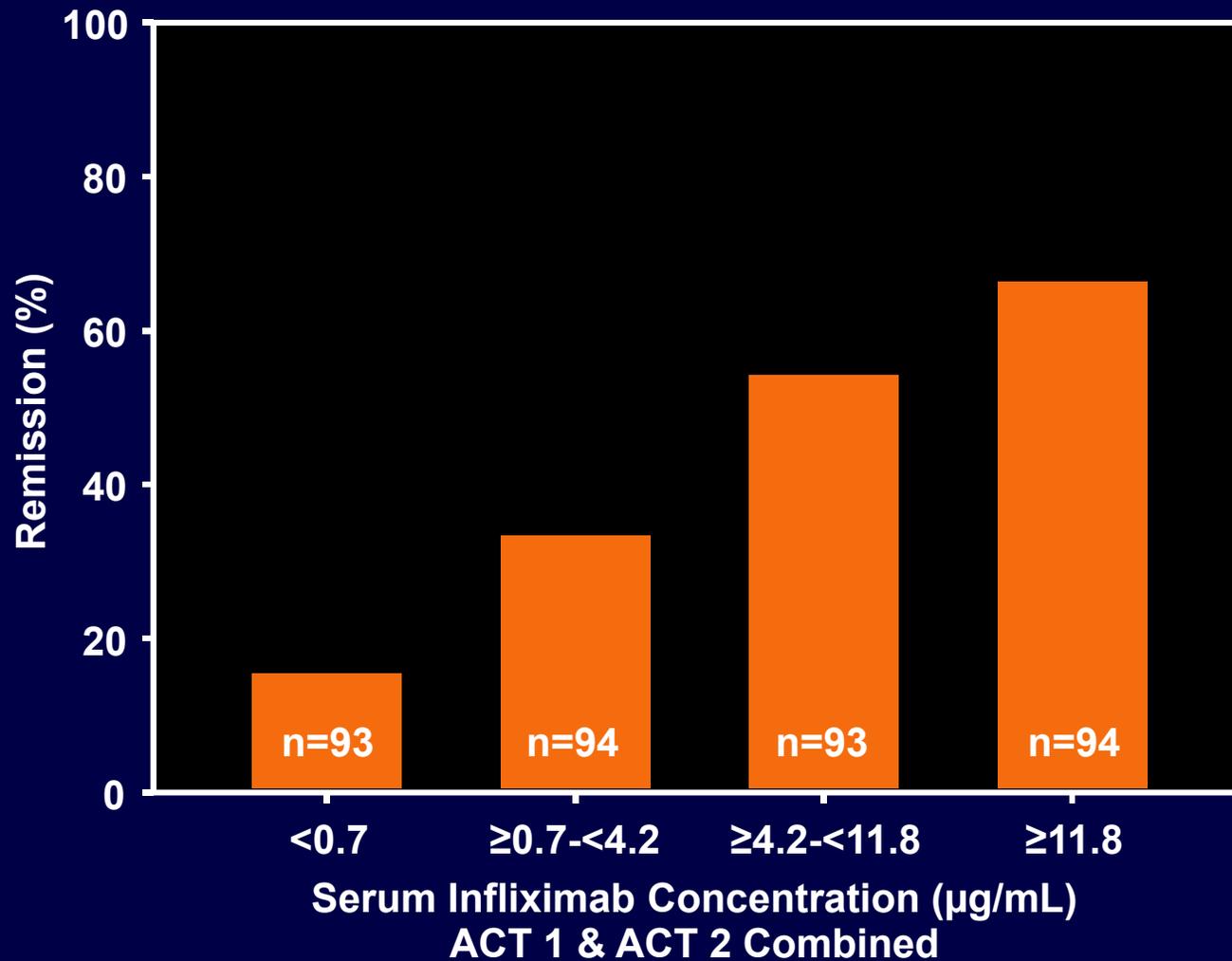
**Maintenance**

# T72: q8w and q12w Group Serum Concentrations



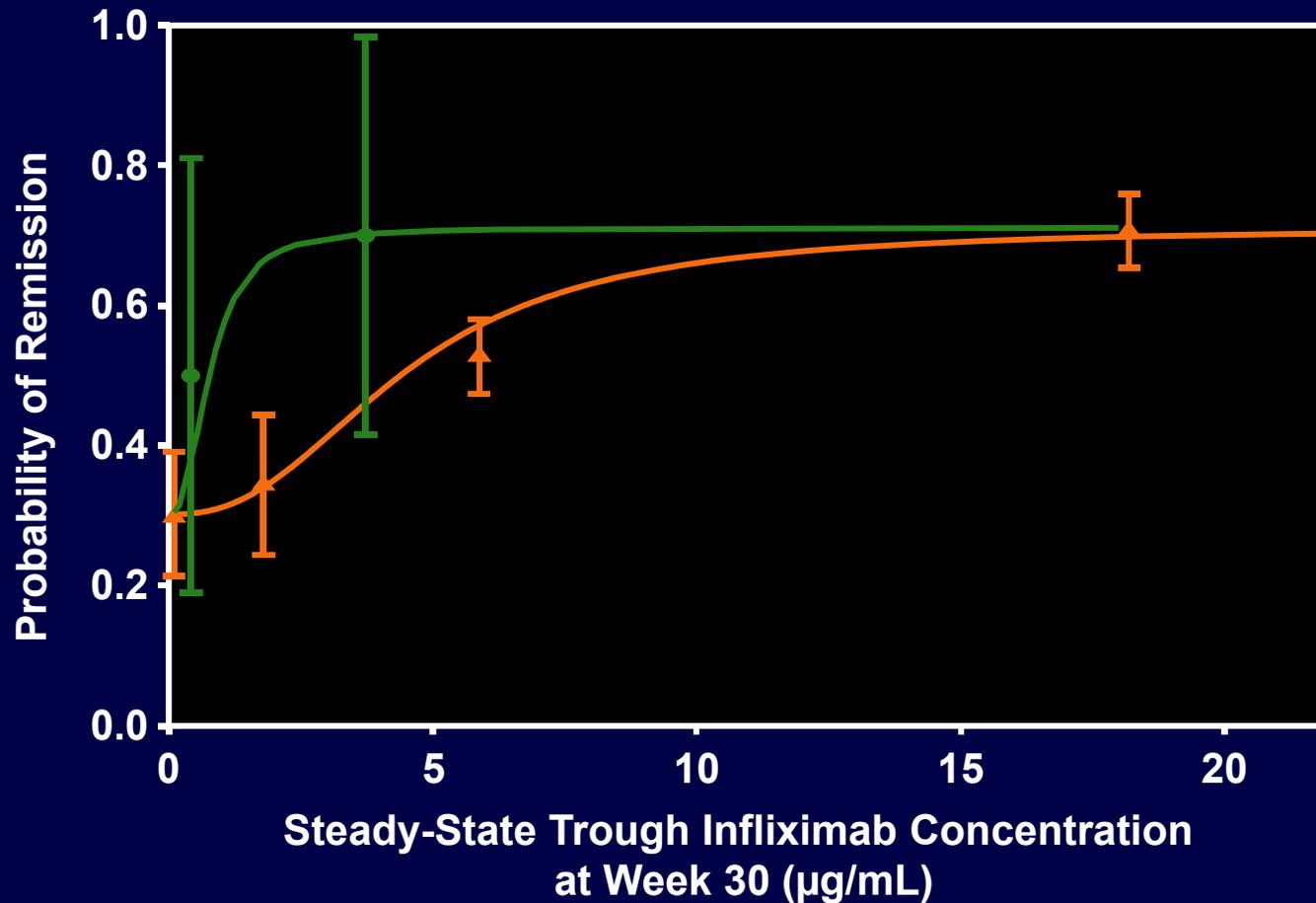
5 mg/kg q8w	n	19	20	19	17	14	12	9	9	5
5 mg/kg q12w	n=	23	23	20	19	10	6	5		

# Higher Serum Concentrations Associated with Higher Clinical Remission Rates at Week 30



Similar trend observed for Week 54

# Relationship Between Remission and Infliximab Concentration at Week 30 in Responders



The response rates in each of the quartiles of the concentration at Week 30 for ACT 1/ACT 2 combined (triangles) are plotted at the mid-point of the values of the concentration at Week 30 quartile ranges. Observed data for pediatric patients (circles) were plotted as medians due to small sample size

# Model-Based<sup>†</sup> Predictions of Remission in Responders: Limited Impact of Increased Infliximab Dose

Maintenance Dose Regimen	Predicted Proportions of Pediatric Patients in Remission at Week 30*
5 mg/kg q8w	41.0%
7.5 mg/kg q8w	45.9%
10 mg/kg q8w	49.2%

<sup>†</sup> Conservative estimates based on **adult E-R model**

\* Predictions based on simulation of 1000 subjects per dosing regimen using the population PK and E-R model

# Summary

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## **For both induction and maintenance:**

- **PK of infliximab in pediatric UC is consistent with adult UC**
- **Comparable exposure-response demonstrated in both pediatric and adult UC**
- **Data support the 5 mg/kg dose regimen**

## Conclusion

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The proposed dose regimen is based on the data from T72 and is confirmed by the E-R modeling and is:

**An induction dose of 5 mg/kg at  
Weeks 0, 2, 6 followed by  
a maintenance dose of 5 mg/kg q8w  
in pediatric patients age 6-17 years**

**REMICADE®**  
**Long-term Safety  
and Benefit/Risk**

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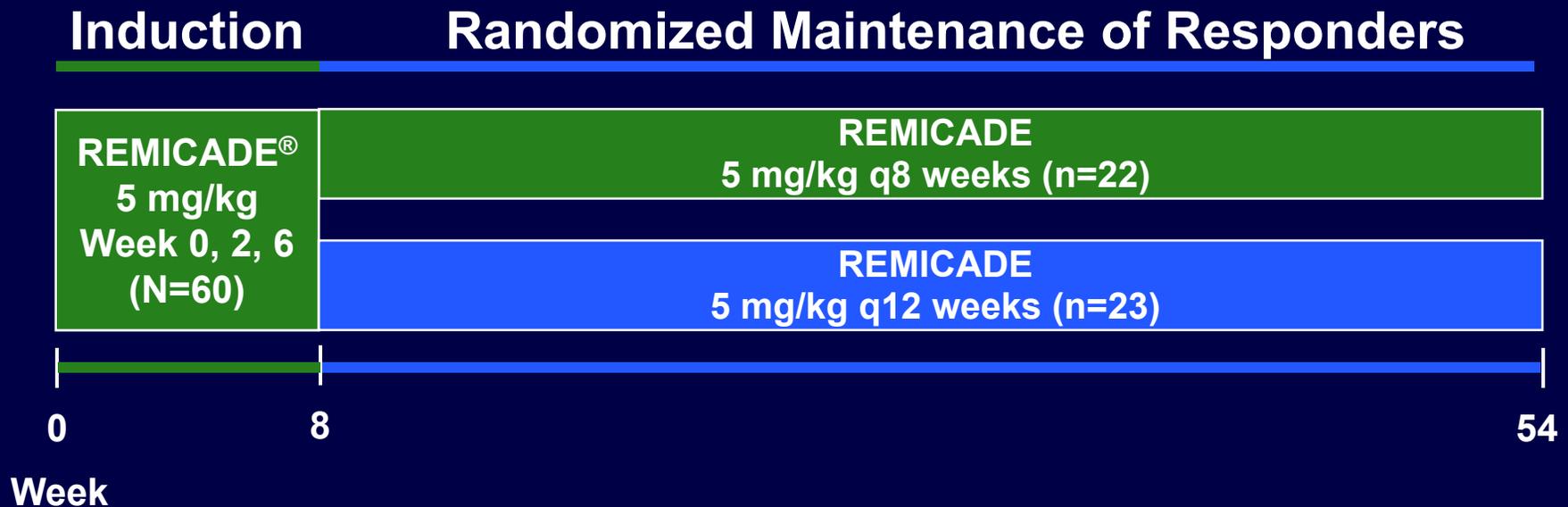
**Robert Diamond, MD**  
**Lead Medical Director**  
**Centocor Ortho Biotech Inc.**

# Presentation Agenda

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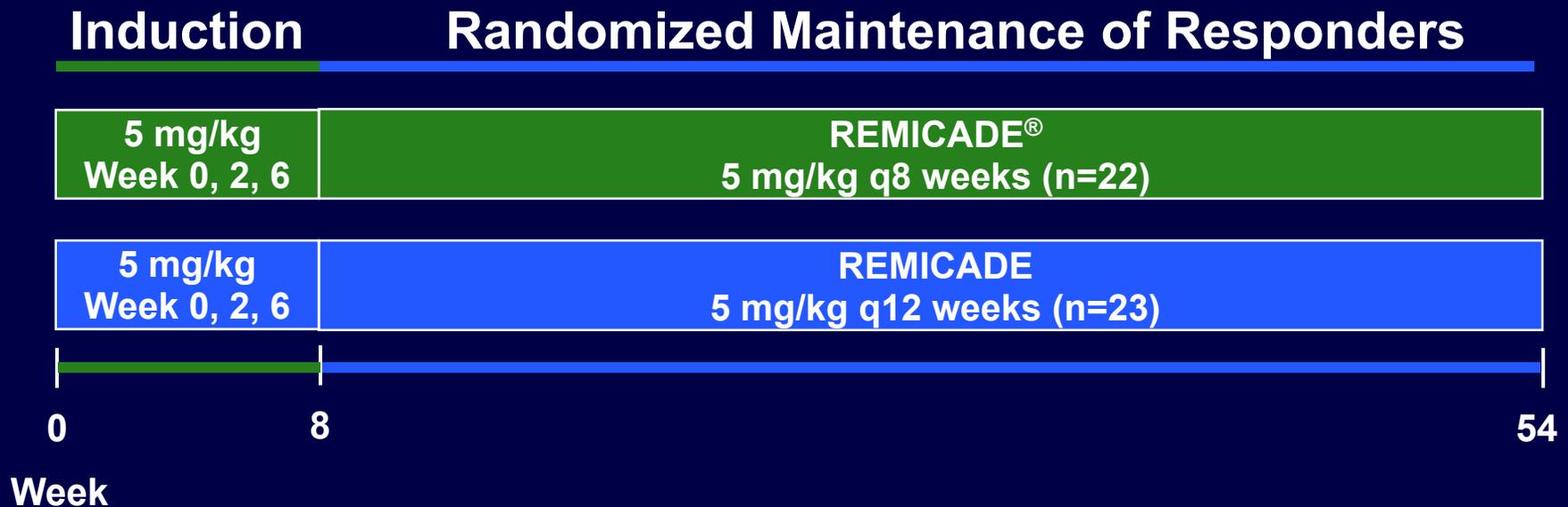
- **T72 Safety**
- **Pediatric IBD post-marketing safety**
- **Malignancies during REMICADE<sup>®</sup> treatment**
- **IBD registries**
- **Benefit / risk**

# T72 Safety Analysis



- Overall population through Week 54

# T72 Safety Analysis



- Overall population through Week 54
- Comparison of q8 with q12 through Week 54

# T72 Safety Through Week 54: Overall Population

	Total (N=60)
Average weeks of follow-up	38.0
AEs	57 (95.0%)
Discontinuations due to AEs	9 (20.0%)
SAEs	14 (23.3%)
Deaths	0 (0.0%)

## Most Common AEs (Frequency $\geq 10\%$ ) Through Week 54: Overall Population

	Total (N=60) n (%)
Ulcerative colitis	27 (45.0)
Upper respiratory tract infection	14 (23.3)
Pharyngitis	11 (18.3)
Abdominal pain	8 (13.3)
Fever	8 (13.3)
Headache	8 (13.3)
Anemia	6 (10.0)
Coughing	6 (10.0)

# Serious Adverse Events Through Week 54: Overall Population

	Total (N=60) n (%)
<b>Ulcerative colitis</b>	<b>8 (13.3)</b>
<b>Infection*</b>	<b>7 (11.7)</b>
<b>Anemia</b>	<b>1 (1.7)</b>
<b>Neutropenia</b>	<b>1 (1.7)</b>
<b>Pancreatitis</b>	<b>1 (1.7)</b>

\* Cellulitis, urinary tract infection, pneumonia, pharyngitis, ulcerative colitis, viral infection, infection not otherwise specified

# Safety Through Week 54: q8 and q12 Week Maintenance Groups

	q8w Maintenance N=22 n (%)	q12w Maintenance N=23 n (%)
Average weeks of follow-up	50.4	44.6
AEs	22 (100.0)	23 (100.0)
Discontinuations due to AEs	3 (13.6)	6 (26.1)
SAEs	4 (18.2)	5 (21.7)
Deaths	0 (0.0)	0 (0.0)

## **Adverse Events of Note Through Week 54**

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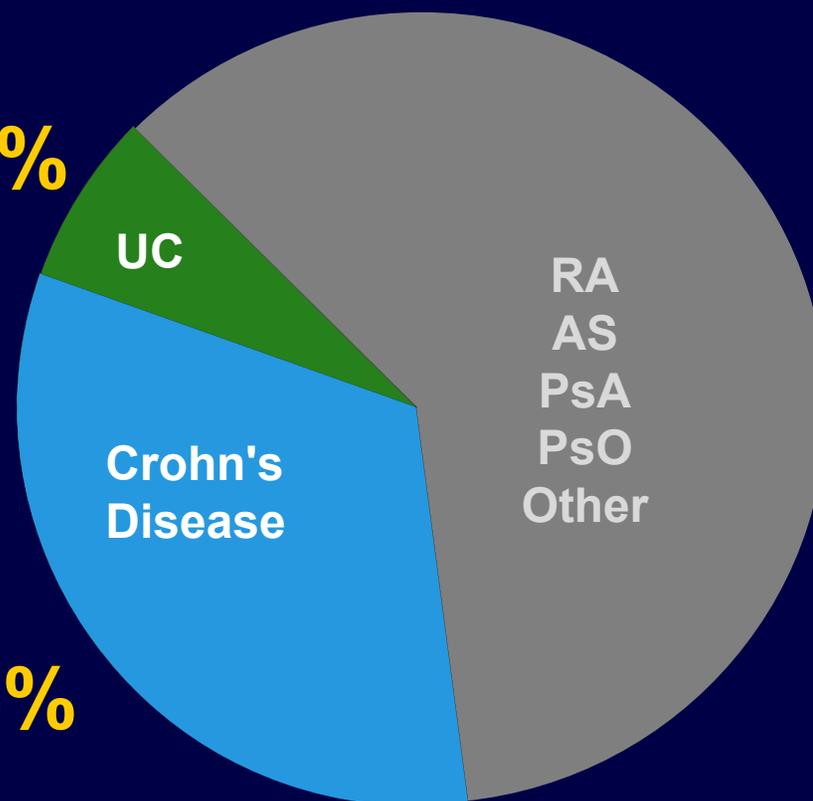
- **17/340 (5%) of infusions with infusion reactions**
  - **None serious**
- **5 (8.4%) colectomies**
- **No TB, malignancies, demyelinating disorders, delayed hypersensitivity or anaphylactic reactions**
- **4 (7.7%) patients positive for antibodies to infliximab**

# Post-marketing REMICADE® Experience

- 1.5 million patients treated worldwide
  - 850,000 in US
- >600,000 IBD patients treated worldwide
  - 320,000 in US
- 19,000 pediatric IBD patients treated worldwide
  - 12,000 in US

**UC: 7%**

**CD: 33%**



# Class Anti-TNF Labeled Safety Information

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- **Serious infections**
  - TB
  - Bacterial sepsis
  - Invasive fungal infections (such as histoplasmosis)
  - Infections due to other opportunistic pathogens
- **Malignancy**
  - Solid tumors
  - Lymphoma
  - HSTCL
- **Other important safety issues**
  - Demyelinating events (e.g. multiple sclerosis)
  - Hypersensitivity reactions
  - Lupus-like syndrome
  - Heart failure
  - Hematologic events

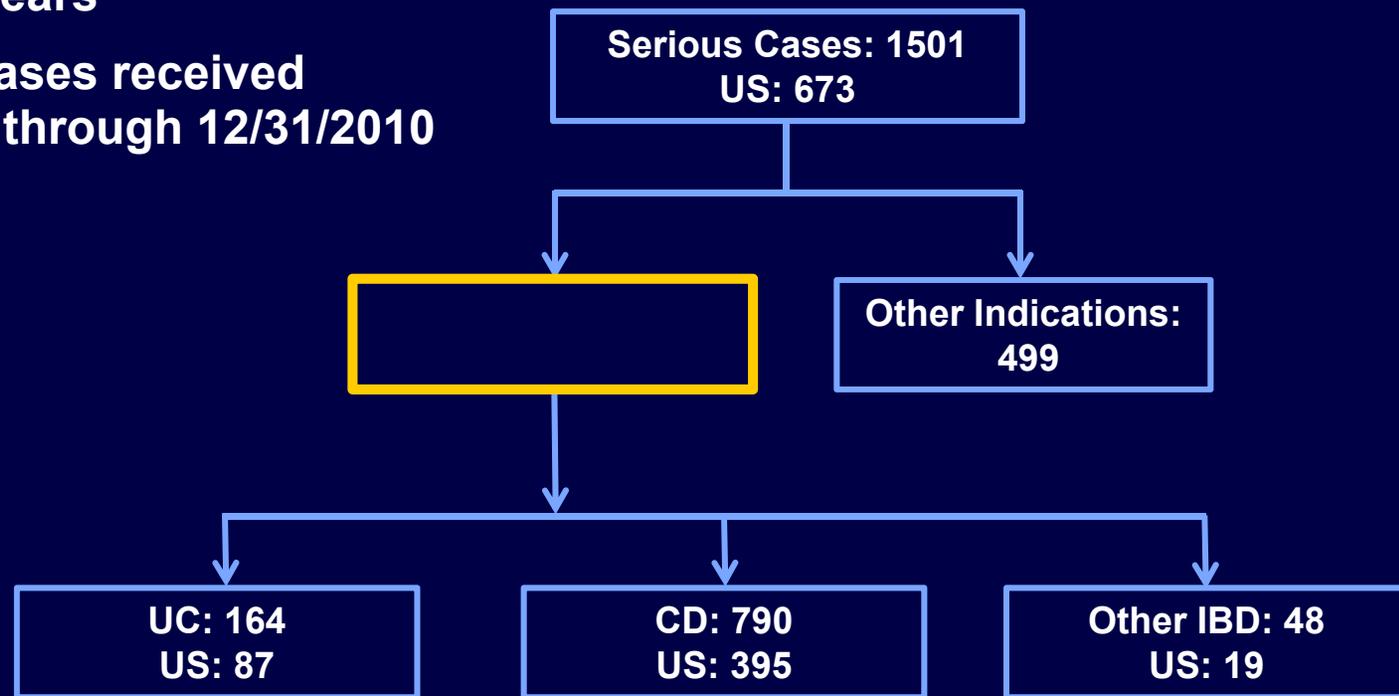
# **Pediatric IBD**

## **Post-Marketing Safety**

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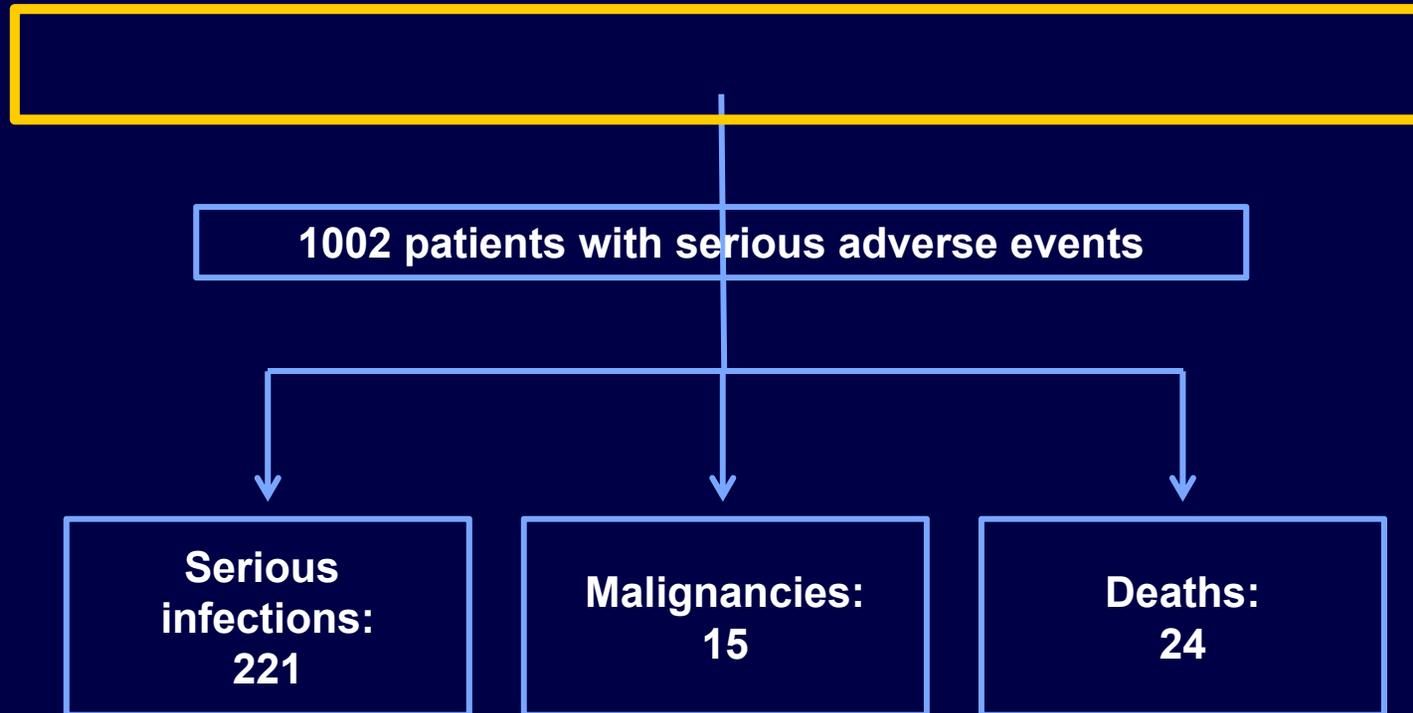
# Post-Marketing Safety Overview in Pediatric IBD Patients (Worldwide – 1998 to 2010)

- Search criteria
  - Age  $\leq 17$  years
  - Serious cases received 8/24/1998 through 12/31/2010

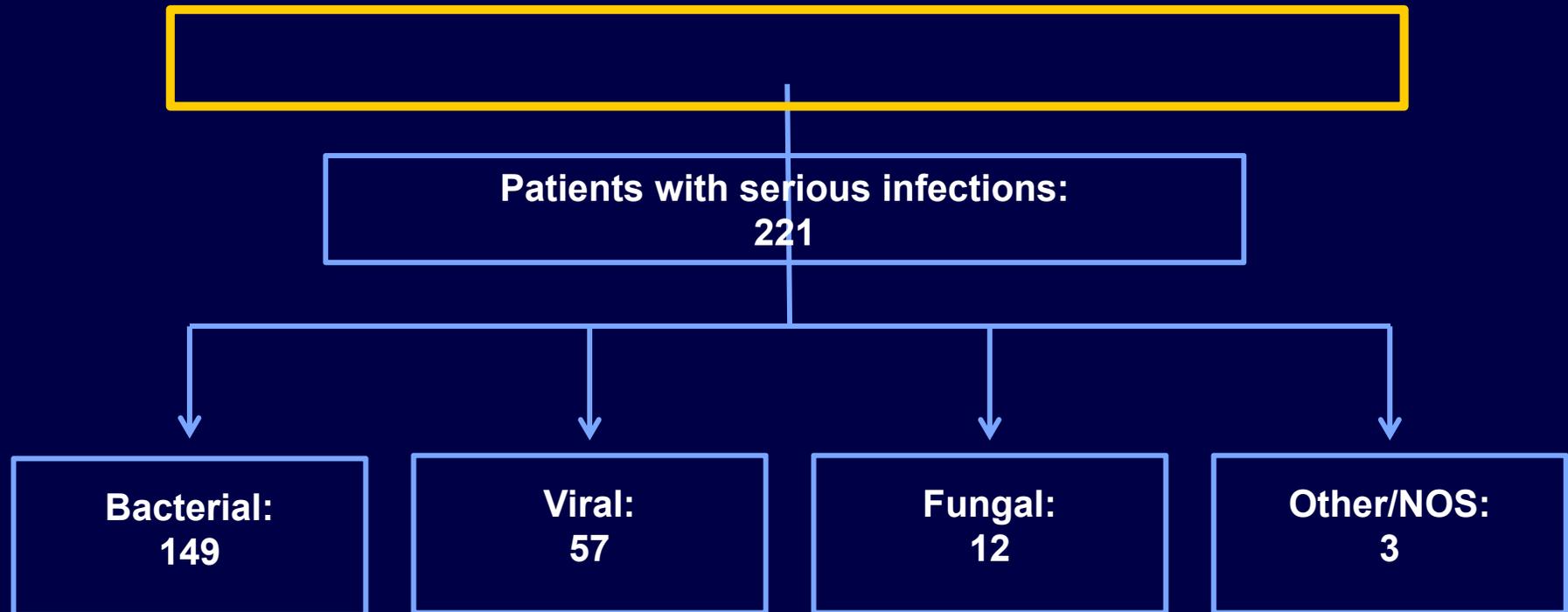


The pattern of AEs reported in IBD pediatric patients is generally consistent with adult IBD patients treated with REMICADE®

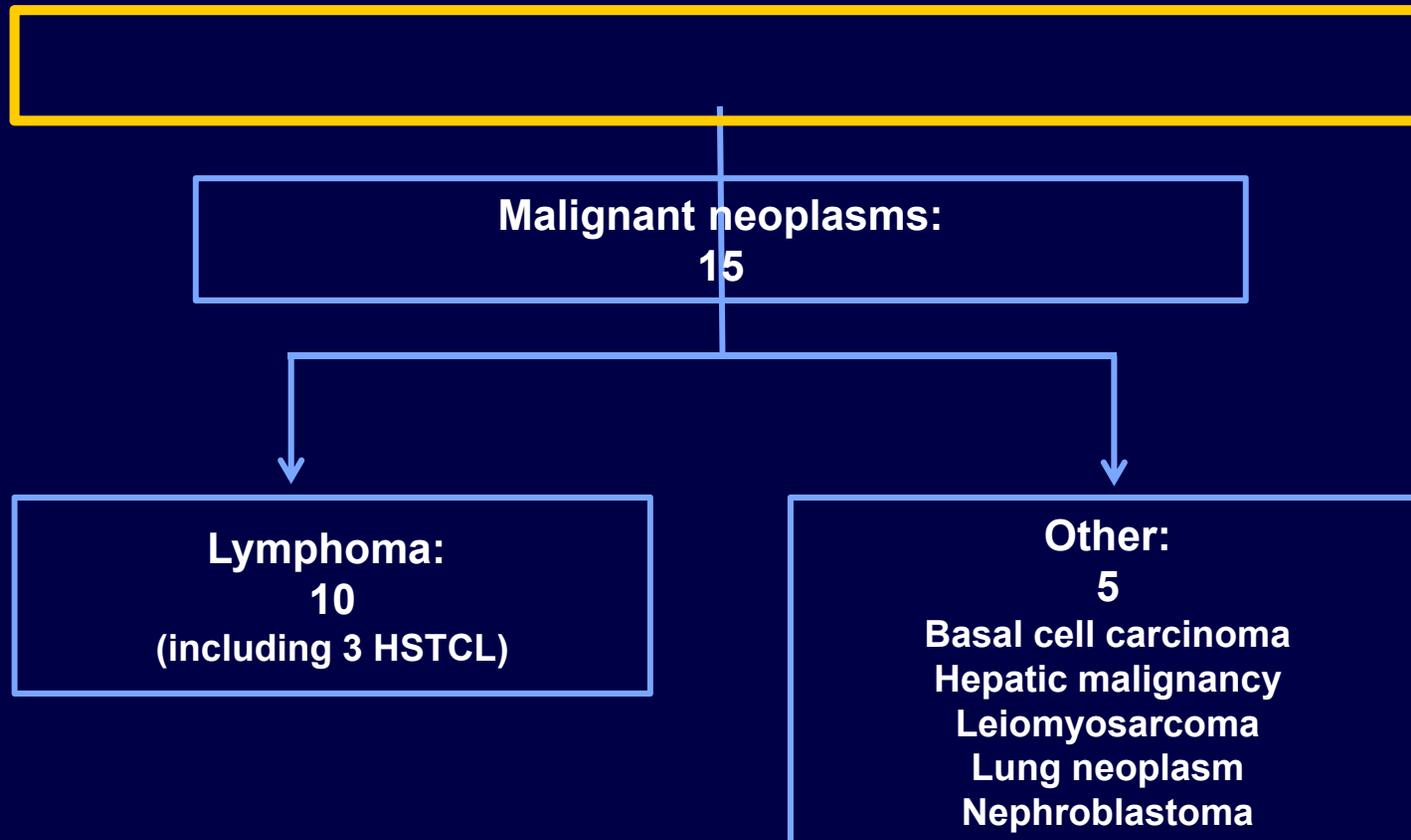
# Post-Marketing Safety Overview in Pediatric IBD Patients (Worldwide – 1998 to 2010)



# Serious Infections in Pediatric IBD Patients (Worldwide – 1998 to 2010)



# Malignant Neoplasms in IBD Pediatric Patients (Worldwide – 1998 to 2010)



- Class labeling for TNF-blockers for pediatric malignancy added in 2009

# Hepatosplenic T-cell Lymphoma in REMICADE<sup>®</sup>-Treated Patients: Cumulative Review

- Rare form of non-Hodgkin's lymphoma
  - Aggressive disease course with fatal outcome
- 27 reported cases with REMICADE + AZA/6-MP
  - All cases in IBD
  - All patients reported long-term exposure to AZA or 6-MP
  - Most had long-term exposure to REMICADE
  - Male predominance- 24/27
  - 23 fatalities
  - Ages:
    - 12-17      3
    - 18-30     15
    - 31-60     9
- No cases in ~750,000 RA patients treated with REMICADE and methotrexate

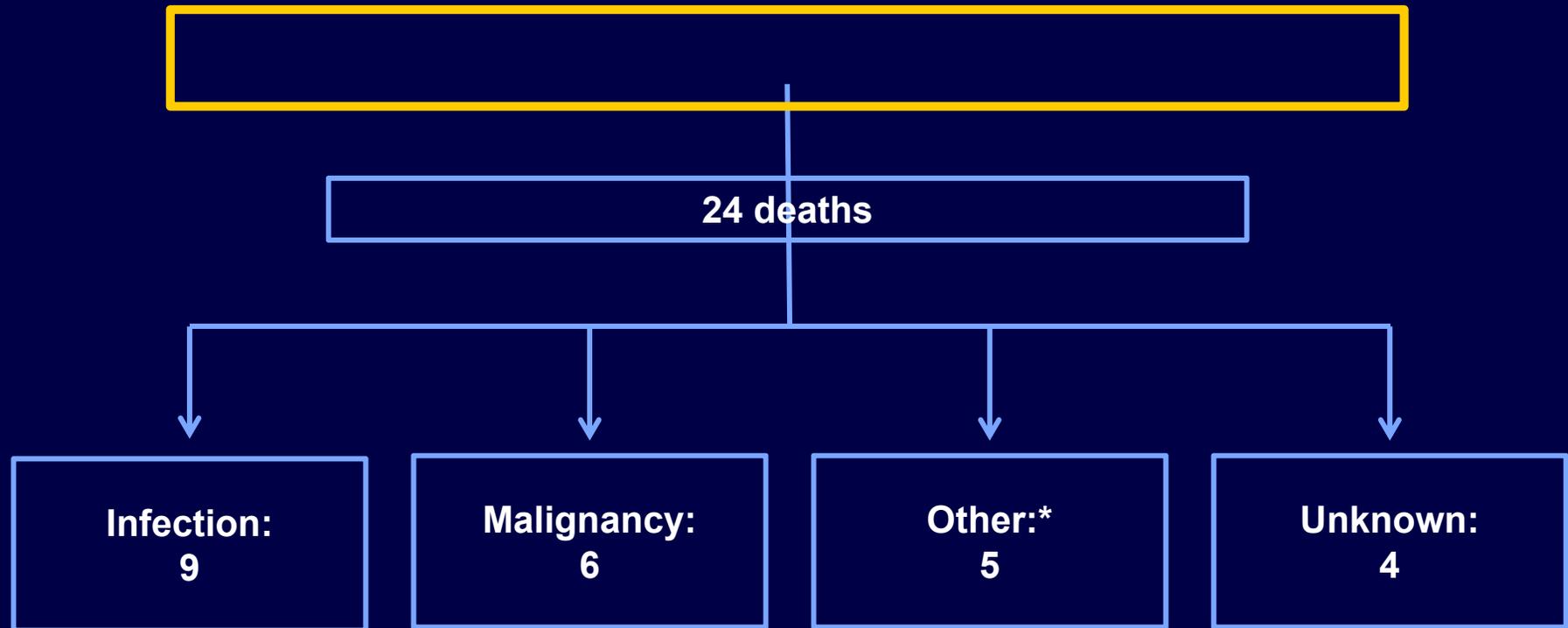
## Published HSTCL Experience with AZA/6-MP

	AZA/6-MP + REMICADE®	AZA/6-MP Alone
Number	20	16
Type of IBD	CD: 85% UC: 15%	CD: 56% UC: 38% IC: 6%
Median age (yrs)	23 (range 12-58)	22.5 (range 15-35)
Gender	Male: 95% Female: 5%	Male: 63% Female: 6% Unknown: 31%
Median duration of thiopurine exposure (years)	5.5 (range 1-14)	6 (range 3-17)
Outcome	Died: 80% Unknown: 20%	Died: 69% Remission: 25% Unknown: 6%

Kotlyar DS, et al. *Clin Gastroenterol Hepatol*. 2011, 9:36-41.

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# Mortality in Pediatric IBD Patients (Worldwide – 1998 to 2010)



\* Cerebral aneurysm or vascular malformation, hemophagocytic syndrome, interstitial lung disease, stoma repair operation, thrombosis

# **Pediatric IBD Post-Marketing Safety Summary**

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- **Significant pediatric IBD exposure, majority in CD**
- **Safety profile in pediatric IBD patients consistent with established REMICADE<sup>®</sup> safety profile in adult IBD patients**
  - **No new safety signals unique to pediatric population**
- **Key concerns include serious infections and malignancies that can lead to fatal outcomes**
  - **Majority of patients received concomitant immunosuppressants**
  - **Many of the fatal outcomes occurred in patients with severe, complex IBD**
- **HSTCL reported in patients who have received REMICADE with concurrent or historical AZA/6-MP therapy**

# IBD Registries

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# IBD Registries

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- **TREAT- Adult CD**
- **DEVELOP- Pediatric IBD**
- **Pediatric IBD Collaborative Research Group Registry**
  - Supported in part by Centocor
- **Advantages of registry data over post-marketing data**
  - Often provide comparator group data
  - Prospectively collected
  - More complete data collection

# TREAT Registry for Adult CD Patients

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- **Mature, prospective, observational registry**
  - Average patient follow-up = 5.2 years
- **Compares REMICADE® with other IBD therapies**
- **6,200 patients fully enrolled in 3 years**
  - Half received REMICADE
  - Ongoing with >30,000 patient-years follow-up
- **Patients who receive REMICADE have substantially worse CD**

# TREAT: Findings

	REMICADE®- Treated Patients	Other Treatment Only Patients
Number of patients	3,420	2,853
Patient-years of follow-up	17,172	13,251
Serious infections per 100 pt-yr	2.01	1.42
Malignancy per 100 pt-yr	0.63	0.71
Deaths per 100 pt-yr	0.54	0.65

## Predictors of serious infection

- Severity of Crohn's disease
- Use of steroids
- Use of REMICADE

## **DEVELOP: Registry for Pediatric IBD Patients**

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- **5000 patient prospective pediatric ( $\leq 17$  years of age) IBD observational registry to be enrolled by 2016**
  - 4,000 CD
  - 1,000 UC
- **As of April 22, 2011: 2,787 enrolled, approximately half have received REMICADE<sup>®</sup>**
  - 2,389 CD
  - 398 UC/IC (337 UC, 61 IC)
- **Commitment to 20 year follow-up**
- **Patients who receive REMICADE have substantially worse IBD**

# DEVELOP: Findings

	REMICADE®- Treated Patients	Other Treatment Only Patients
Number of patients	1,253	1,534
Patient-years of follow-up	1,992	1,705
Serious infections per 100 pt-yr	3.2	2.0
Malignancy per 100 pt-yr	0.2	0.2
Deaths per 100 pt-yr	0.05*	0

## Predictors of serious infection

- Severity of Crohn's disease
- Use of REMICADE
- Use of immunomodulators

\* 1 motor vehicle accident 6 weeks after infusion

# Pediatric IBD Collaborative Research Group Registry

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- **Description**
  - Inception registry established 2002, total 34 sites in North America
  - Patients  $\leq 16$  years of age at diagnosis
- **February 28, 2011: 568 REMICADE<sup>®</sup>-treated patients enrolled (2,153 pt-yr)**
  - 447 CD
  - 121 UC/IC (98 UC, 23 IC)
- **Patients who receive REMICADE have substantially worse IBD**

# Pediatric IBD Collaborative Research Group Registry: Findings

	REMICADE®- Treated Patients	Other Treatment Only Patients
Number of patients	568	1,168
Patient-years of follow-up with REMICADE exposure	1,385	0
Patient-years of follow-up without REMICADE exposure	768	3,347
Serious infections per 100 pt-yrs	1.30	0.87
Malignancy	1	0
Deaths	1	1

\*Recorded for 533/568 patients who received REMICADE on or after 1/1/2005

**Data for serious infections, malignancy and mortality is similar to that seen in other IBD registries**

## **IBD Registry Conclusions**

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- **Safety findings generally consistent across IBD registries**
- **Patients treated with REMICADE<sup>®</sup> have more severe IBD**
- **Serious infections occur more frequently in REMICADE-treated patients**
  - **Other contributing factors include disease severity and use of other immunosuppressive medications**
- **Rates of malignancy and deaths are consistent among REMICADE and non-REMICADE-treated patients**

# Safety Monitoring and Risk Minimization

## Safety Monitoring

- **Pharmacovigilance**
  - **Post-marketing safety reports**
- **IBD Registries**
  - **TREAT**
  - **DEVELOP**
  - **Pediatric IBD Collaborative Research Group Registry**

## Risk Minimization

- **REMS**
- **Medication guide**
- **Health care provider education**
  - **Clinical science liaisons**
  - **Medical education presentations**
  - **Medversation Website**
  - **Printed educational materials**

# Benefit / Risk

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## Benefits of REMICADE® in Pediatric UC

- **Moderate to severe pediatric ulcerative colitis is an orphan disease with significant morbidity**
- **Limited approved therapies, with none for maintenance in the moderate to severe population**
- **REMICADE is highly effective in reducing the signs and symptoms of pediatric UC in patients who have inadequately responded to conventional therapies**
- **Response to REMICADE is:**
  - **Rapid in onset**
  - **Consistent across multiple endpoints**
  - **Maintained with 5 mg/kg q8 week dosing**
  - **Highly consistent with response seen in adult UC (ACT 1 and ACT 2)**

## **Risks of REMICADE® in Pediatric UC**

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- **REMICADE approved since 1998 with 1.5 million patients treated globally with 40% in IBD**
- **Well established safety profile in both adult and pediatric IBD**
- **Associated with serious safety risks, most importantly, serious infection and malignancy**
  - **Confounded by disease severity and concomitant meds**
  - **Education and support services in place to facilitate accurate diagnosis and appropriate treatment**
- **Irreversible or fatal safety risks are rare but should be considered prior to initiation of therapy**
- **Robust plan for monitoring safety and educating HCPs**

## Basis for REMICADE® Pediatric UC Indication

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- Disease course is similar in children and adults ✓
  - Treatment effects are similar in children and adults ✓
  - PK is comparable in children and adults ✓
  - Exposure-response relationship is comparable in children and adults ✓
  - Safety is characterized in children ✓
- 

### Additional Support

- Efficacy in T72 consistent with ACT 1 and ACT 2

## Conclusion

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- REMICADE<sup>®</sup> is an appropriate option and should be available as a choice for pediatric patients as it is for adults
- Proposed indication:
  - REMICADE is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult **and pediatric** patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- The data also support the proposed dosing regimen of 5 mg/kg at Weeks 0, 2, and 6 then q8 weeks