Remicade® (infliximab)

GI Advisory Committee Meeting

Opening Remarks

July 21, 2011

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FDA, CDER, DGIEP

Proposed Indication: Pediatric Ulcerative Colitis

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.

Level of Evidence:
Legal Requirements

- 1962 Drug Amendments to the FDC Act
  - Required establishment of effectiveness of the drug as a prerequisite for marketing approval
  - Effectiveness established by "**Substantial Evidence**"
    - typically interpreted as 2 **adequate and well-controlled studies** *(i.e., randomized, DB, PC)*

Extrapolation

- **Pediatric efficacy can be *"extrapolated"* from adequate and well-controlled adult studies**
  - In 1994, FDA finalized a set of rules for extrapolating efficacy to the pediatric population
  - Later strengthened and had incentives added (exclusivity)
  - Reflected in Regulations under 21 CFR 314.55

Extrapolation: Legislation

[505B(a)(2)(B)]

(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.

(i) IN GENERAL. - **If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary 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.**

Why Extrapolation?

- Extrapolation increases the efficiency of pediatric drug development and avoids unnecessary pediatric trials
- Should be used to
  - Better utilize limited resources
  - Limit exposure of children to unnecessary studies
  - Obtain trial results more quickly to increase access to efficacious medications

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

Pediatric Ulcerative Colitis

- FDA currently accepts extrapolation of **efficacy** as a valid strategy for pediatric studies in UC
- Nevertheless, clinical data derived from pediatric UC studies may be informative for this approach
  - Supportive evidence of effectiveness
  - Dose-response analyses

Extrapolation

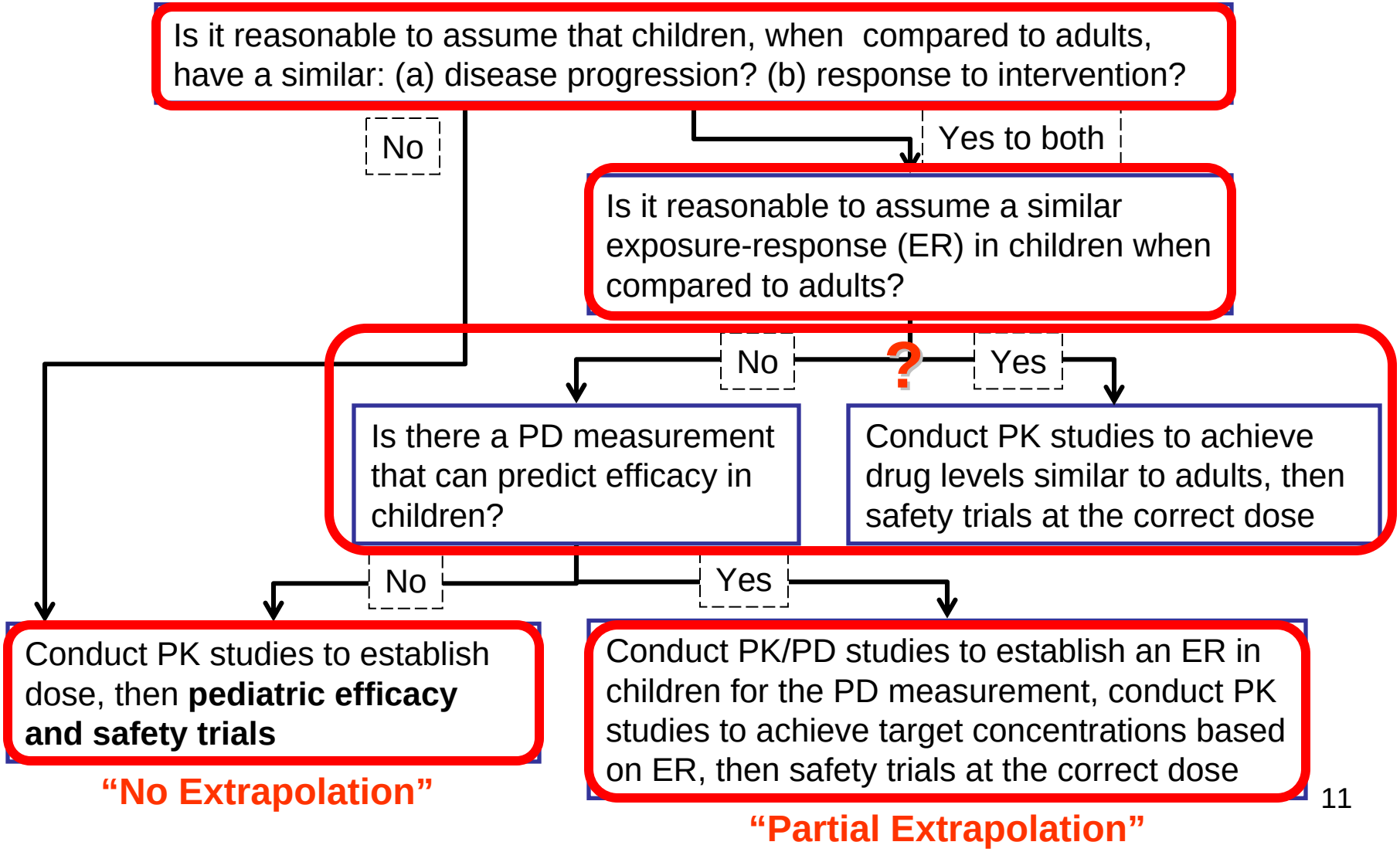
- Extrapolation of efficacy was *assumed* when designing the Remicade Pediatric UC trial (T72) and later explored through PK & exposure-response analyses
- Consider how data from T72 provides evidence to support extrapolation of proposed efficacy claims from adults
- If extrapolation is possible, a pediatric drug development program does not necessarily need to demonstrate efficacy in pediatric studies

Appropriate Pediatric Dosing

- The appropriateness of the proposed pediatric dose needs careful evaluation
- In T72, the **dose** selected for study was based on data from external studies and indications:

	CD	UC
Adults	IND: 5mg/kg IV 0,2,6 wks MAINT: 5mg q8wks *(may ↑ to 10mg/kg)*	IND: 5mg/kg IV 0,2,6 wks MAINT: 5mg q8wks
Children	IND: 5mg/kg IV 0,2,6 wks MAINT: 5mg q8wks	*IND: 5mg/kg IV 0,2,6 wks* *MAINT: 5mg q8wks*

Pediatric Extrapolation Decision Tree



"No Extrapolation"

"Partial Extrapolation"

Summary

- **The review team considers extrapolation of efficacy to be appropriate in pediatric UC**
  - Pediatric studies in UC do not need to be designed as adequate and well-controlled clinical *efficacy* trials
  - In the setting of extrapolation of efficacy appropriate **dosing** & **safety** in children must be established

Questions

1. Is it reasonable to assume that the course of ulcerative colitis and its response to treatment in adult and pediatric patients are sufficiently similar to be able to extrapolate efficacy from adult to pediatric patients for:

    a. Induction of clinical remission *(Vote)*
    b. Maintenance of clinical remission *(Vote)*
    c. Induction of mucosal healing *(Vote)*
    d. Maintenance of mucosal healing *(Vote)*
    e. Eliminating corticosteroid use *(Vote)*

Questions (cont'd)

2. Assuming extrapolation is appropriate, do the pediatric data support the dosing for the proposed pediatric indications of:

   a. induction of clinical remission (5mg/kg IV at 0, 2 & 6 weeks): *(Vote)*

   b. maintaining clinical remission (5mg/kg IV every 8 weeks): *(Vote)*

Questions (cont'd)

3. For those pediatric patients who fail to adequately respond to the proposed dose, do the data support labeling recommendations to increase dosing to 10 mg/kg every 8 weeks for maintaining clinical remission? *(Vote)*

Questions (cont'd)

4. Assuming extrapolation is appropriate, do the pediatric data support the dosing for the proposed pediatric indications of:
    a. induction of mucosal healing (5mg/kg IV at 0, 2 & 6 weeks): *(Vote)*
    b. maintaining mucosal healing (5mg/kg IV every 8 weeks): *(Vote)*
    c. eliminating corticosteroid use (5mg/kg IV 0, 2, & 6 weeks, then every 8 weeks): *(Vote)*

Questions (cont'd)

5. In light of the pediatric safety data provided in T72, the post-marketing safety analyses, and the PK and exposure response data, are there safety concerns that have not been adequately addressed? *(Vote)*

   If yes, what additional safety data should be collected?

   Discuss whether this data should be collected prior to or post approval.

Questions (cont'd)

6. Does the benefit:risk profile support approval of Remicade for the pediatric UC indications of:

    a. Induction of clinical remission *(Vote)*
    b. Maintenance of clinical remission *(Vote)*
    c. Induction of mucosal healing *(Vote)*
    d. Maintenance of mucosal healing *(Vote)*
    e. Eliminating corticosteroid use *(Vote)*

Thank You

Gastrointestinal Drugs Advisory Committee Meeting

Infliximab (Remicade®)

Jessica J. Lee, M.D., M.M.Sc.
Medical Officer
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

Proposed Ulcerative Colitis Indication

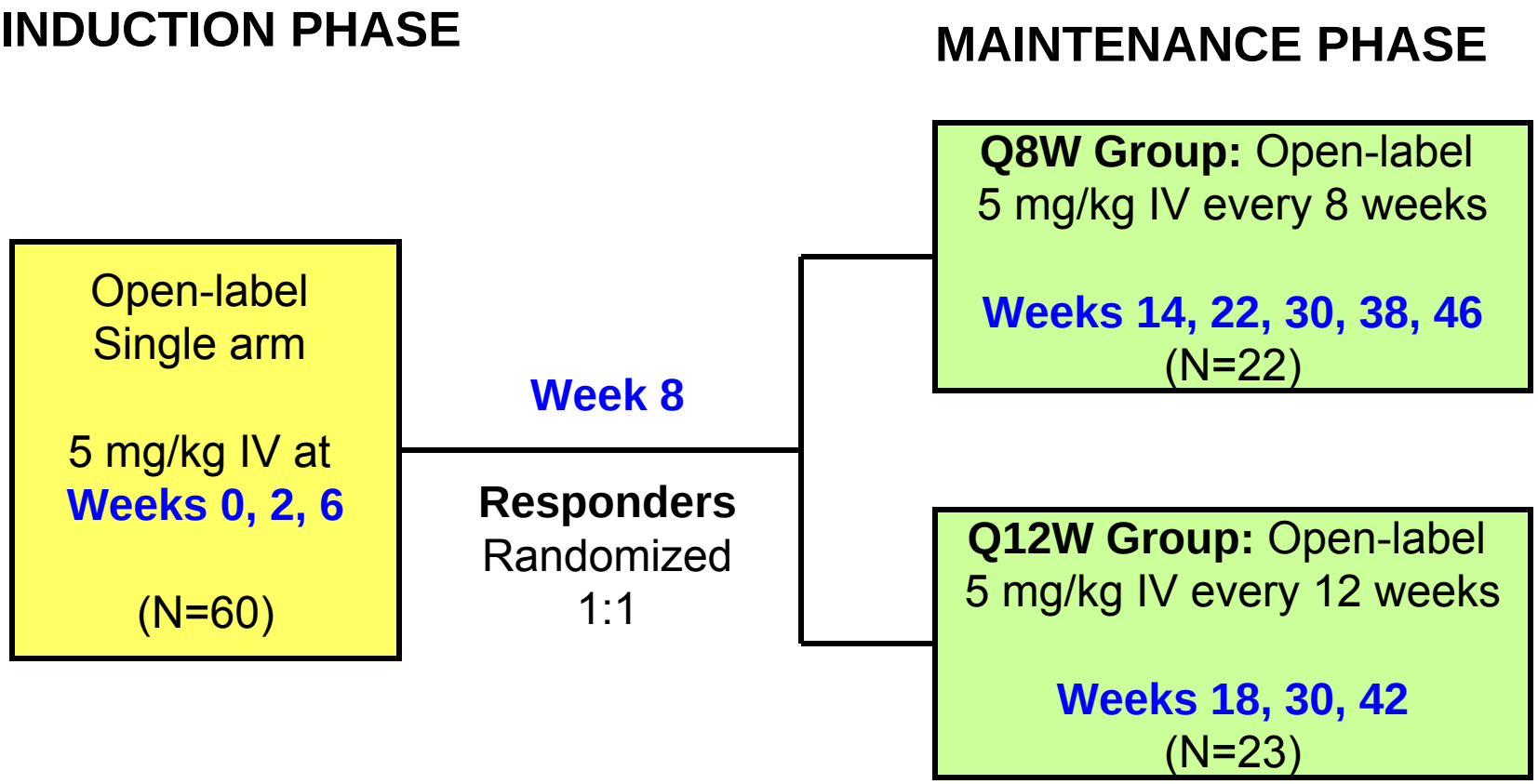
- Remicade® is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in **adult and pediatric** patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Infliximab Adult UC Approval

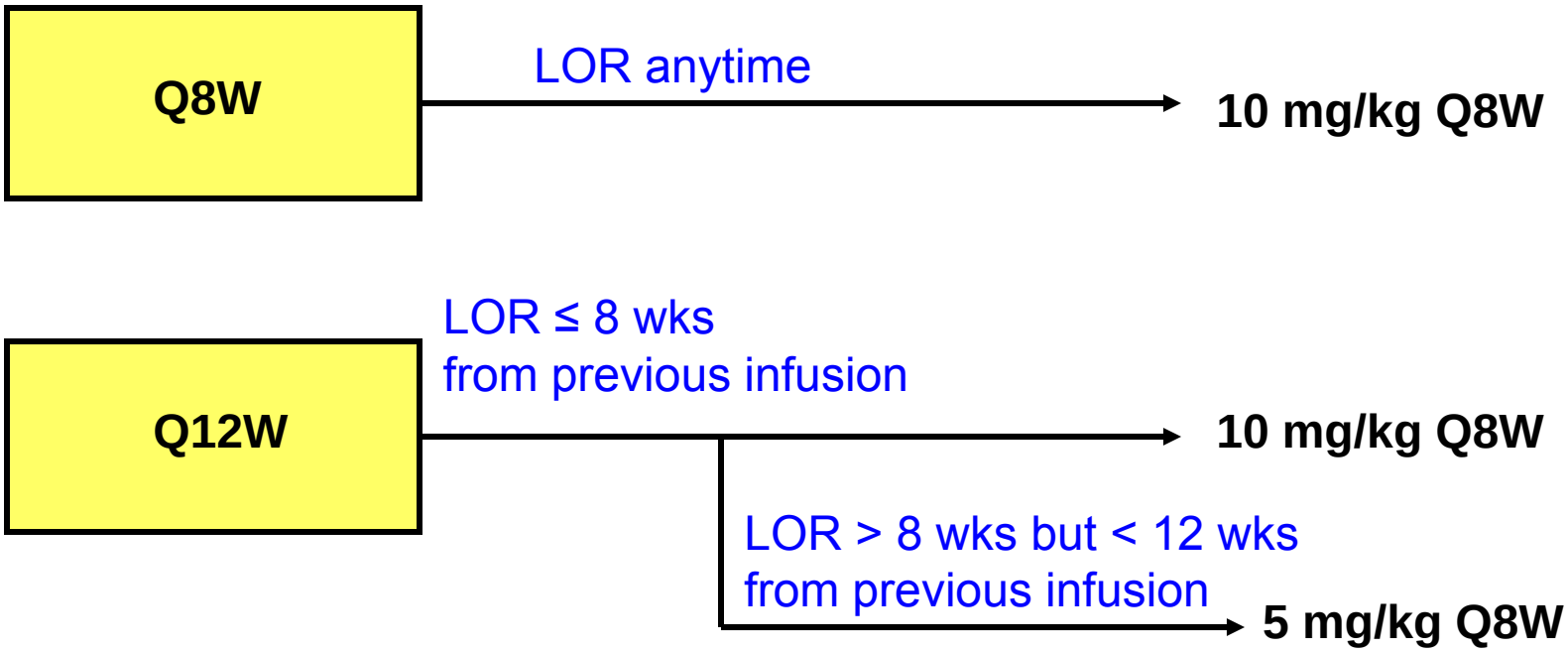
- 9/15/2005 Based on ACT 1 & ACT 2 data until Week 30:
  "reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy"

- 10/13/2006 Based on ACT 1 data through Week 54:
  Expanded the indication to include "… inducing and maintaining clinical remission and mucosal healing…"

Pediatric UC (T72) Study



Step-Up During Maintenance



LOR (loss of response):

1) ↑ in the partial Mayo score ≥2 from the Week 8 partial Mayo score at 2 consecutive visits at least 7 days apart.

OR

2) ↑ in the partial Mayo score ≥3 from the Week 8 partial Mayo score at any scheduled/unscheduled visit.

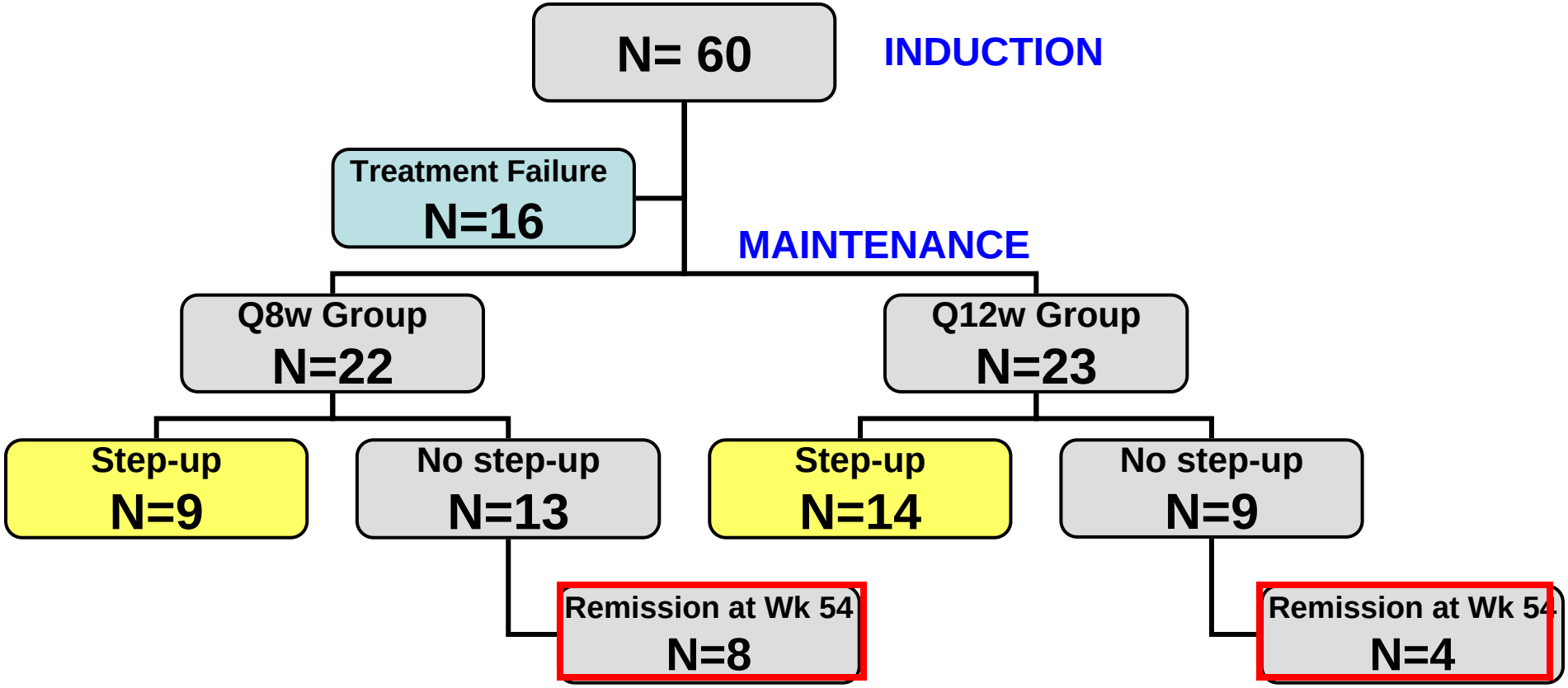
T72 Study Design

- Open label
- Single arm induction phase without a control/comparison group
- Small sample size in the maintenance phase (N=45, with 22 patients receiving 5 mg/kg q8w)

Patient Characteristics

- **47%** Males and **82%** Caucasians
- Median age **14.5 years**
- Median duration since diagnosis **1.4 years**
- **77%** extensive/pancolitis
- Median C-reactive protein **0.3 mg/dL**
- Mostly moderately active disease cohort:
  - Median Mayo score **8.0** (10% with severe disease)
- **62%** on baseline systemic corticosteroid
  - Median dose **0.5 mg/kg/day** prednisone equivalent
- **53%** on baseline immunomodulator (6-MP/AZA/MTX)

T72: Patient Disposition



A total of 30 patients (50%) discontinued infliximab treatment before trial completion.

Review of Proposed Efficacy Indications

Induction Phase

Primary Endpoint: Clinical Response at Week 8

	T72	Combined ACT 1 and 2	
	IFX 5 mg/kg	IFX 5 mg/kg	Placebo
Patients treated	60	242	244
Patients in clinical response at Wk 8	44 (**73%**)	162 (**67%**)	81 (**33%**)
95% CI	(62%, 85%)	(61%, 73%)	(27%, 39%)

Source: Applicant's Summary of Clinical Efficacy Appendix 1.1

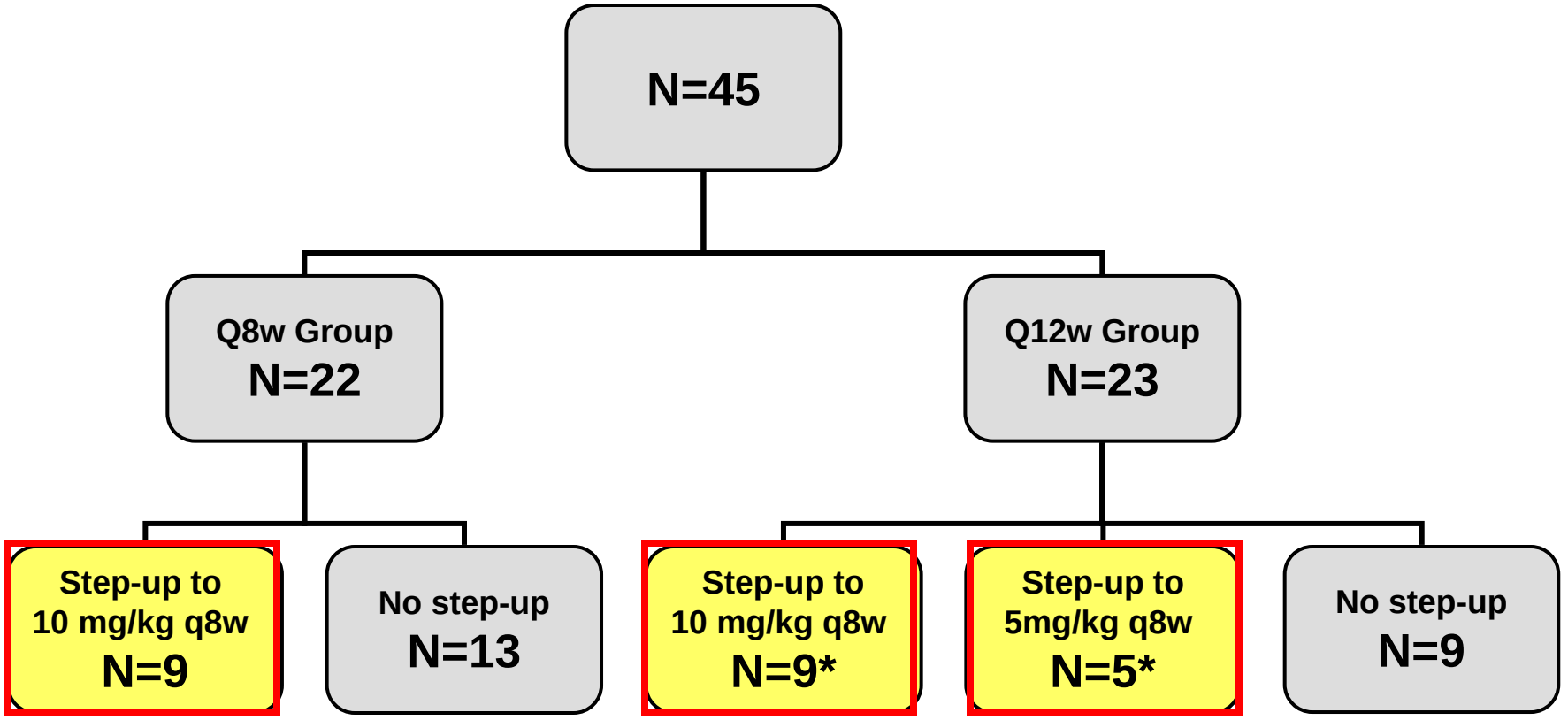
"Inducing Clinical Remission and Mucosal Healing"

	Evaluable Patients	Outcome
Clinical Remission at Week 8 (Mayo)	60	24/60 (40%)
Clinical Remission at Week 8 (PUCAI)	51	17/51 (33%)
Mucosal Healing at Week 8 (Mayo Endo)	60	41/60 (68%)

Source: Applicant's Summary of Clinical Efficacy Appendices 1.15 and 1.19

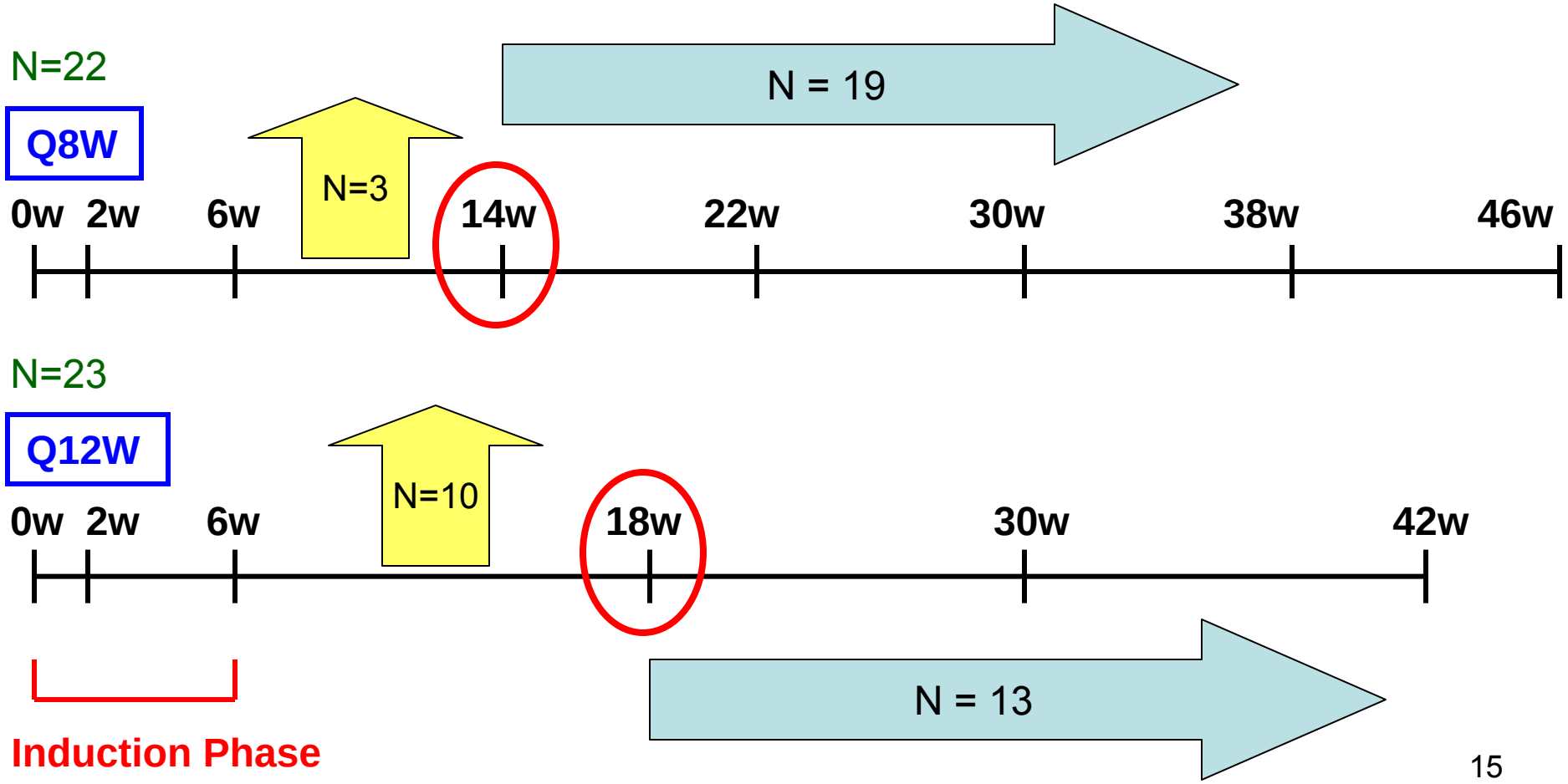
Maintenance Phase

23 of 45 patients stepped up to a higher and/or more frequent dose during maintenance



*One patient in the Q12W group received an incorrect step-up dose from the originally assigned step-up dose (10 mg/kg Q8W instead of 5 mg/kg Q8W).

13 patients stepped up *prior to* receiving their 1st scheduled maintenance treatment



"Maintaining Clinical Remission: Q8W vs. Q12W"

Patients in Clinical Remission at Week 54

	T72	
	5 mg/kg Q8W	**5 mg/kg Q12W**
Patients randomized	22	23
Patients with evaluable PUCAI	21	22
Patients remaining at 1st maintenance treatment	19	13
Patients in clinical remission at Wk 54	8/21 (**38%**)	4/22 (**18%**)

Source: Adapted from Applicant's Clinical Study Report Table 8

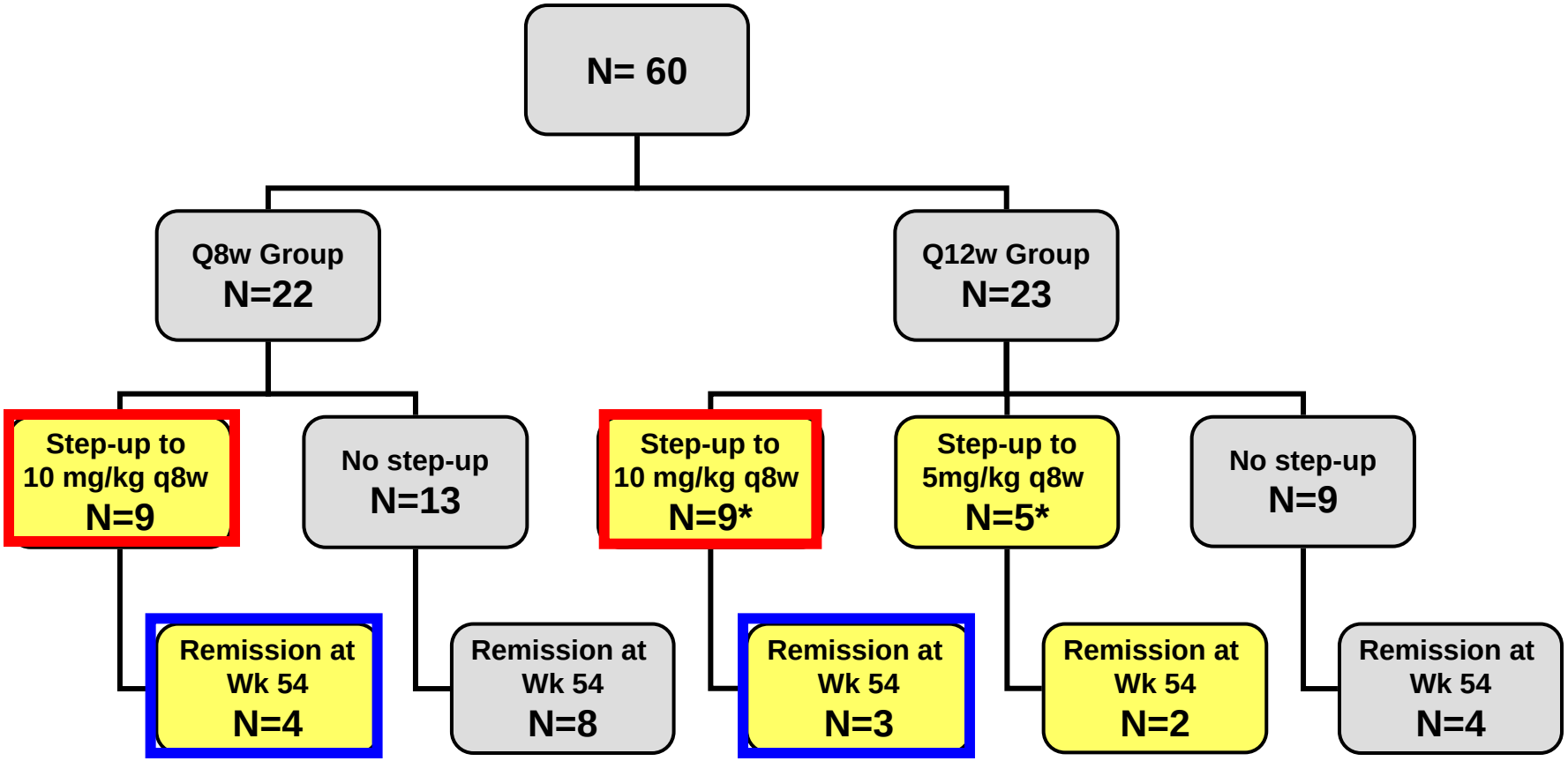
"Maintaining Clinical Remission: Comparison to ACT 1"

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 Wk 54	8/21 (**38%**)	42/121 (**35%**)	20/121 (**17%**)

Source: Applicant's Summary of Clinical Efficacy Appendix 1.17

7 of 18 patients who stepped up to 10 mg/kg Q8W achieved clinical remission at Week 54



*One patient in the Q12W group received an incorrect step-up dose from the originally assigned step-up dose (10 mg/kg Q8W instead of 5 mg/kg Q8W).

Maintenance of mucosal healing at Week 54: Limitations of analysis

- 9 of 45 patients in the maintenance phase of T72 (4 from Q8W and 5 from Q12W) underwent optional endoscopy at Week 54.

- 8 of 9 patients maintained mucosal healing through Week 54:
  - 3 patients in Q8W
  - 5 patients in Q12W

- 2 of 8 patients who maintained mucosal healing through Week 54 received step-up therapy to 10 mg/kg Q8W during the maintenance phase.
  - If step-up patients are treated as failures, only 6 of 9 patients who underwent endoscopy at Week 54 maintained mucosal healing.

"Eliminating Corticosteroid Use"

Daily Corticosteroid Dose through Wk 54 (Pred Eq Dose mg/kg/d)

	5 mg/kg Q8W	5 mg/kg Q12W
Patients randomized	**22**	**23**
Baseline corticosteroid		
N	**14**	**14**
Median	0.5	0.5
Week 8		
N	**14**	**14**
Median	0	0.2
Week 30		
N	**8**	**2**
Median	0	0.2
Week 54		
N	**6**	**0**
Median	0	NA

Source: Applicant's Response to FDA's Information Request, May 25, 2011, Table 2

Clinical Summary (1)

- T72 was not designed to be an efficacy trial.
- Induction treatment resulted in clinical response/clinical remission/mucosal healing data at week 8 that are comparable to adult data.
- Maintenance phase results are supported by a small number of evaluable patients, especially for the “maintenance of mucosal healing” and “eliminating corticosteroid use” claims.

Clinical Summary (2)

- Some patients required step-up therapy during the maintenance phase and achieved clinical remission with a higher dose of infliximab.

- It would be important to assess whether induction and maintenance dosing are appropriate based on pharmacokinetic and exposure-response data.

Gastrointestinal Drugs Advisory Committee Meeting

Infliximab (Remicade®)

Nitin Mehrotra, Ph.D.
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Office of Clinical Pharmacology
CDER/FDA

July 21, 2011

Pediatric Dose Selection for UC

- No prior dose ranging studies conducted in pediatric UC patients

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

- T72 trial design included q12 week dosing regimen: Responders at week 8 randomized to 5 mg/kg q8 or q12 week dosing regimen

Relevant Question for the Committee

Assuming extrapolation is appropriate, do the pediatric data support the dosing for the proposed pediatric indications of:

a. induction of clinical remission
(5mg/kg IV at 0, 2 & 6 weeks): (yes/no)

b. maintaining clinical remission
(5mg/kg IV every 8 weeks): (yes/no)

Clinical Pharmacology Key Conclusions (Question-Based Review)

1. Does the exposure-response relationship provide supportive evidence for effectiveness?
   - Induction phase: Yes, Week 8 concentration-clinical response relationship was demonstrated
   - Maintenance phase: Limited information to evaluate C_{min}- week 54 remission relationship
2. Does exposure-response relationship and clinical results support the proposed dosing regimen in the induction and maintenance phase?
   - Induction phase: Yes, based on (1) similar exposures, (2) similar response rate compared to adults
   - Pediatric week 8 concentration-clinical response relationship is not different from adults
   - Maintenance phase: Supportive clinical evidence (Limitations)

Clinical Pharmacology Key Conclusions (Question-Based Review)

3. Is it possible to assess the immunogenicity rate and impact of immunogenicity on PK, efficacy and safety?

- No, current assay is not suitable for assessing the immunogenicity rate due to drug interference
- Not feasible to assess the impact of immunogenicity on PK, efficacy, and safety

Clinical Pharmacology Key Questions

1. Does the exposure-response relationship provide supportive evidence of effectiveness?

2. Does exposure-response relationship and clinical results support the proposed dosing regimen in the induction and maintenance phase?

3. Is it possible to assess immunogenicity rate and impact of immunogenicity on PK, efficacy and safety?

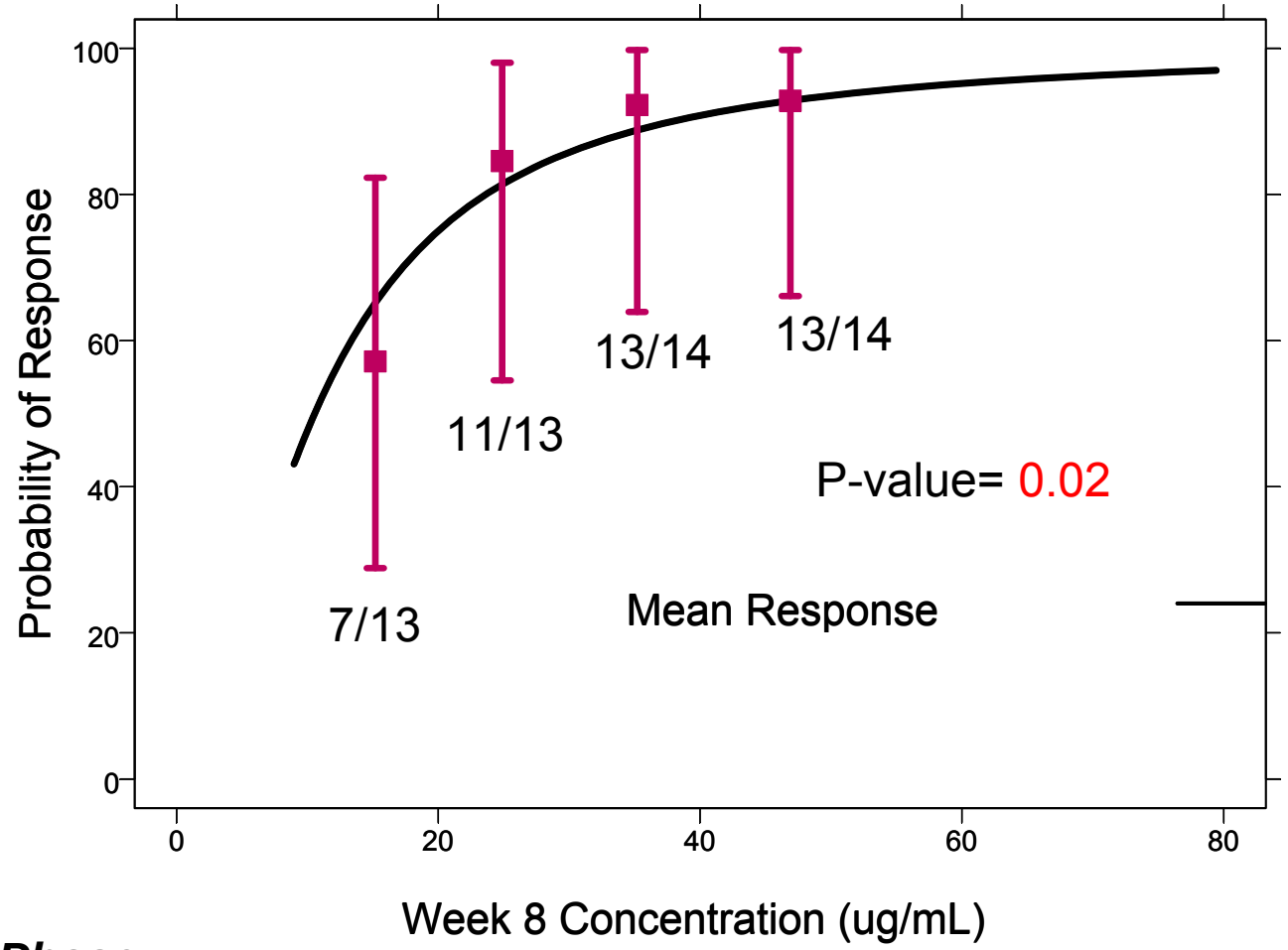
Data Used for Exposure-Response Analysis for the Induction Phase

- Exposure : Week 8 concentration
- Response: Clinical response at week 8

- Pediatric exposure-response analysis based on 55 patients with 5 mg/kg at week 0, 2, 6 from T72 trial
  - 5 patients withdrew from study before week 8

- Adult exposure-response analysis based on pooled data at 5 (N=114) and 10 mg/kg (N=108) at week 0, 2, 6 from the ACT1 trial

Significant Exposure-Response Relationship Provide Supportive Evidence of Effectiveness



Induction Phase

Limited Information to Evaluate Exposure-Response in the Maintenance Phase

- Exposure: Steady state trough concentration in the maintenance phase
- Response: Clinical remission or response at week 54
- Few pediatric patients with both PK and clinical response (N=9) or clinical remission data (N=17) at week 54

Clinical Pharmacology Key Questions

1. Does the exposure-response relationship provide supportive evidence of effectiveness?

2. Does exposure-response relationship and clinical results support the proposed dosing regimen in the induction and maintenance phase?

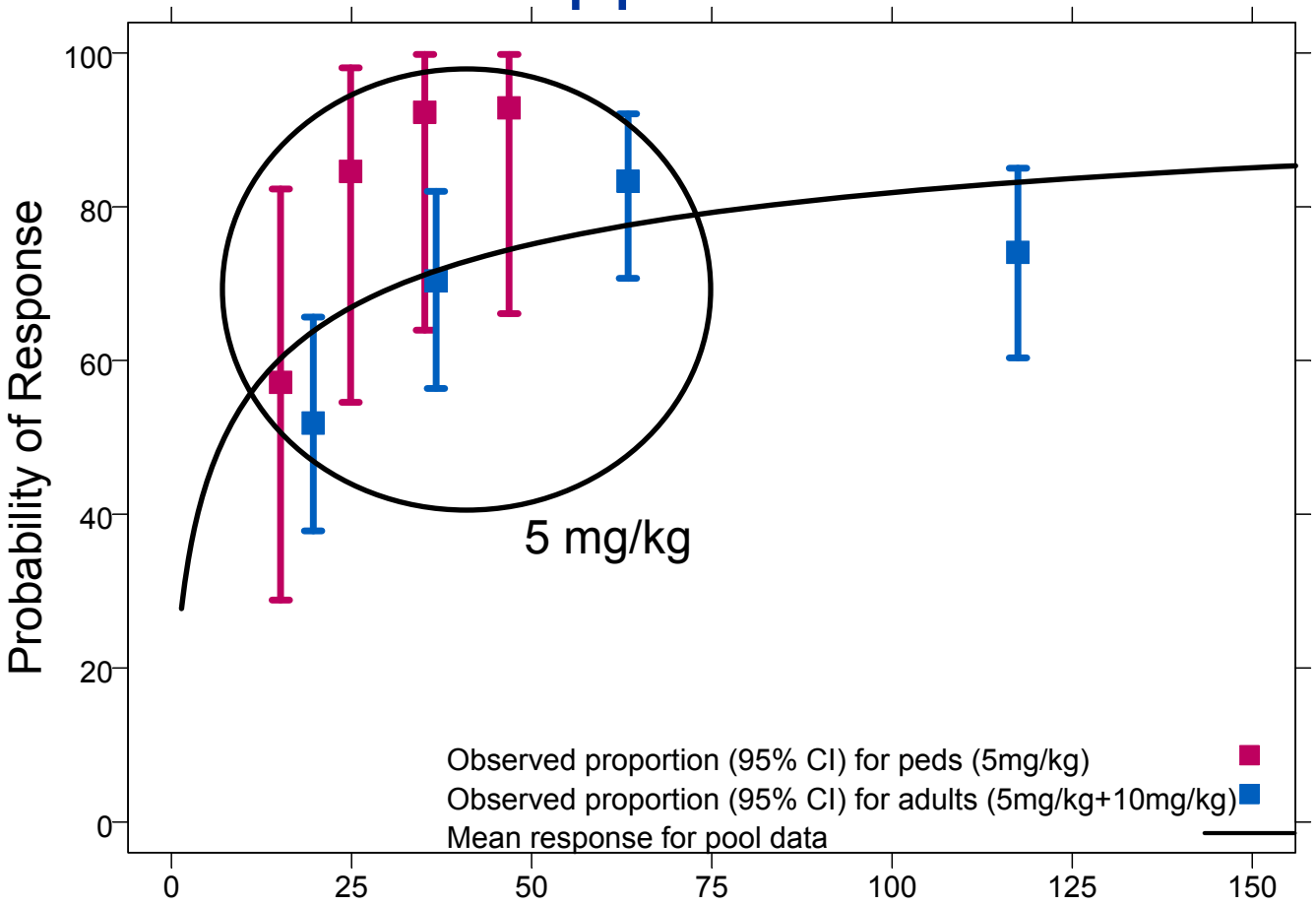
3. Is it possible to assess immunogenicity rate and impact of immunogenicity on PK, efficacy and safety?

Median Concentration and Response Rate at Week 8 are Similar in Pediatrics and Adults

	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)**

Induction Phase

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



Induction Phase

Clinical Observations that Could Potentially Support the Maintenance Dose

- 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*

- At the 5 mg/kg q8w dose, the observed clinical remission rate at Week 54 appears similar for pediatrics (8/21, 38%) and adults (42/121, 35%)

Limitations to Consider When Evaluating Maintenance Dose

- T72 trial (Pediatric) unlike ACT1 (Adult) had an enrichment trial design where induction non-responders were excluded at week 8

- Clinical remission is defined using PUCAI score for pediatrics and MAYO score for adult patients

- Remission rate of 38% in pediatrics at week 54 based on small sample size (8/21)

Clinical Pharmacology Key Questions

1. Does the exposure-response relationship provide supportive evidence of effectiveness?

2. Does exposure-response relationship and clinical results support the proposed dosing regimen in the induction and maintenance phase?

3. Is it possible to assess immunogenicity rate and impact of immunogenicity on PK, efficacy and safety?

Limitations in Anti Drug Antibody (ADA) Assay

- All samples were analyzed for
  - ADA response using ELISA
  - Infliximab concentration using ELISA

    Note: *ADA assay was developed in early 1990's to support initial product licensure*
- No drug "tolerance" for immunogenicity assay
  - Infliximab @ 8 ng/mL can interfere with ADA assay
  - Infliximab @125 ng/mL reduces ADA signal by 95%
  - Infliximab PK limit of quantitation: 100 ng/mL

Even though plasma infliximab level may be not quantifiable, it could interfere with the ADA assay

Negative ADA response ≠ Antibody Negative Status Due to Drug Interference on ADA assay

Presence of Infliximab	ADA Assay Response	
	+	-
Infliximab NOT present	Ab Positive	Ab negative
Infliximab present	Ab Positive	Ab Inconclusive

Inconclusive Ab Status in Majority of Patients Precludes Assessment of Immunogenicity Impact

- 60 patients in the pediatric trial
- 52/60 patients had appropriate samples

Ab Positive	Ab Inconclusive	Ab Negative
4/52	37/52	11/52

The Agency's assessment:

- Possible underestimation of immunogenicity rate
- Not feasible to determine immunogenicity impact on PK, efficacy and safety

Clinical Pharmacology Key Conclusions Revisited

1. Does the exposure-response relationship provide supportive evidence for effectiveness?
   - Induction phase: Yes, Week 8 concentration-clinical response relationship was demonstrated
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   - Induction phase: Yes, based on (1) similar exposures, (2) similar response rate compared to adults
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Clinical Pharmacology Key Conclusions Revisited

3. Is it possible to assess the immunogenicity rate and impact of immunogenicity on PK, efficacy and safety?

- No, current assay is not suitable for assessing the immunogenicity rate due to drug interference
- Not feasible to assess the impact of immunogenicity on PK, efficacy, and safety

Safety Considerations in Pediatric UC

Serious Adverse Events associated with the use of TNF-antagonist

- Serious infections: tuberculosis, invasive fungal infections that are often disseminated, including histoplasmosis, coccidiomycosis, candidiasis, aspergillosis, blastomycosis, pneumocystosis, and other opportunistic infections.

- Malignancy: lymphoma and other malignancies.

Hepatosplenic T-cell lymphoma (HSTCL)

- Majority occurred in adolescent and young adult males treated with TNF-antagonist and concomitant 6-MP/AZA.
- Rare form of non-Hodgkin lymphoma comprising < 5% of T-cell lymphomas
- Aggressive disease course and fatal

Infliximab: Hepatosplenic T-cell Lymphoma in Children and Young Adults with Inflammatory Bowel Disease

Ann Corken Mackey, RPh, MPH
Safety Evaluator Team Leader
Division of Pharmacovigilance 1
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology

Outline

- All malignancies in children using TNF antagonists
- Hepatosplenic T-cell lymphoma (HSTCL) signal
- Use data
- HSTCL cases
- Regulatory actions
- Ongoing concerns/considerations regarding HSTCL
- Conclusions

Immunomodulators

- Tumor necrosis factor (TNF) antagonists (e.g., infliximab, adalimumab, etanercept) treat serious conditions (e.g., Crohn's disease [CD], rheumatoid arthritis [RA], ulcerative colitis [UC])
  - Block the effects of cytokines
- Thiopurines (i.e., azathioprine, mercaptopurine) are used to treat CD and UC
  - Impede DNA synthesis and thus inhibit cell proliferation
- These products suppress the immune system which predisposes patients to develop infections and some malignancies

All Malignancies in Children Using TNF antagonists up to April 2008*

- 48 malignancies reported in children 0-18 yrs to the FDA Adverse Event Reporting System (AERS) as of April 29, 2008: infliximab (31), etanercept (15), adalimumab (2)†
- 25 cases reported in children treated for CD (21) and UC (4)
  - Infliximab (24), infliximab to adalimumab switch (1)
  - HSTCL (10), NHL other (4), Hodgkin's lymphoma (2)
  - One each for chronic myeloid leukemia, leiomyosarcoma, nephroblastoma, melanoma, basal cell, hepatic malignancy, metastatic hepatocellular, thyroid, colorectal

* Diak P et al. Arthritis & Rheumatism 2010; 62(8): 2517-24.

† Note that most of these patients were receiving concomitant immunosuppressants.

All Malignancies in Children Using TNF Antagonists

- Underreporting to AERS is well known*
- Malignancies reported at rates higher than background incidence rates in the pediatric population (17/100,000 per SEER data)†
- Cases confounded with potential risk of malignancy associated with underlying illness and concomitant immunosuppressants
- Causal relationship could not be established
- HSTCL stands out due to very low background and population

* Rogers AC et al. Arch Intern Med 1988; 148: 1596-1600.

† Surveillance, Epidemiology, and End-Results Cancer Statistics Review 1975–2005, Table XXIX-1, ages 0–19 years.

Hepatosplenic T-cell Lymphoma (HSTCL)

- First recognized in 1990
- Neoplasm of gamma/delta and alpha/beta T-cells that infiltrate sinusoids of the spleen, liver, and bone marrow
- Rare tumor comprising 5% of peripheral T-cell lymphomas (PTCL; all ages)
- Aggressive cancer – most patients die within one year of diagnosis
- Usually associated with drugs used for chronic immune suppression as in organ transplantation

Why Are We Concerned about a Few Cases?

- It is known that TNF antagonists suppress the immune system and can lead to increased risk for cancer and infections; thiopurines suppress the immune system and are known to be mutagenic
- HSTCL is a rare cancer (< 200 cases published in literature)
- Pediatric Inflammatory Bowel Disease (IBD) population estimated at 100,000 in US (< 18 years of age)†
  - Patients with severe IBD would be fewer
- Initially, with low use of infliximab in pediatric IBD patients, a number of HSTCL cases were observed

† Crohn's and Colitis Foundation, www.ccfa.org, accessed May 15, 2008.

Why Are We Concerned about a Few Cases? (cont)

- A retrospective cohort study of 17,000 Inflammatory Bowel Disease adult patients found no increased disease-related risk of lymphoma*
  - Risk for lymphoma in patients with IBD receiving conventional immunosuppressant therapy remains controversial
- Because there are fewer numbers of children with CD or UC than adults treated with infliximab or other immunosuppressants, a finding of malignancy is a concern

* Lewis et al. Gastroenterology 2000; 121: 1080-7.

Use of Infliximab and Thiopurines to Treat IBD

- Thiopurines (azathioprine and mercaptopurine) used for decades to treat IBD; infliximab approved for use in adult CD in 1998 (childhood CD in 2006)
- Use data for infliximab versus thiopurines is obtained from different data sources making comparisons across products difficult
- Limitations in the precision and accuracy of use data:
  - Low numbers making projections uncertain
  - Lack of nationally projected patient-level estimates of use for infusion therapies by age

Infliximab Claims-Based Use Data*

- April 2006 to March 2011 (5-year period): 58,903 unprojected numbers of patients with a medical claim for infliximab per sample of the non-retail pharmacy setting (95% adults).
  - Of the 16,000 pts with a diagnosis of CD, 1724 (11%) were children (0 to 17 years of age)
  - Of the 6,840 pts with a diagnosis of UC, 526 pts (8%) were children (0 to 17 years of age)

* Source: Wolters Kluwer Health's Source® Lx. Extracted 5/11. File: WKCPA 2011 1164 Remicade 5-3-11.xls

Use data provided by Stephen H. Chang, PharmD, Drug Use Data Analyst, OSE Division of Epidemiology

Thiopurine Use Data*

- Azathioprine: From July 2005 through June 2010 (5-year period), approximately 7,000 and 10,000 pediatric patients (0 to 16 years of age) were treated for CD and UC respectively (projected data)

- Mercaptopurine: From July 2005 through June 2010 (5-year period), approximately 4,000 pediatric patients (0 to 16 years of age) were treated for CD (projected data)

* Source: SDI Total Patient Tracker and Physician Drug and Diagnosis Audit, Data Extracted 7/2010.
Use data provided by Patty Greene, PharmD, Drug Use Data Analyst, OSE Division of Epidemiology

Summary of HSTCL Cases (all ages) as of December 31, 2010 (n=42)§

- Infliximab, n=19*
- Infliximab/adalimumab, n=5*
- Etanercept, n=1
- Adalimumab, n=2
- Certolizumab/golimumab, n=0
- Azathioprine, n=12†
- Mercaptopurine, n=3†

§ Cases reported to the FDA Adverse Event Reporting System, literature, HSTCL Cancer Survivors Network; these cases involve domestic and foreign patients; differs from counts provided in the Drug Safety Communication because it was determined that one patient using infliximab did not have HSTCL

* All patients were receiving concomitant azathioprine or mercaptopurine

† These patients had never used and were not using TNF antagonists

Infliximab: Cases Of HSTCL as of December 31, 2010 (n=24)§†

- CD (20), UC (4)
- Male (22), female (2)
- Age (yrs; tumor diagnosis; 11 pts < 17 yrs at immunosuppressant initiation)= 24 median, 12 to 58 range
  - 0 to 17 (3)
  - 18 to 28 (12)
  - 30 to 58 (9)
- Latency: 2 to 11 yrs (mean=5.6 yrs; any immunosuppressant)
  - Doses of TNF antagonist received: 1 to 24 (1 to 3 doses [8 pts])
- Concomitant thiopurine use (24, natalizumab [1/24])
- Death (22)

§ Cases reported to the FDA Adverse Event Reporting System, literature, HSTCL Cancer Survivors Network; all patients irrespective of history of use of other immunosuppressants

† Five patients were switched from infliximab to adalimumab

Thiopurines: HSTCL Cases as of December 31, 2010 (n=15)§ *

- CD (9), UC (5), hepatitis/UC (1)
- Male (11), female (1), not reported (3)
- Age (yrs; tumor diagnosis; 7 pts < 17 yrs at thiopurine initiation): 22 median, 15 to 45 range (n=13)
  - 0 to 17 (1)
  - 18 to 27 (9)
  - 35 to 45 (3)
- Latency: 4 to 17 years (median=6 yrs) (n=15)
- Death (13)

§ Cases reported to the FDA Adverse Event Reporting System, literature, HSTCL Cancer Survivors Network

* Patients with concomitant or previous use of TNF antagonist exposure were excluded.

Regulatory Actions

- May 2006: Infliximab approved for use in pediatric pts with moderate- to severely-active CD who have failed other therapies (HSTCL added to Boxed Warning section of the label)
- April 2010: Increased risk of lymphoma and other malignancies in children and adolescent patients added to Boxed warning for all TNF antagonists
- March-May 2011: HSTCL added to Boxed Warning for adalimumab and azathioprine and the Warnings for mercaptopurine

Findings

- HSTCL and infliximab/thiopurine combination use (n=24)
  - 22/24 male
  - 15/24 < 28 years of age at tumor diagnosis (median=24 years)
  - Latency* 5.6 years (mean)
  - 22/24 fatal
- HSTCL and thiopurine use without TNF antagonists (n=15)
  - 11/15 male (gender not reported for 3 patients)
  - 9/15 < 28 years of age at tumor diagnosis (median=22 years)
  - Latency* 6 years (mean)
  - 13/15 fatal
- All patients had underlying CD or UC (n=39)

* Latency calculated from initiation of any immunosuppressant to tumor diagnosis

Findings (cont)

- No known cases of HSTCL with use of TNF antagonist without previous or concomitant thiopurine use
  - Few patients have been studied; this is currently not the standard of care
  - Unable to obtain concomitant or sequential use data
- Use of infliximab and thiopurines in children with IBD is low

Unanswered Questions

- Why are children/young adults using infliximab and other immunosuppressants more vulnerable to developing HSTCL than adults?
  - Children have developing immune systems
  - Individuals diagnosed as children may have a more aggressive form of CD/UC compared to adults and need more aggressive treatment
    - They may be more steroid dependent
    - They may be more sensitive to the effects of radiation used for diagnostic procedures*
  - It is known that azathioprine and mercaptopurine cause DNA damage (the contribution of infliximab vs thiopurine is unknown)

* Fuchs Y et al. JPGN 2011; 52(3): 280-5.

Unanswered Questions (cont)

- Why is HSTCL found predominantly in CD and UC patients using immunosuppressants as opposed to other indications?
  - Gamma-delta T cells are abundant in the intestinal epithelium*
- Why is there a male predominance to HSTCL?
  - Not known, there is no overwhelming predominance of males versus females with IBD†

* Cooke C et al. Blood 1996; 88: 4265-74.

† Crohn's & Colitis Foundation, www.ccfa.org, accessed July 8, 2011.

Considerations

- HSTCL is a relatively recently-recognized entity; the first AERS case was received in 2003 (pt using thiopurine/ infliximab)
- Clinical trials may be too short to detect an event with long latency
  - Patients with more serious condition may be excluded
- Voluntary registries are likely too small to detect rare events
- Reporting rates are not useful because of low (unstable) numbers and an uncertain denominator (underreporting)
- HSTCL incidence is higher in young males with IBD; an overall population incidence rate would not reflect this treatment subgroup

Conclusions

- Use of immunosuppressants in children is low; cases of rare tumor (HSTCL) have been identified
- HSTCL appears to be strongly associated with children/young adult males using infliximab and thiopurines (e.g., azathioprine, mercaptopurine) to treat CD and UC
  - It is uncertain whether infliximab's link to HSTCL risk is stronger or similar to the risk effects of thiopurines. In conjunction with infliximab, risk for HSTCL could be affected by the patient's underlying disease activity, exposure to radiation, or other factors.
- Clinicians should consider individual benefit risk when prescribing infliximab in children to treat IBD.

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Overall Summary

- **Induction**
  - Adequate PK and E-R data
  - Supportive clinical data

- **Maintenance**
  - Limited PK and E-R data
  - Limited but supportive clinical data (based on small sample size)

- **Safety**
  - No new safety signals in T72
  - Ongoing concerns of infections and cancers in general, including HSTCL

Thank you