WWW.IBD-AMC.NL

Induction and Maintenance of Remission in IBD: Where Are We Coming from; Where Could We Go?

Geert D'Haens MD, PhD
AMC Amsterdam

CONFLICTS OR INTEREST

Abbvie: research support, lecture fee, consultant; Ablynx: consultant; Actogenix: consultant; Amakem: consultant; Amgen: consultant; AM Pharma: consultant; AstraZeneca: consultant; BMS: consultant; Boerhinger Ingelheim: consultant; Cosmo: consultant; Elan: consultant; Ferring: consultant, research support, lecture fee; DrFALK Pharma: research support, lecture fee; Celgene: consultant ; Celltrion: consultant; Centocor/Jansen Biologics: consultant, research support, lectur;e fee; Engene: consultant; Galapagos: consultant; Giuliani: lecture fee; GivenImaging: research support, consultant; GSK: consultant, research support, consultant; Hospira: consultant; Medimetrics: consultant; Millenium/Takeda: consultant, research support, lecture fee; Mitsubishi Pharma: consultant; MSD: consultant, research support, lecture fee; Mundipharma: consultant; Novonordisk: consultant; Norgine: lecture fee; Otsuka: consultant, lecture fee; Pfizer: consultant; Photopill: research support; PDL: consultant; Prometheus laboratories: consultant, research support; Receptos: consultant; Robarts Clinical Trials: Scientific Director, research support; Salix: consultant; Sandoz: consultant; Setpoint: consultant; Shire: consultant, lecture fee; TEVA: consultant; Tigenix: consultant; Tillotts: consultant, lecture fee; Topivert: consultant; UCB: consultant, lecture fee; Versant: consultant; Vifor: consultant, lecture fees.

HISTORY

ULCERATIVE COLITIS

- Sulfasalazine
- Aminosalicylates
- Corticosteroids (BUD)
- Thiopurines
- Cyclosporin
- Tacrolimus
- Methotrexate
- Infliximab
- Adalimumab
- Golimumab
- Vedolizumab

CROHN'S DISEASE

- Sulfasalazine
- Aminosalicylates
- Corticosteroids (incl topical)
- Thiopurines
- Methotrexate
- Infliximab
- Adalimumab
- Vedolizumab

ULCERATIVE COLITIS

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 29 1955

CORTISONE IN ULCERATIVE COLITIS

FINAL REPORT ON A THERAPEUTIC TRIAL

BY

S. C. TRUELOVE, M.D., M.R.C.P. AND L. J. WITTS, M.D., F.R.C.P.

Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford

With the co-operation of Professor R. E. TUNBRIDGE and Dr. G. WATKINSON (Leeds), Dr. F. AVERY JONES and Dr. RICHARD DOLL (North-west London), Professor T. L. HARDY and Dr. C. R. ST. JOHNSTON (Birmingham), Dr. W. I. CARD and Dr. MAXWELL WILSON (Edinburgh), and Sir JOHN TAYLOR (Medical Research Council)

First Landmark Trial in UC: Steroids

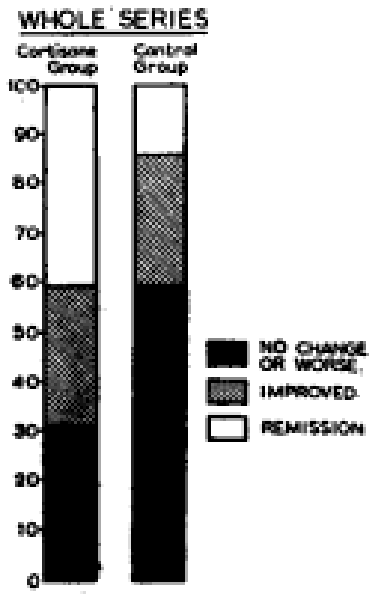


FIG. 1

FIG. 1.—Effect of treatment—whole series. FIG. 2.—Effect of treatment, showing first attacks and relapses separately.

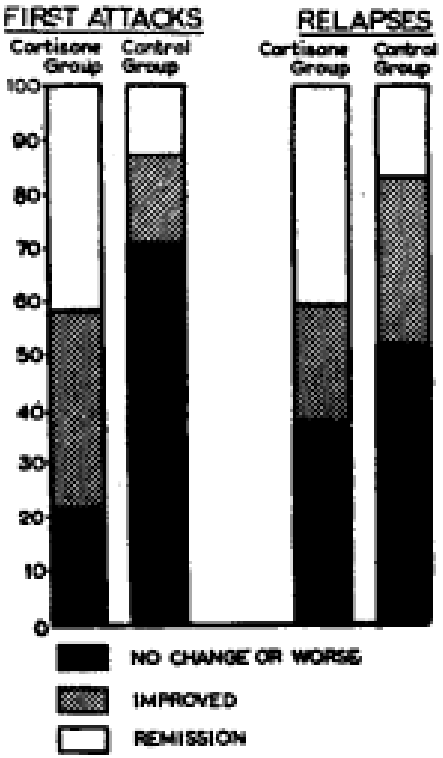


FIG. 2

Dosage.—The actual dosage of cortisone used in the 109 patients who received it was as follows:

100 mg. a day for six weeks	38	patients
100 mg. a day for two to three weeks, followed by smaller doses of 50–75 mg. a day	38	"
Doses exceeding 100 mg. a day	17	"
Therapy for less than six weeks	16	"

Truelove et al., BMJ 1955

TABLE IV.—*Sigmoidoscopic Appearances in 120 Patients Examined at the End of Treatment*

	Cortisone Group	Control Group
Normal or near-normal ..	19	6
Improved	14	12
No change or worse.. ..	30	39
Total	63	57

$\chi^2 = 7{\cdot}81$. n = 2. P ≃ 0·02.

Truelove et al., BMJ 1955

Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial

D Rachmilewitz on behalf of an international study group

***Interventions*—Coated mesalazine (Mesasal) 1·5 g daily or sulphasalazine 3·0 g daily for eight weeks. Compliance monitored by pill counts.**

***End point*—Clinical and endoscopic remission.**

Department of Gastroenterology, Hadassah University Hospital, Jerusalem, Israel
D Rachmilewitz, MD,
professor of medicine and head of department

The investigators making up the international study group are listed at the end of this paper.

Rachmilewitz et al., BMJ 1989

Rachmilewitz score: CAI

Web Table 3. Clinical Activity Index (CAI) also known as the Rachmilewitz Index

Variable	Scores				
	0	1	2	3	4
Number of stools weekly	<18	18-35	36-60	>60	
Blood in stools (weekly average)	None	--	Little		A lot
Investigator's global assessment of symptomatic state	Good	Average		ry poor	
Abdominal pain/cramps	No		te	Severe	
Temperature due to colitis (°C)				>38	
Extraintestinal manifestations (each rated 3 points)				Iritis, Erythema nodosum, Arthritis	
Laboratory findings		ESR>50 in 1st hr	ESR>100 In 1st hr		Hemoglobin <100 g/l

7 days
No clear definitions

Reprinted with permission from: Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ 1989;298:82-6.

RANGE: 0-29; remission ≤ 4

Web Table 7. Simple Clinical Colitis Activity Index (SCCAI)

Variable	Scores				
	0	1	2	3	4
Bowel frequency (day)	1-3	4-6	7-9	> 9	
Bowel frequency (night)		1-3	4-6		
Urgency of defecation		Hurry	Immediately	Incontinence	
Blood in stool		Trace	Occasionally frank	Usually frank	
General well-being	Very well	Slightly below par	Poor	Very poor	Terrible
Arthritis, pyoderma gangrenosum, erythema nodosum, uveitis		1 per manifestation			

Reprinted with permission from: Walmsley RS, Ayres RCS, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut 1998:43:29-32.

Range 0-19; Remission and response criteria not defined in the original study
Patient defined remission: < 2.5 points
Patient Defined Significant Improvement: Decrease of > 1.5 points from baseline

“Mayo score”

Coated Oral 5-Aminosalicylic Acid Therapy for Mildly to Moderately Active Ulcerative Colitis

Kenneth W. Schroeder, M.D., Ph.D., William J. Tremaine, M.D., and Duane M. Ilstrup, M.S. N ENGL J MED 1987; 317:1625-1629

Web Table 13. Mayo Score [also known as the Mayo Clinic Score and the Disease Activity Index (DAI)].

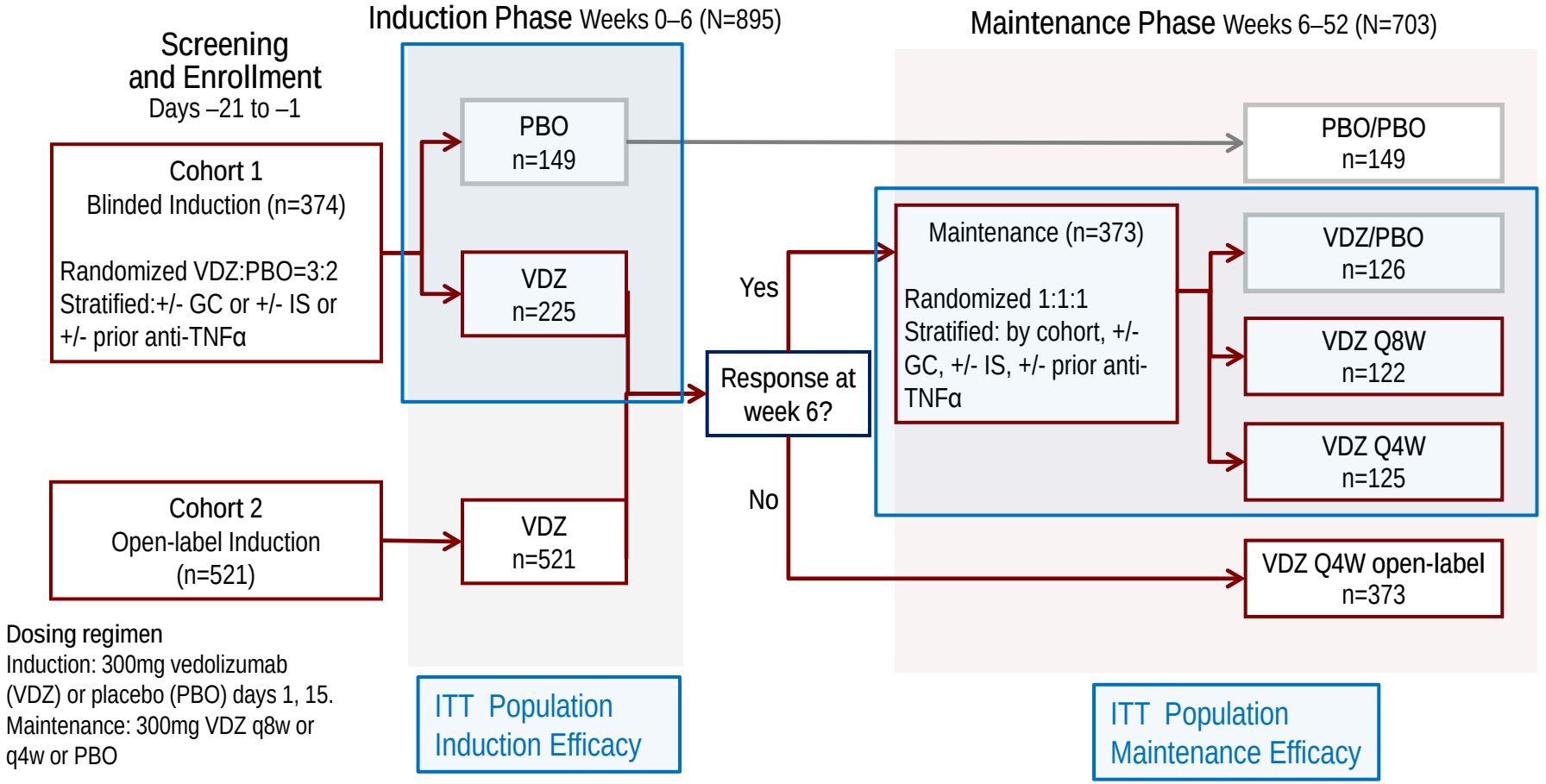
Stool frequency* 0 = Normal no. stools for this for this patient 1 = 1-2 stools more than normal 2 = 3-4 stools more than normal 3 = 5 or more stools more than normal * Each patient served as his or her own control to establish the degree of abnormality of the stool frequency.
Rectal bleeding** 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passed ** The daily bleeding score represented the most severe day of bleeding.
Findings of flexible proctosigmoidoscopy 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment 0 = Normal (there are no symptoms of colitis, the patient feels well, and the flexible proctosigmoidoscopy score is 0) (stool frequency = 0, rectal bleeding = 0, patients functional assessment = 0, flexible proctosigmoidoscopy findings = 0) 1 = Mild disease (mild symptoms and proctoscopic findings that were mildly abnormal) (the subscores should be mostly 1's: stool frequency = 0 or 1; rectal bleeding = 0 or 1; patients functional assessment = 0 or 1; sigmoidoscopy findings = 0 or 1) 2 = Moderate disease (more serious abnormalities and proctosigmoidoscopic and symptom scores of 1 to 2) (the subscores should be mostly 2's: stool frequency = 1 or 2; rectal bleeding = 1 or 2; patients functional assessment = 1 or 2; sigmoidoscopy findings = 1 or 2) 3 = Severe disease (the proctosigmoidoscopic and symptom scores are 2 to 3 and the patient probably requires corticosteroid therapy and possibly hospitaliziation) (the subscores should be mostly 3's: stool frequency = 2 or 3; rectal bleeding = 2 or 3; patients functional assessment = 2 or 3; sigmoidoscopy findings = 2 or 3)

“Mayo score”

- Active disease: 6-12; endoscopy 2-3
- Response: Decrease in Mayo score by ≥ 30% and ≥ 3 points, with decrease in RBS of ≥ 1 or a RBS of 0/1
- Remission: Total Mayo score ≤ 2 points, with no individual subscore >1

Vedolizumab in Ulcerative Colitis - Study Design

- Induction and maintenance study in patients with moderate to severe Ulcerative Colitis (UC)
- Randomized, double-blind, placebo-controlled multicenter phase 3 study (211 centers / 34 countries)



GC, glucocorticoid; IS, immunosuppressant; IT, intent-to-treat; TNF, tumor necrosis factor

14

Derived from: Feagan BG et al. N Engl J Med 2013; 369 : 699-710 & supplement

Challenges in UC Trials

What should be the population to be included ?

1. Severity of symptoms (Mayo 6-12; other scores ??)
2. Endoscopic severity (Mayo 2-3)
3. Combination of the above ?

Aspects or relevance:

1. Recruitability
2. Reduction of placebo response
3. Feasibility of repeated endoscopies
4. Timing of primary endpoint

Challenges in UC Trials

Which patients can enter the maintenance phase ?

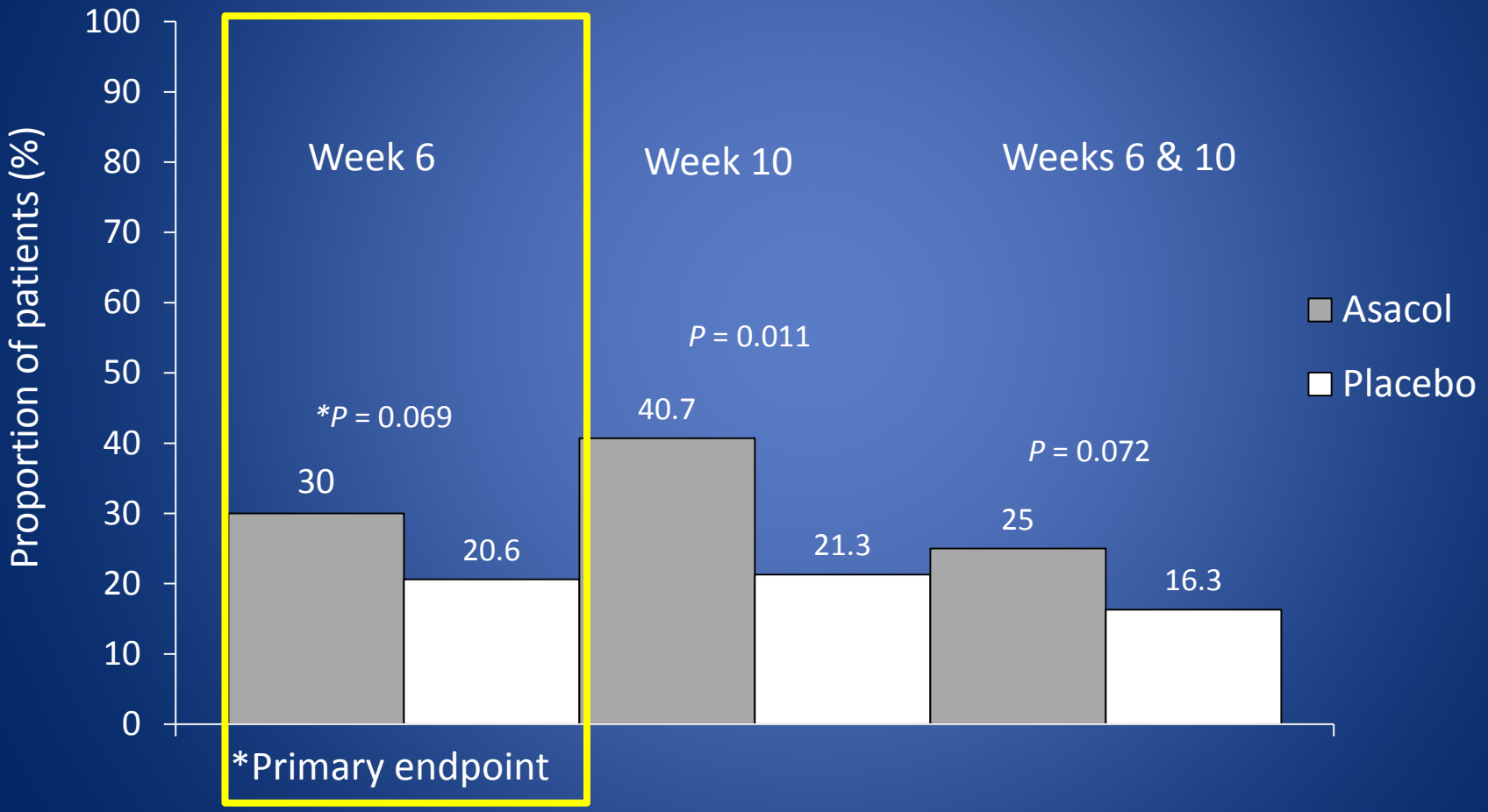
1. Mayo score response
2. Mayo remission
3. Endoscopic response
4. Endoscopic remission
5. Other biochemical/imaging criteria
6. All patients

Aspects or relevance:

1. Attractivity
2. Rerandomization of responders to placebo ?

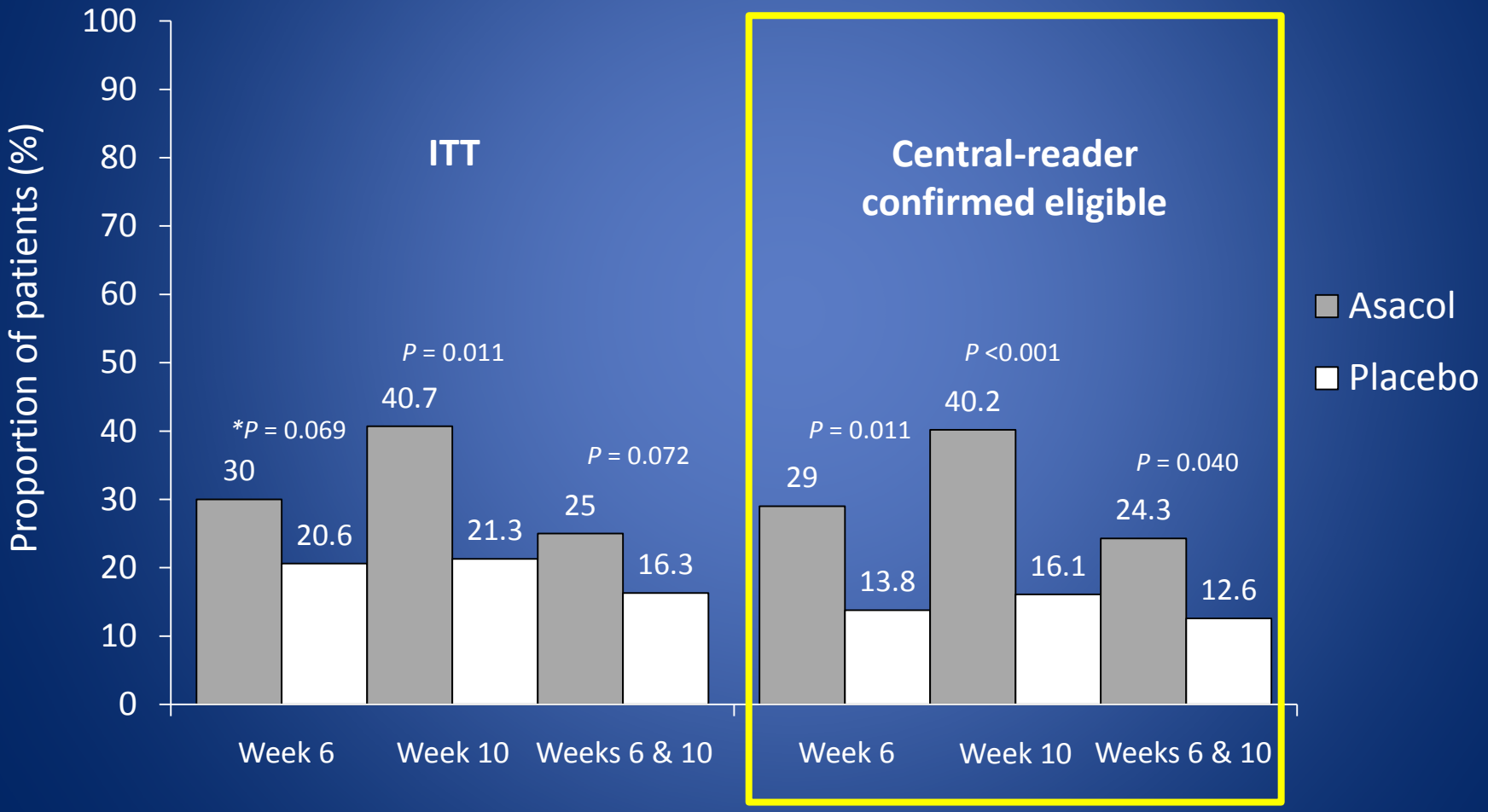
OBJECTIVE (INDEPENDENT) ASSESSMENT

Clinical Remission with Mesalazine



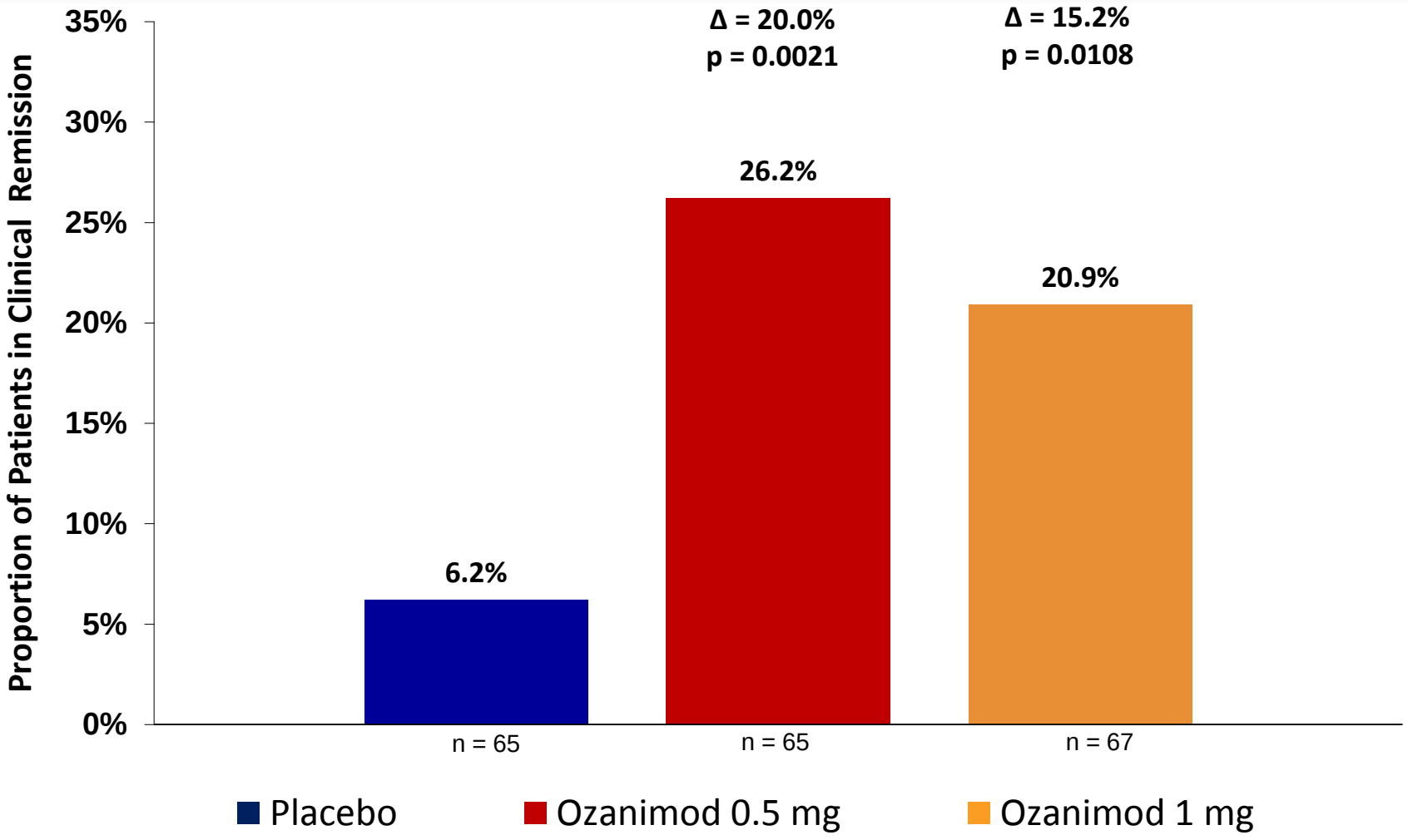
Feagan BG, Sandborn WJ, D'Haens G, et al. Gastroenterology 2013

Clinical Remission



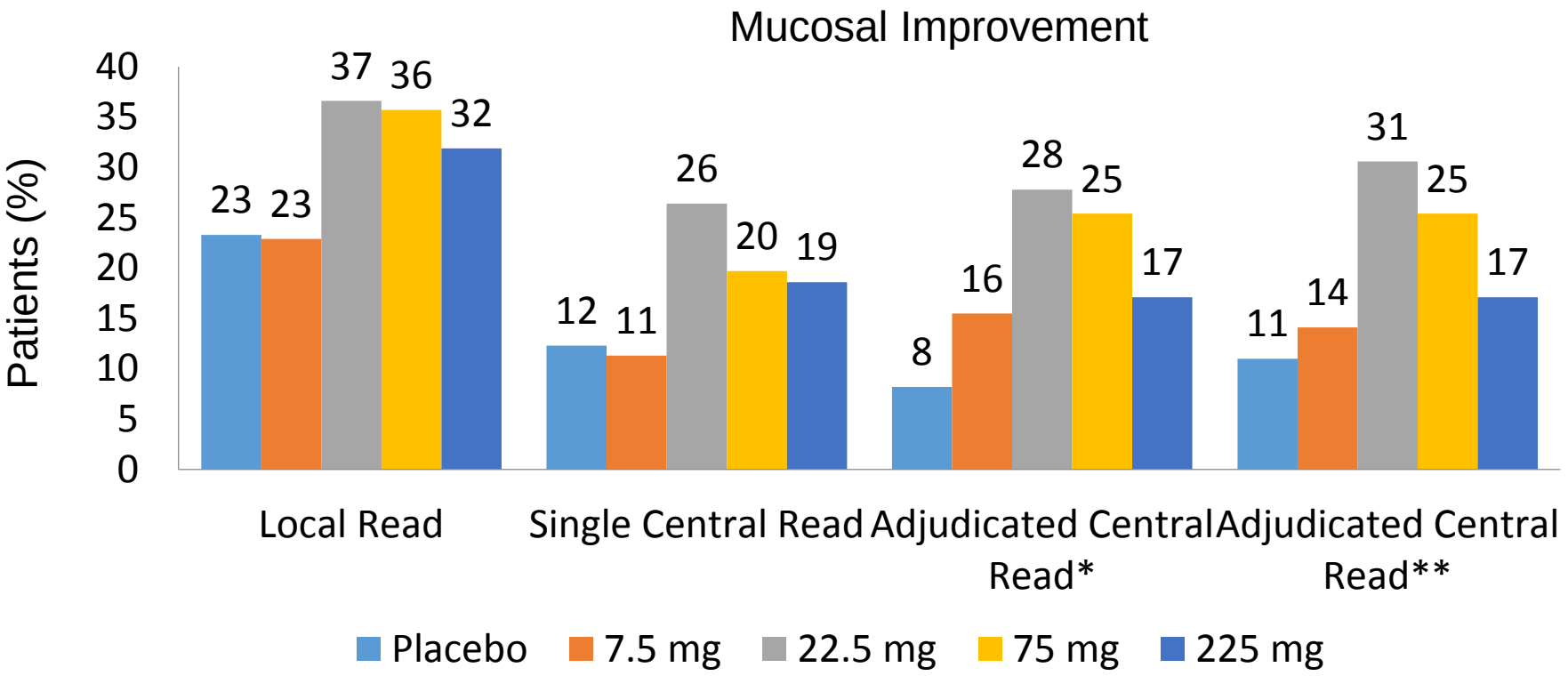
Feagan BG, Sandborn WJ, D'Haens G, et al. Gastroenterology 2013

Proportion of Patients in Clinical Remission at Week 32 (Adjudicated Central Read - ITT)



Sandborn, ECCO 2015

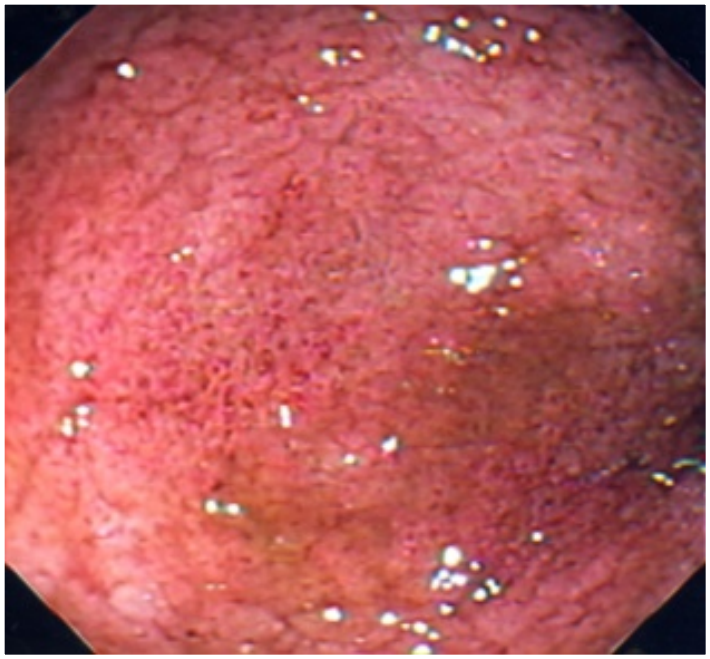
Anti-MAdCAM-1 Antibody (PF00547659) for UC: Different Endoscopic Assessment Modalities

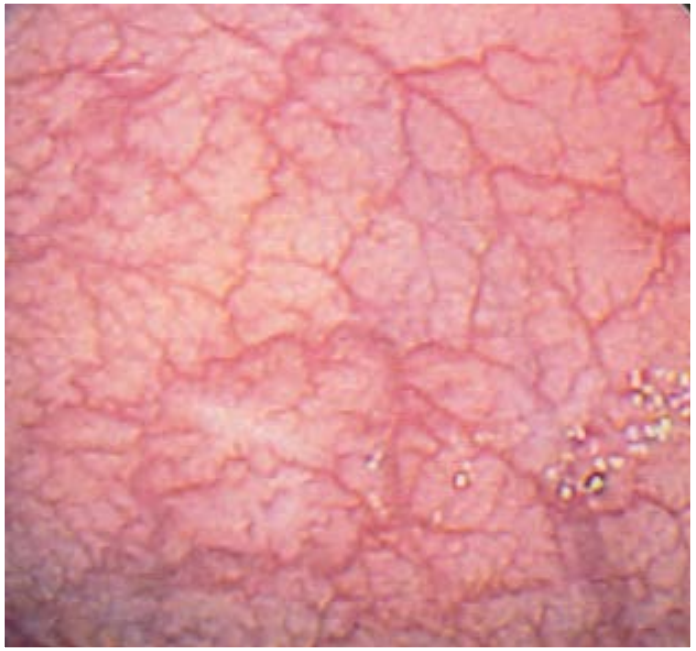


*All patients scored with 2 central reads, in the case of discrepancy, then consensus between 2 central reads

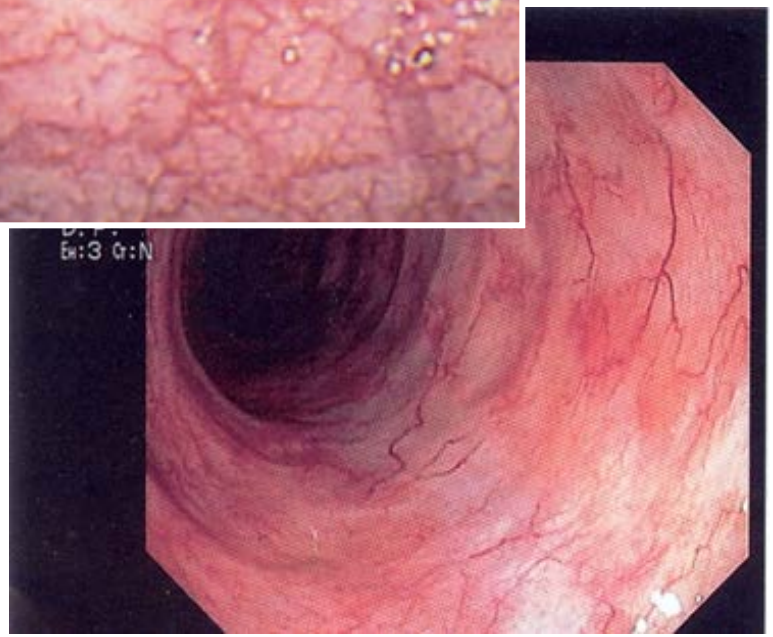
**For patients with discrepancy between 1st central read and local read, then 2nd central read, in case of discrepancy, then consensus between 2 central reads

Vermeire ECCO 2015





?


Bw:3 Gr:N

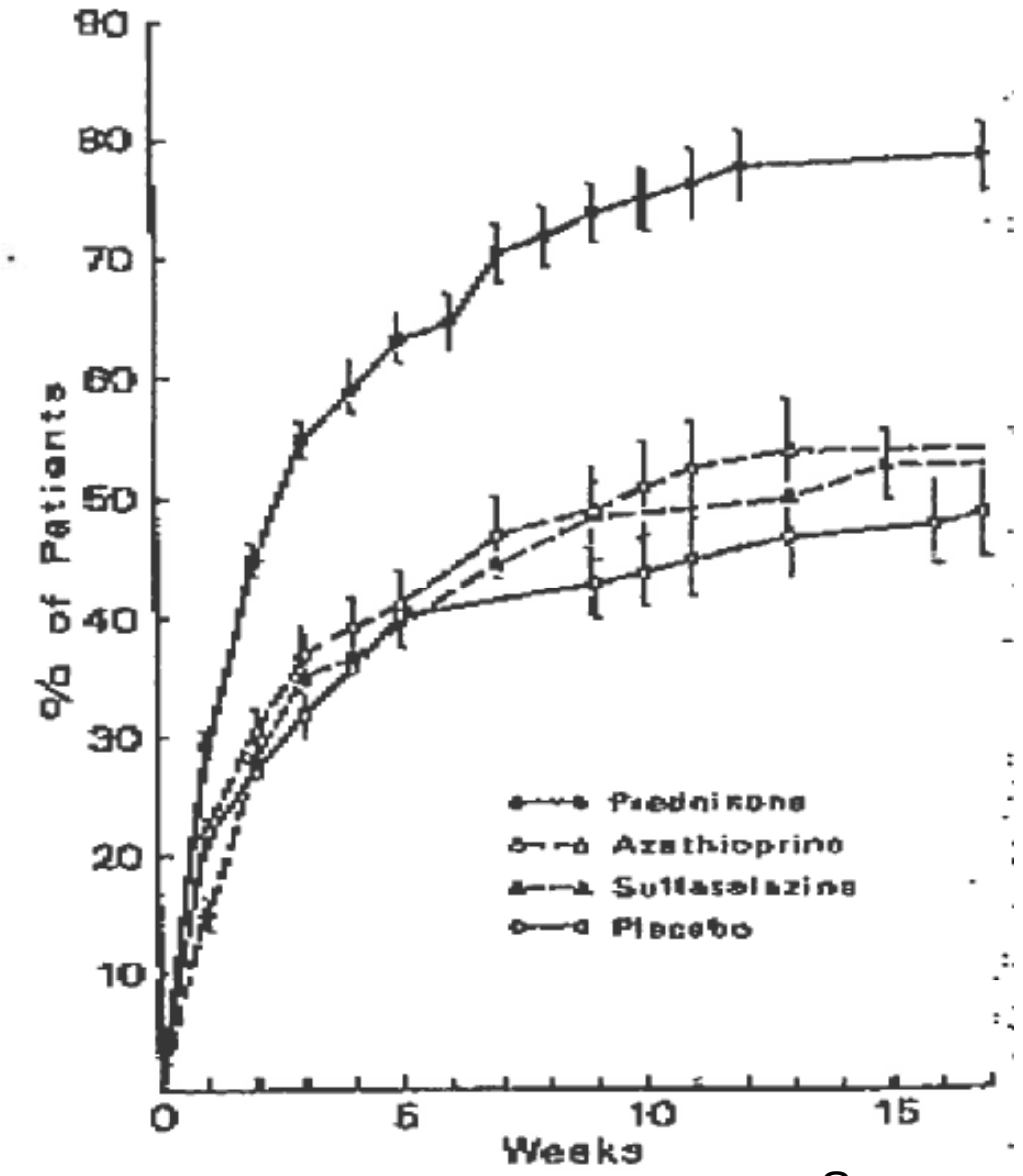
ULCERATIVE COLITIS: CONCLUSIONS

ULCERATIVE COLITIS: CONCLUSIONS

- Independent read of entry endoscopy and end-of-induction endoscopy appears essential
- Single reads are usually sufficient
- Available disease instruments to measure disease activity all have their flaws. Rectal bleeding and BM frequency alone (both PRO's) *in addition to* endoscopy may suffice. Duration of symptom scoring (1-3-7 days) remains matter of debate.

CROHN'S DISEASE

The National Cooperative Crohn's Disease Study



Summers, Gastroenterology 1979

Activity Indices in Crohn's disease (adults)

Clinical activity

- CDAI developed by the NCCDS
- HBI Harvey - Bradshaw simple index

Endoscopic activity

- CDEIS Crohn's disease endoscopic index of severity
- SES-CD Simplified version of CDEIS
- Rutgeerts Score: dedicated to postoperative recurrence

Histologic activity

- D'Haens, Geboes et al. Scoring system for histological abnormalities in CD biopsies

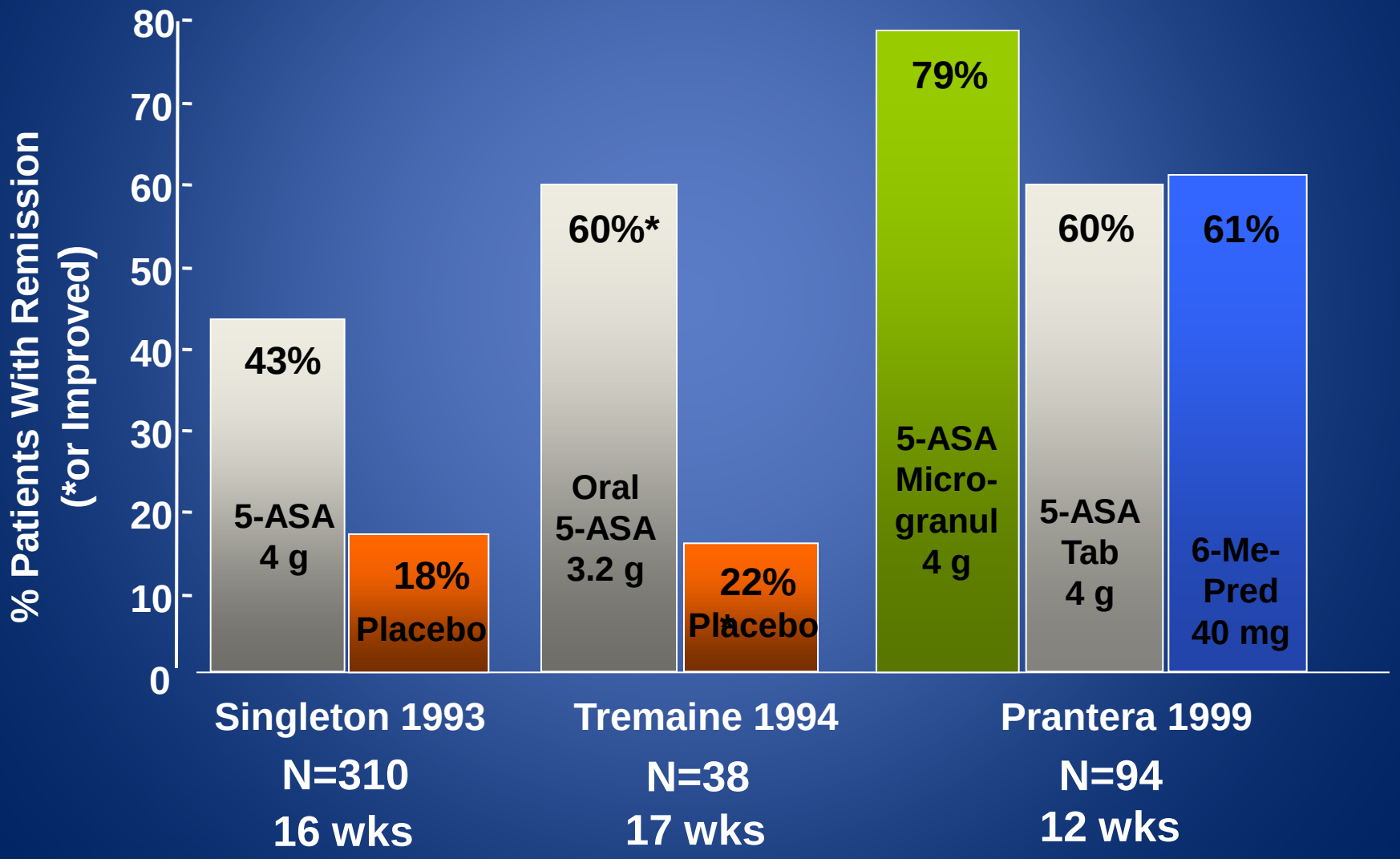
THE CDAI

Number of liquid/semisolid BM's per day (x7)	N x 2
Abdominal pain score 0-3 (x7)	N x 5
General Well-Being 0-4 (x7)	N x 7
EIM's, fever, fistula	N x20
Antidiarrheals	+ 30
Abdominal mass no-questionable-definite	0-20-50
Weight (compared to 'normal')	
Hematocrit (compared to 'normal')	

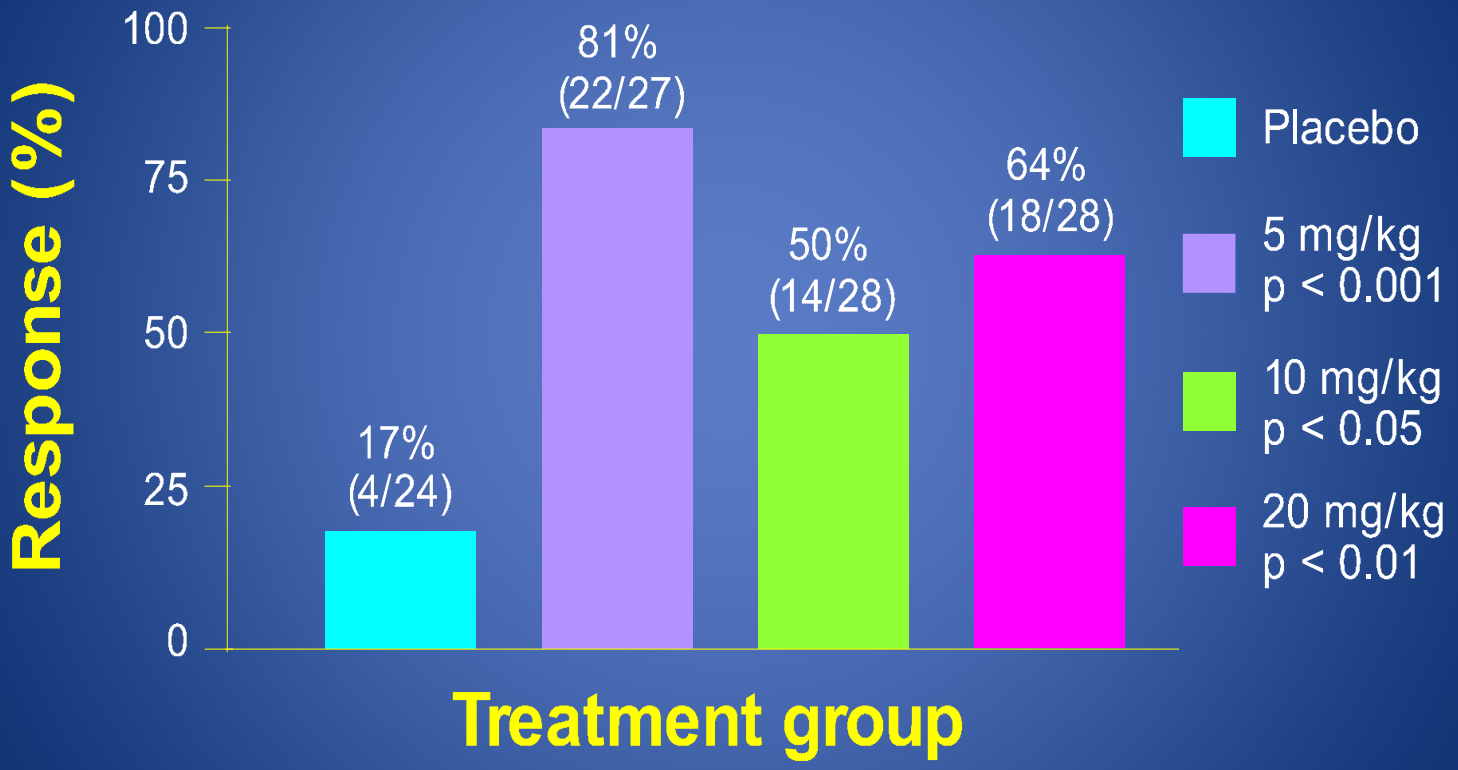
PRO

Remission:<150
Mild disease: 150-220
Moderate: 220 (250) -450
Severe:>450

Mesalazine in CD: Induction of Remission



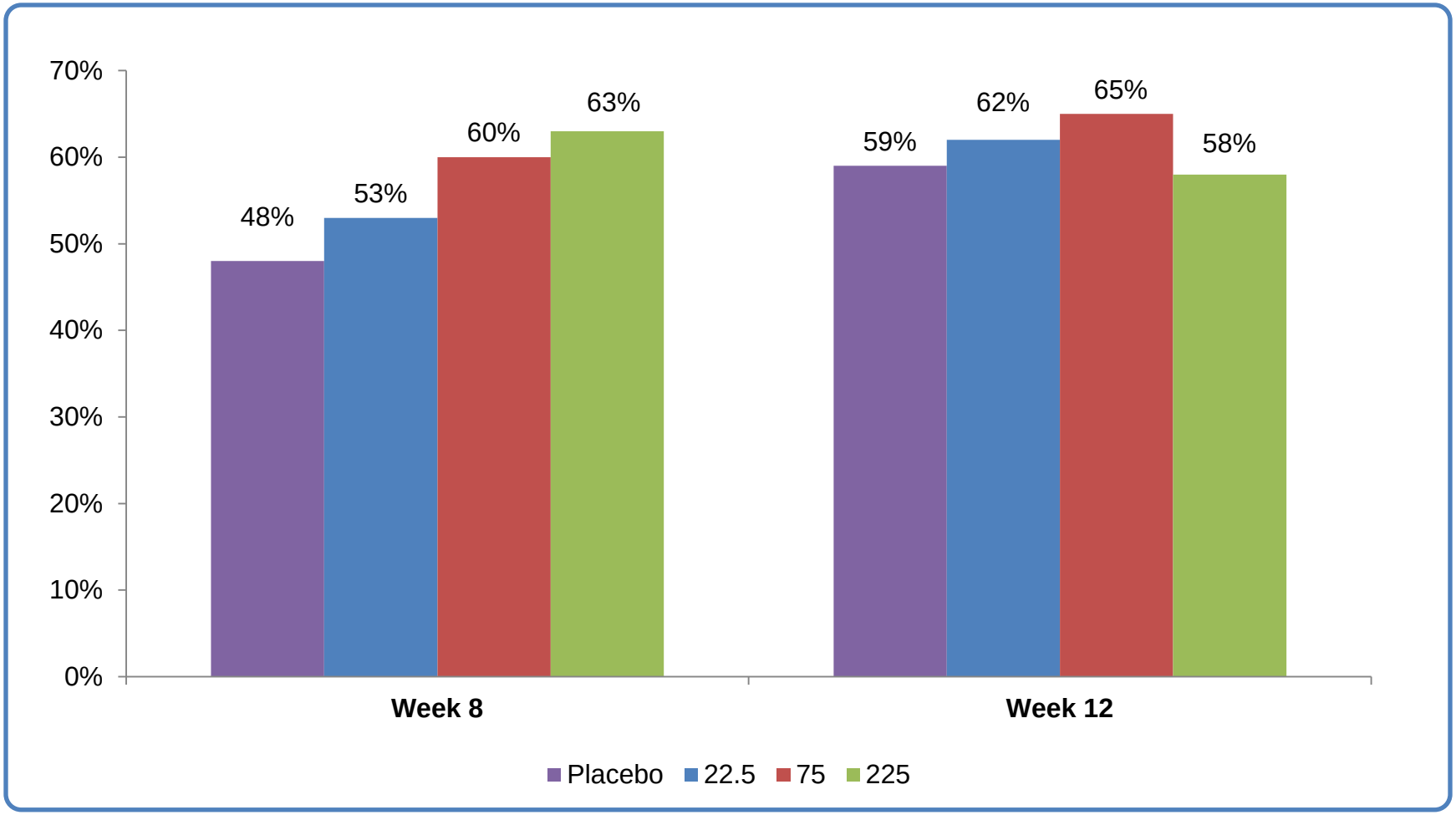
Clinical Response with IFX at 4 W



Clinical response defined as a ≥ 70-point decrease in CDAI score from baseline.

Targan SR et al. N Engl J Med. 1997

Anti-MAdCAM and Placebo CDAI-70 Response

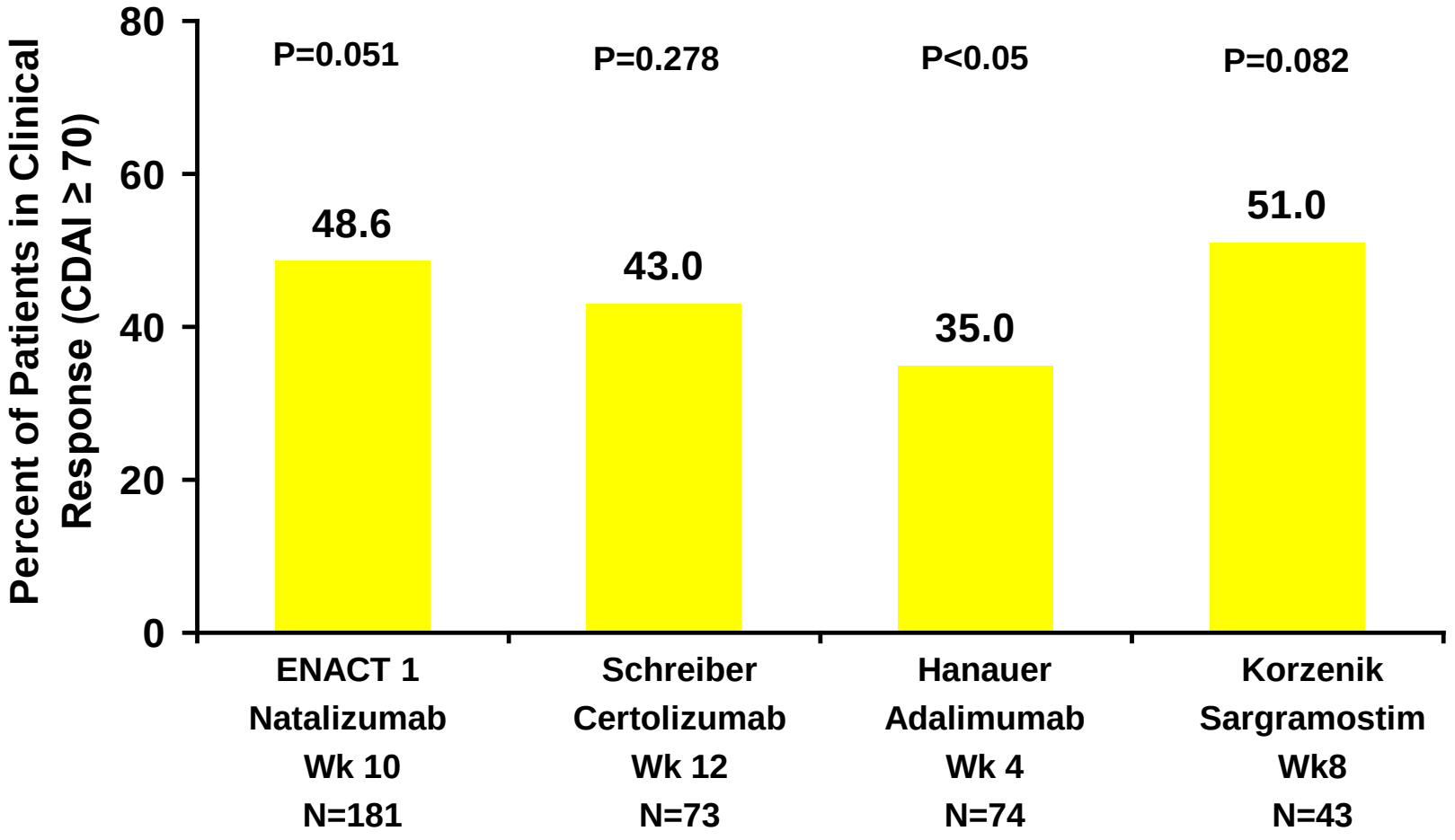


RESPONDERS COULD MOVE ON TO THE MAINTENANCE PHASE

D'Haens, ECCO 2015

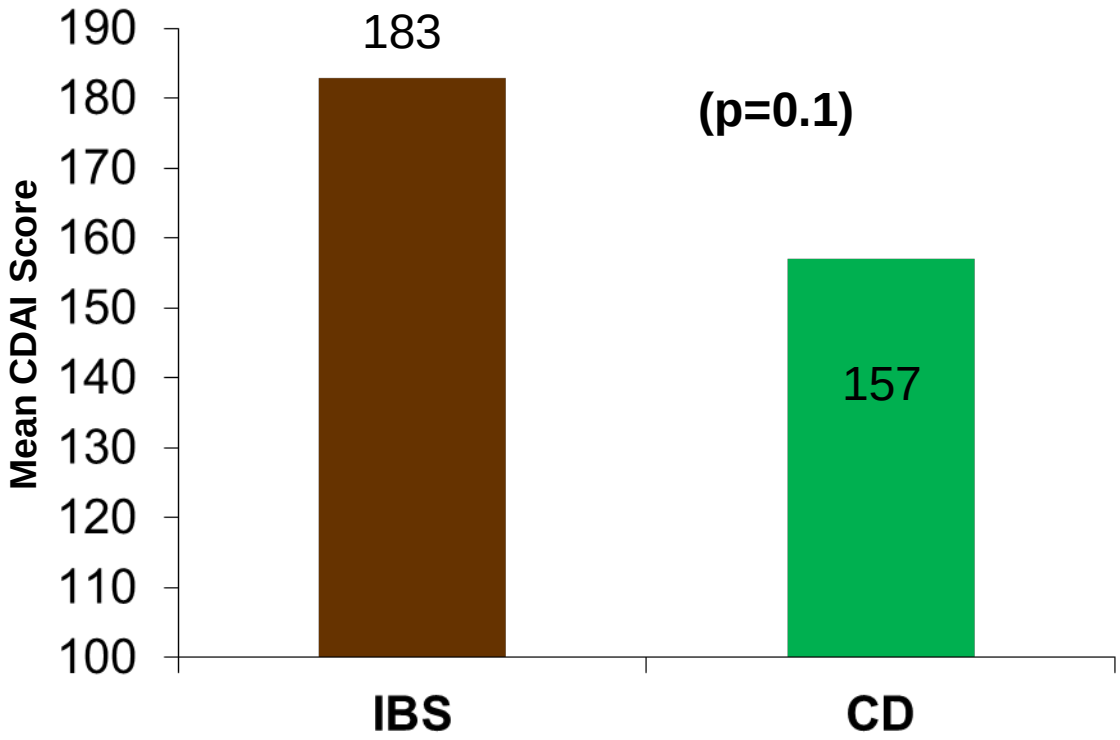
What’s wrong with the CDAI ?

High Placebo Response in Some Recent CD Trials



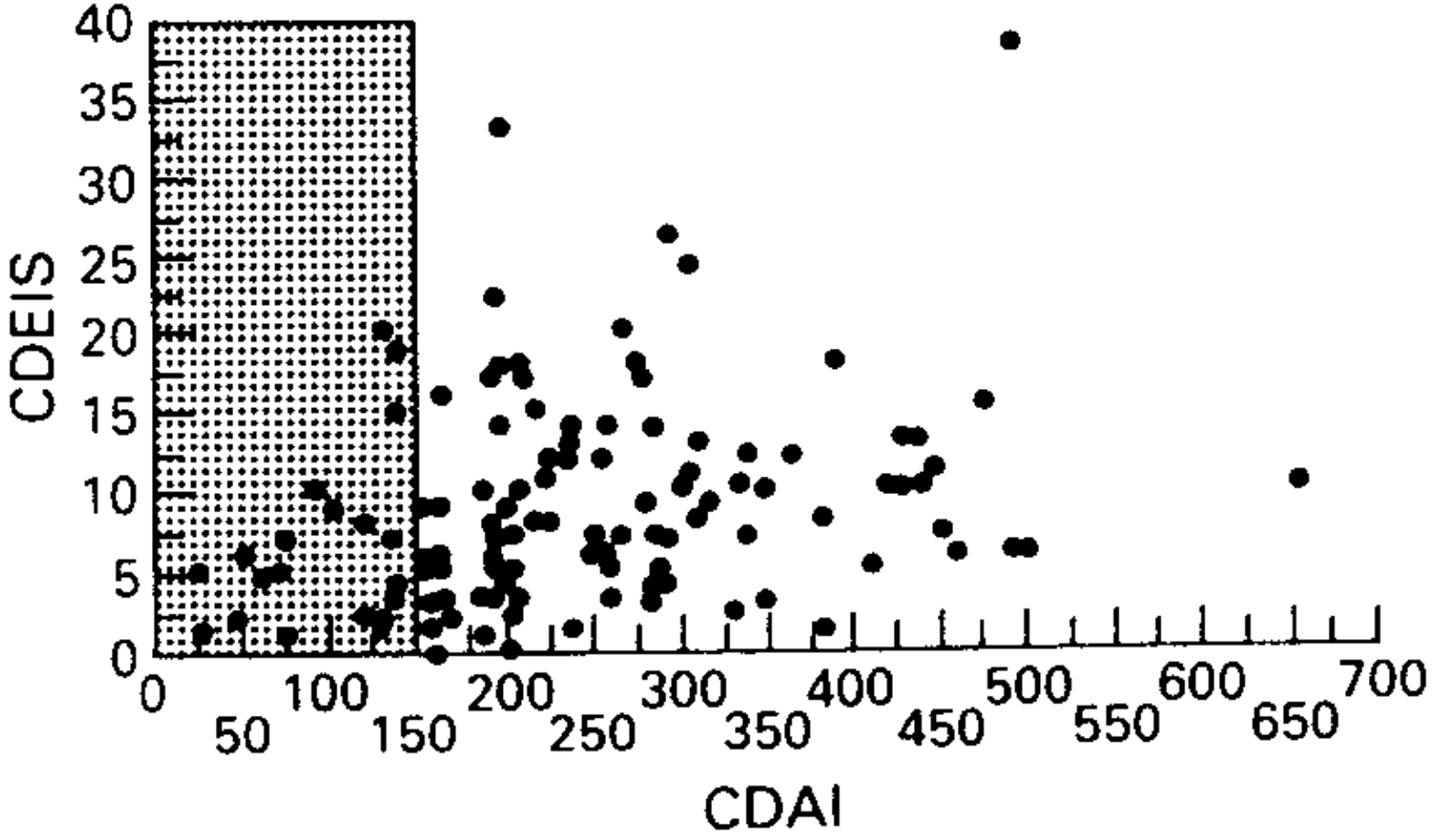
The CDAI- Subjective and Non-Specific

- **Cohort study – 91 consecutive patients with CD or IBS**
- **CDAI scores and item scores calculated**
- **Higher CDAIs in IBS patients**
- **Pain scores higher**



Lahiff C. et al. Aliment Pharmacol Ther. 2013

Lack of Correlation with Inflammation



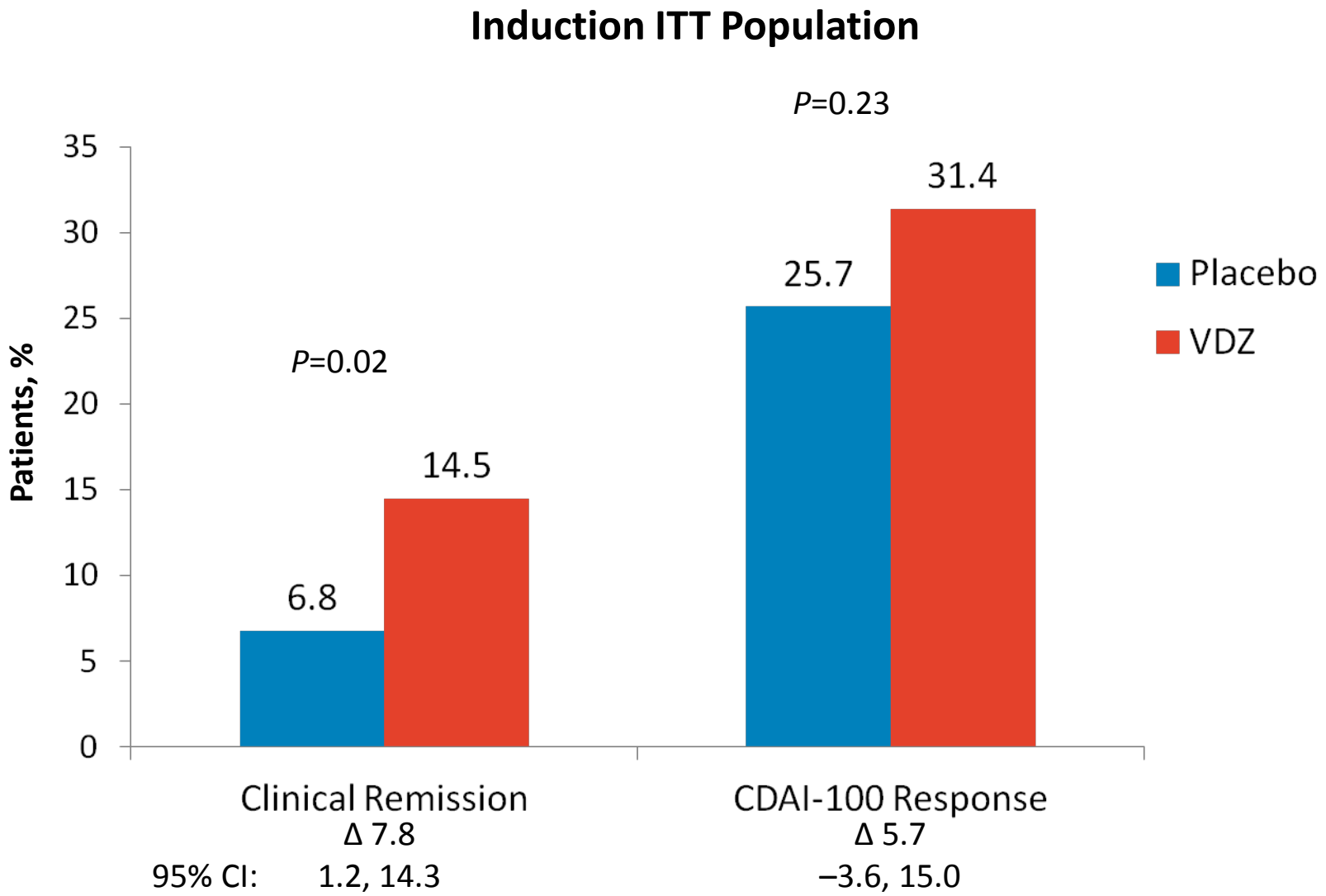
Cellier C. et al. Gut. 1994

GEMINI II: Vedolizumab in Crohn's Disease - Inclusion Criteria

Main Criteria	Value
Age	• 18 - 80 years old
Moderate to severe, active CD (for ≥3 months and within 7 days prior to randomization)	• CDAI score: 220 – 450 *and* - CRP level > 2.87 mg/L *or* - Ileocolonoscopy with ulcerations (within 4 months of randomization) *or* - Fecal calprotectin >250 µg/g (in conjunction with radiography or endoscopy within 4 months prior to screening)
Additional criteria	
Prior treatment failure (≥ 1) with: - Glucocorticoids - Immunosuppressives - TNFα antagonists	• Lack of response • Unacceptable AEs
Permitted concomitant medications	- Prednisone (or equivalent) ≤ 30 mg/day - Budesonide (≤9 mg per day) - Immunosuppressives at stable doses -Mesalamine - Antibiotics

Sandborn WJ et al. N Engl J Med 2013

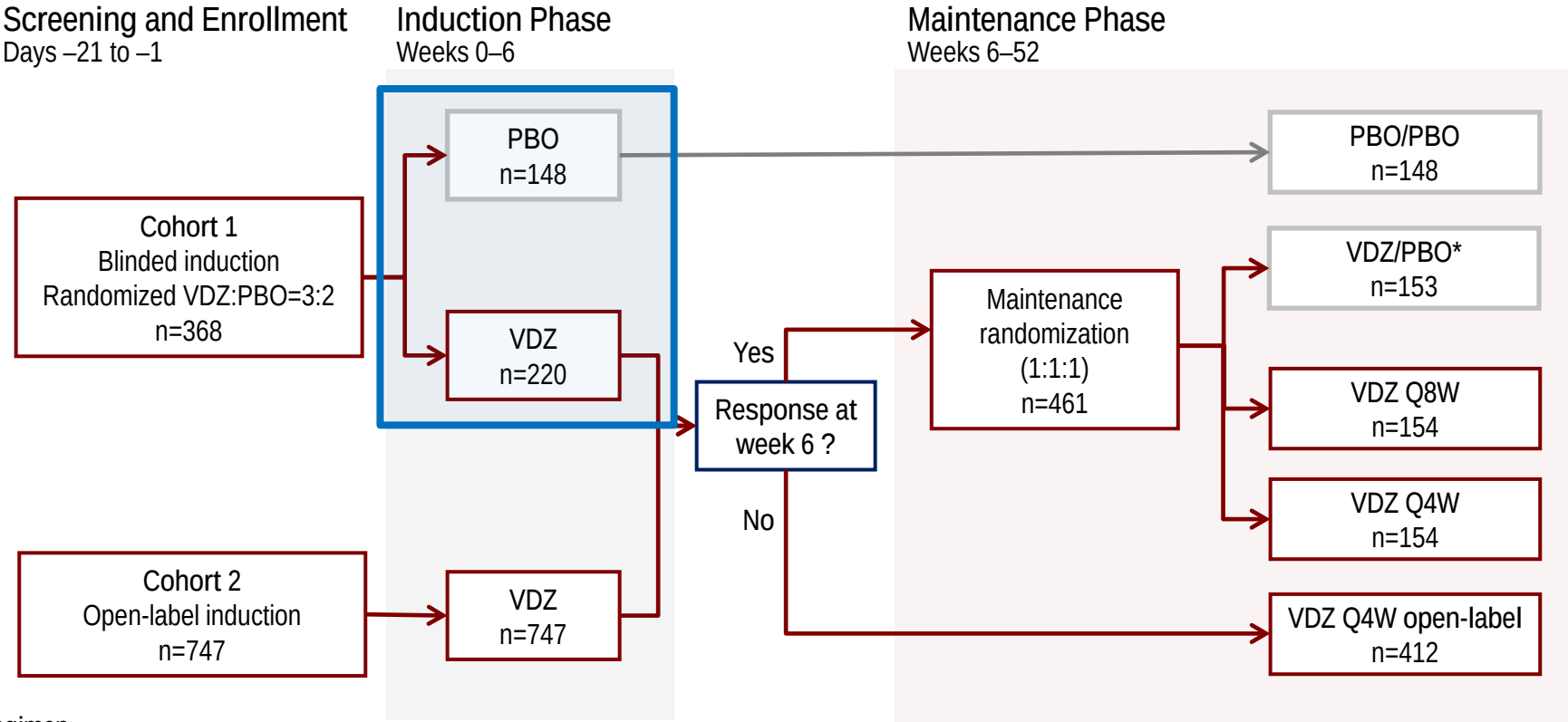
GEMINI 2: Remission & CDAI-100 Response at 6 W



Sandborn WJ et al. N Engl J Med 2013

GEMINI II: Vedolizumab in Crohn's Disease

- Induction and maintenance study in patients with moderate to severe Crohn's disease (CD)



Dosing regimen
Induction: 300mg vedolizumab (VDZ) or placebo (PBO) days 1, 15.
Maintenance: 300mg VDZ q8w or q4w or PBO

* VDZ/PBO is used to distinguish the placebo group patients in the maintenance phase that had received VDZ during induction (Cohorts 1 & 2), from the placebo group from Cohort 1 induction. PBO, placebo; VDZ, vedolizumab

Sandborn WJ et al. N Engl J Med 2013

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 24 July 2008
Doc. Ref. CPMP/EWP/2284/99 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE DEVELOPMENT OF NEW MEDICINAL PRODUCTS FOR THE TREATMENT OF CROHN'S DISEASE

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 24 July 2008
Doc. Ref. CPMP/EWP/2284/99 Rev. 1

Choice of comparator

The choice of comparator will depend on the indication for which the drug is being developed. In order to support a first line indication in the treatment of active Crohn's disease, it is necessary to demonstrate that the drug has either the same or an improved risk/benefit profile as the standard of care, which currently in the majority of cases includes glucocorticosteroids. Therefore, clinical trials aiming at supporting a first line indication should always include comparison with the accepted first line treatment. Unless the study is aiming at demonstrating superiority, the trial should (when ethically justifiable) also include a placebo arm to provide internal validation of the study.

In order to support an indication for add-on to established therapy, the drug should be compared with add-on placebo. For a second-line indication in patients with insufficient response to established therapy, it is advised that the established therapy is continued in the control arm as background therapy while in the experimental arm, established therapy or placebo may be used in combination with the experimental agent.

For patients with severe, steroid and immunosuppressive refractory CD, a comparison with an anti-TNF compound is recommended.

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 24 July 2008
Doc. Ref. CPMP/EWP/2284/99 Rev. 1

4.2.2 Maintenance of remission/Prevention of relapse

Patients to be included

Patients who are in remission for at least one month may be included into the trials. In all cases, it is recommended that the diagnosis and extent of CD be documented by recent (within approximately 18 months) visualisation of the gastrointestinal (GI) tract by e.g., radiology, endoscopic examination and histological examination. The site of disease and associated complications must be defined. Patients with surgically induced remission can be entered directly and within one month after surgery and should preferably be studied in separate studies. Trials combining induction treatment and maintenance treatment should preferably only enter patients that have achieved remission (in either the trial drug or comparator group), into the maintenance phase. If only remitters to the trial drug are allowed to enter the maintenance phase of the study, this will be reflected in the labelling. A re-randomisation is recommended. Without re-randomisation interpreting results from combination trials is problematic as results from the induction phase will influence the final results of the maintenance phase. For combined studies, it is required that statistically and clinically significant results are obtained for both phases of the trial.

Challenges in CD Trials

What should be the population to be included ?

1. CDAI > 220 or 250 ?
2. Markers of active inflammation: CRP, calpro, ESR,…?
3. Presence of endoscopic lesions: baseline severity ?
4. Combination of the above ?

Aspects or relevance:

1. Recruitability
2. Reduction of placebo response
3. Feasibility of repeated endoscopies
4. Timing of primary endpoint

Challenges in CD Trials

What effect size (DELTA) over placebo should lead to approval of a drug ?

(or is any statisticaly significant benefit over placebo OK)

Challenges in CD Trials

Which patients can enter the maintenance phase ?

1. CDAI response (reduction 70 or 100 pts)
2. CDAI remission
3. Endoscopic response: definition ?
4. Endoscopic remission: definition ?
5. Other biochemical/imaging criteria
6. All patients

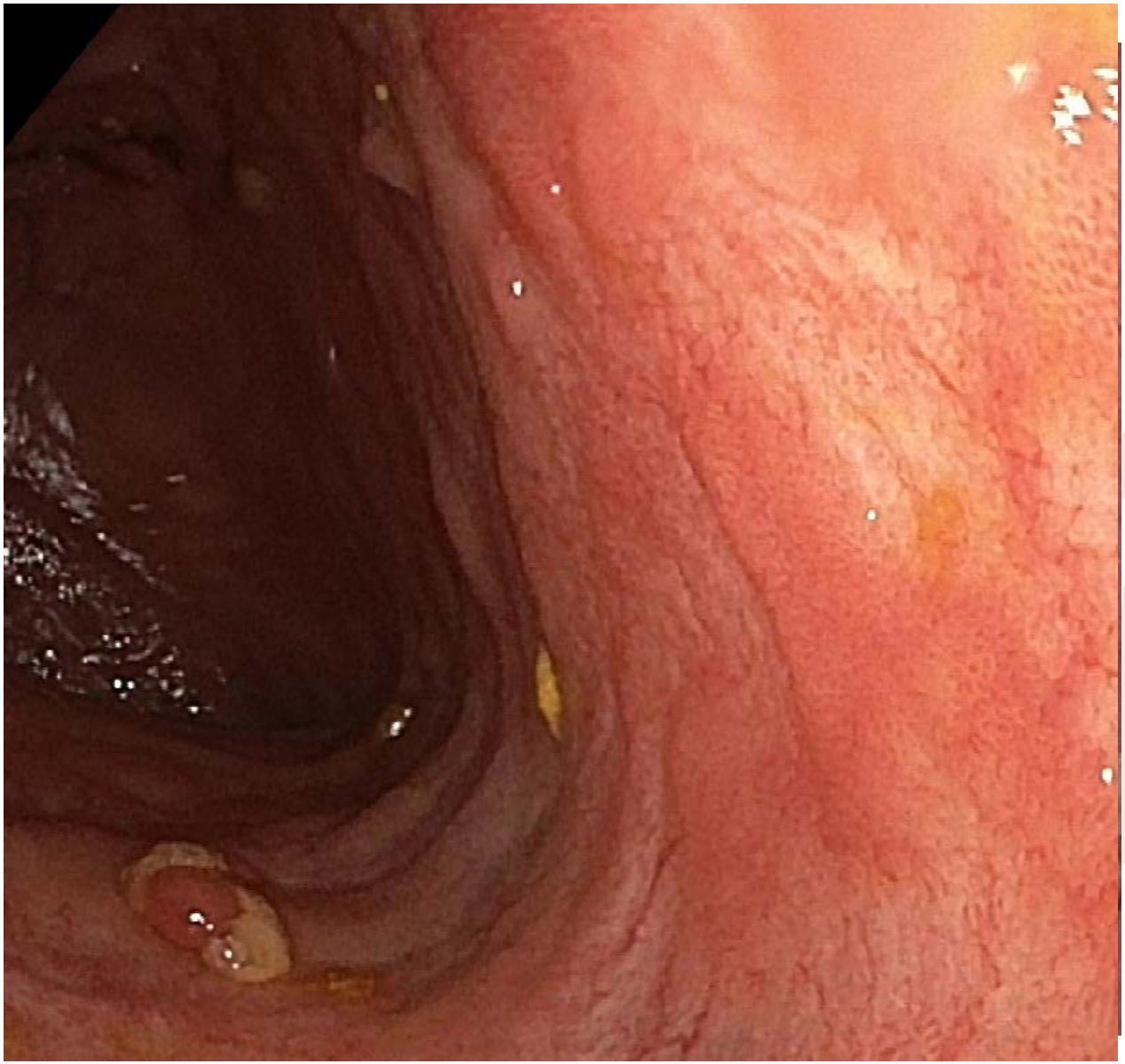
Aspects or relevance:

1. Attractivity
2. Rerandomization of responders to placebo ?

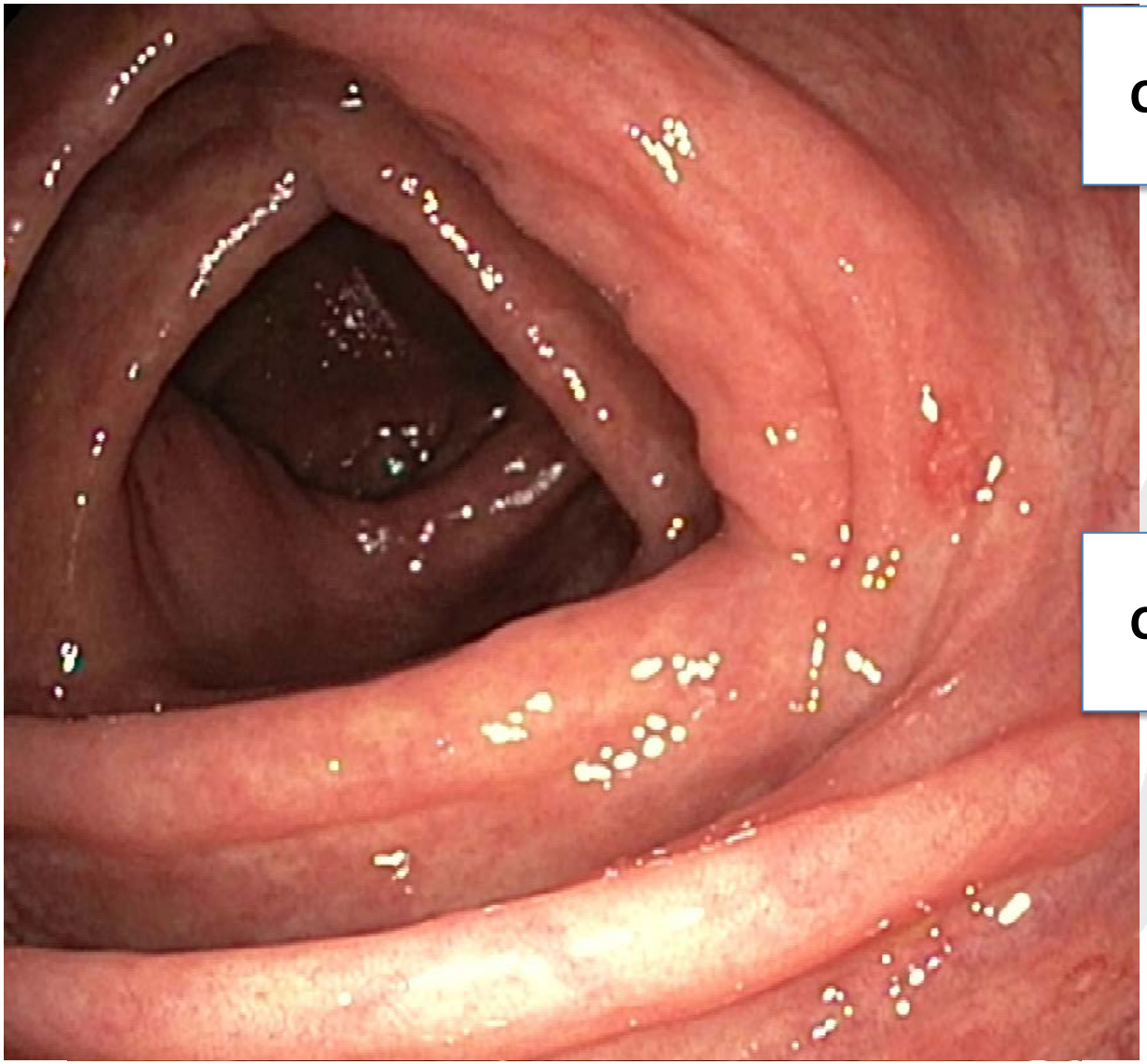
Mimimising the placebo response

- Reduce concomitant medication (steroids)
- More robust endpoints
- Enter patients with active disease (CRP/endoscopy)
- Short duration for induction studies
- Minimize n clinic visits

12 weeks IFX + AZA



3 months ADA



CDAI 324

CDAI 286

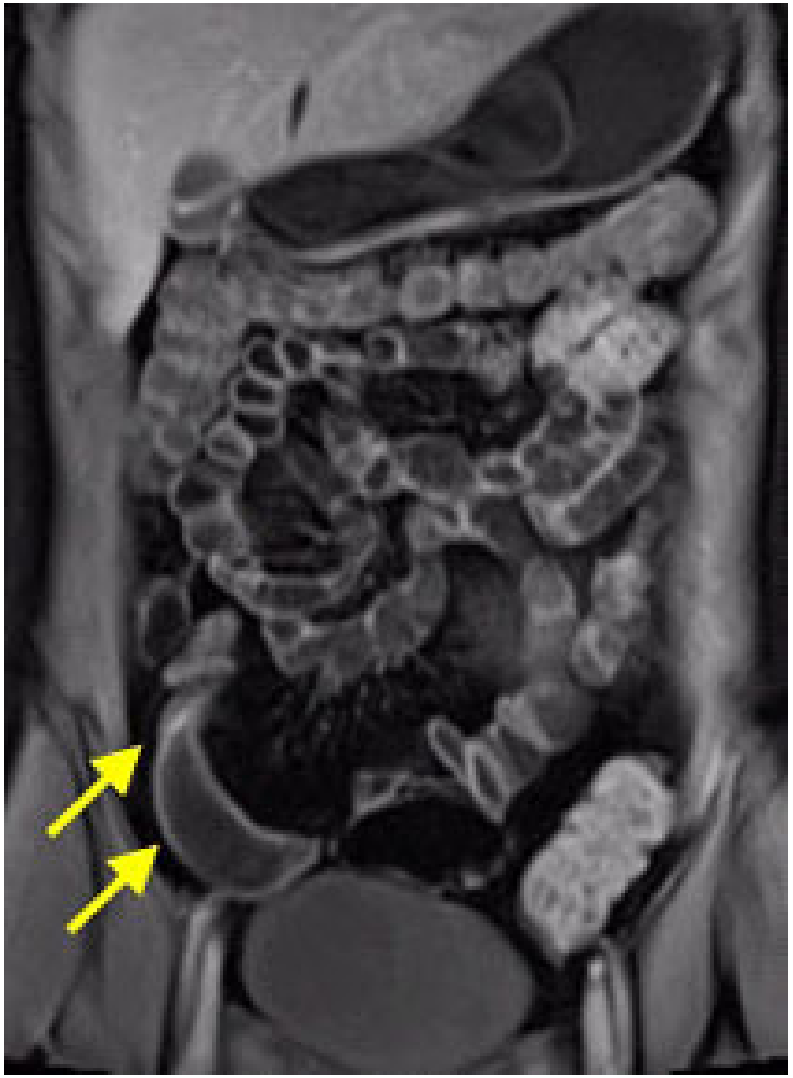
Central Reading of Endoscopic Disease Activity in CD

- 4 central readers
- 50 ileocolonoscopic videos of patients with CD – randomly observed in triplicate
- ICCs for inter and intra observer for SES CD + CDEIS and VAS

	CDEIS	SES-CD	VAS
	(95% CIs)		
Intra-observer ICC	0.89 (0.86 to 0.93)	0.91 (0.87 to 0.94)	0.81 (0.75 to 0.86)
Inter-observer ICC	0.71 (0.61 to 0.79)	0.83 (0.75 to 0.89)	0.62 (0.52 to 0.73)

Khanna R. et al. Gut 2015

MR Enterography: the Future ?



Rimola et al Gut 2009

Patient Reported Outcomes

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

- Dis ts
- Rec ation of inte
- For selection, vali)
- Ler

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

MTX vs PLC in Active CD: Effect Size at Week 16 by CDAI

Outcome Measure	Populations						
	Total Population N = 141				Orosomucoid at Baseline > 88 N = 65		
		N	N Remission	Effect Size (P-Value)	N	N Remission	Effect Size (P-Value)
Crohn's Disease Activity Index (CDAI) – Based Outcomes							
CDAI ≤ 150 alone	**MTX**	94	50	13% (0.17)	42	23	16% (0.11)
	Placebo	47	19		23	9	
CDAI ≤ 150, No Prednisone	**MTX**	94	37	20% (0.025)	42	19	28% (0.021)
	Placebo	47	9		23	4	
CDAI ≤ 150, Normal Orosomucoid	**MTX**	94	44	15% (0.12)	42	19	15% (0.22)
	Placebo	47	15		23	7	
CDAI ≤ 150, No Prednisone, Normal Orosomucoid	**MTX**	94	35	18% (0.04)	42	17	23% (0.037)

Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, Rolleri RL, Bortey E, Paterson C, Forbes WP, Levesque BG.Aliment Pharmacol Ther. 2015

MTX vs PLC in Active CD: Effect Size at Week 16 by 2 Item PRO (pain, stool frequency)

Outcome Measure	Populations						
	Total Population N=141				Orosomucoid at Baseline > 88 N = 65		
		N	N Remission	Effect Size (P-Value)	N	N Remission	Effect Size (P-Value)
Results Using Two Item Patient Reported Outcome (PRO2) – Based Outcomes							
PRO2 alone	**MTX**	94	38	15%	42	20	13%
	Placebo	47	12	(0.12)	23	8	(0.13)
PRO2, No Prednisone	**MTX**	94	27	20%	42	16	25%
	Placebo	47	4	(0.012)	23	3	(0.017)
PRO2, Normal Orosomucoid	**MTX**	94	32	17%	42	16	16%
	Placebo	47	8	(0.051)	23	5	(0.15)
PRO2, No Prednisone, Normal Orosomucoid	**MTX**	94	25	18%	42	14	20%
	Placebo	47	4	(0.019)	23	3	(0.031)

CROHN'S DISEASE: CONCLUSIONS

- CDAI is a suboptimal instrument with many weaknesses that may lead to bias and high placebo response
- Objective confirmation of active (endoscopic) disease at baseline is a major leap forward - independent assessment is essential
- Genuine PRO's are in development but this process takes time (years !); so far PRO-2 appears a valid alternative though response criteria are vague
- Response to treatment should probably be best assessed by a combination of clinical symptoms (or PRO's) and endoscopic change
- Definitions of meaningful endoscopic improvement yet to be defined
- **EMA and FDA should talk**