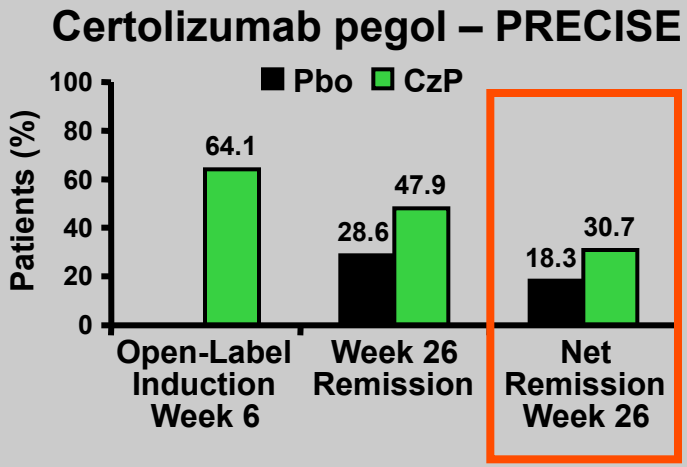
New Treatments in UC

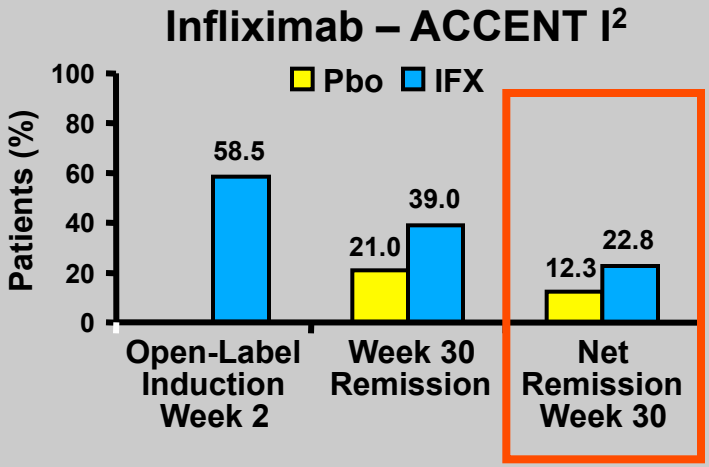
Brian G. Feagan
Professor of Medicine, Epidemiology and Biostatistics
University of Western Ontario
London, Ontario, Canada

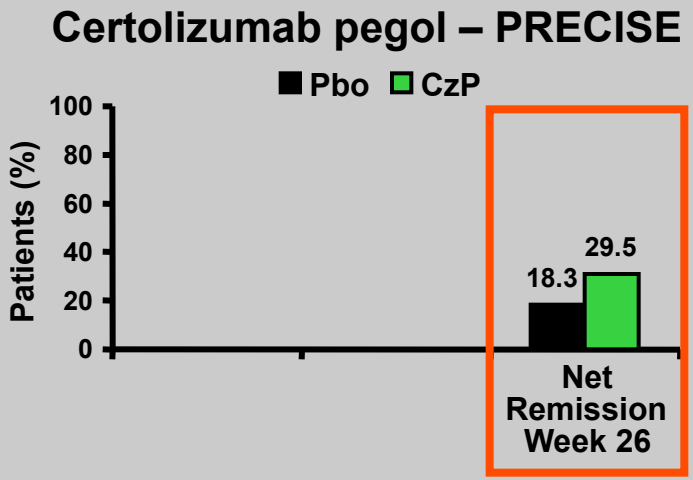
Overview and Goals

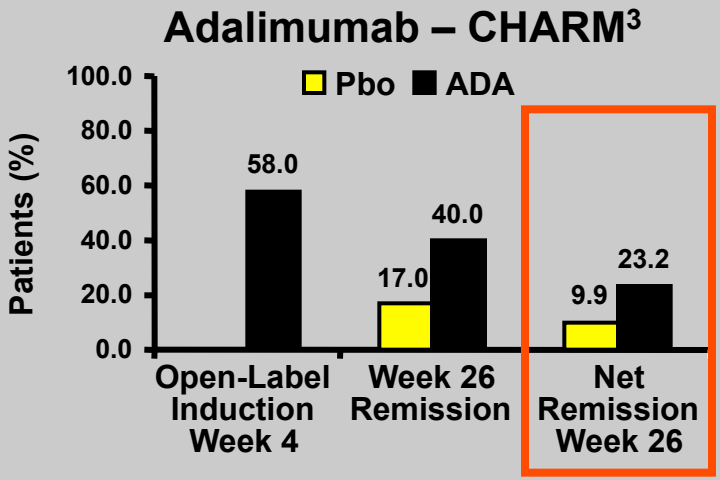
- Why alternatives to our current treatments for IBD are needed
- Review data regarding the currently available and developmental drugs in this class
  - s.c. TNF antagonists
  - Selective leukocyte adhesion molecules
- Future directions and conclusions

The Clinical Need: Net Remission at 6 Months with TNF Antagonists



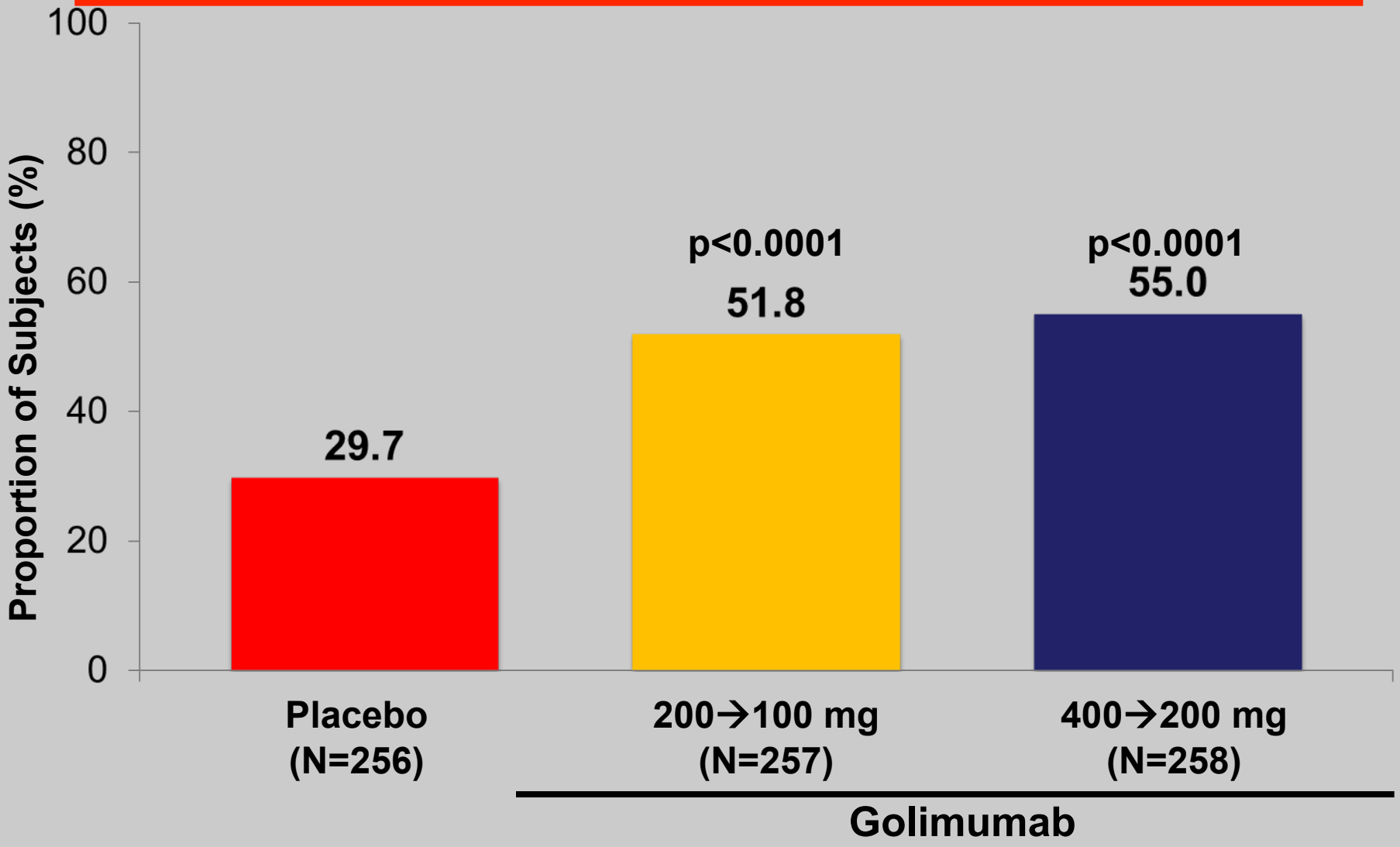






1. Schreiber S et al. *N Engl J Med*. 2007;357:239. 2. Hanauer SB et al. *Lancet*. 2002;359:1541.
3. Colombel JF et al. *Gastroenterology.* 2007;132:52. 4. Sandborn WJ et al. *N Engl J Med.* 2007;357:228.

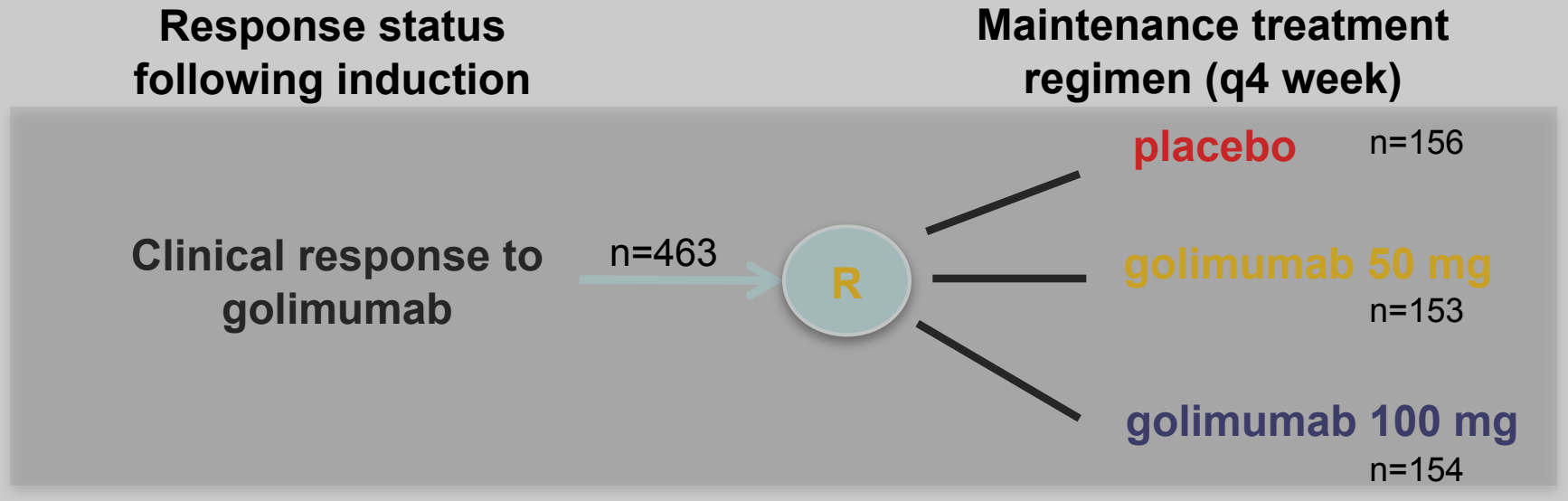
Golimumab: PURSUIT- Induction SC: Clinical Response* at Week 6



**Defined as a decrease from Week 0 in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1*

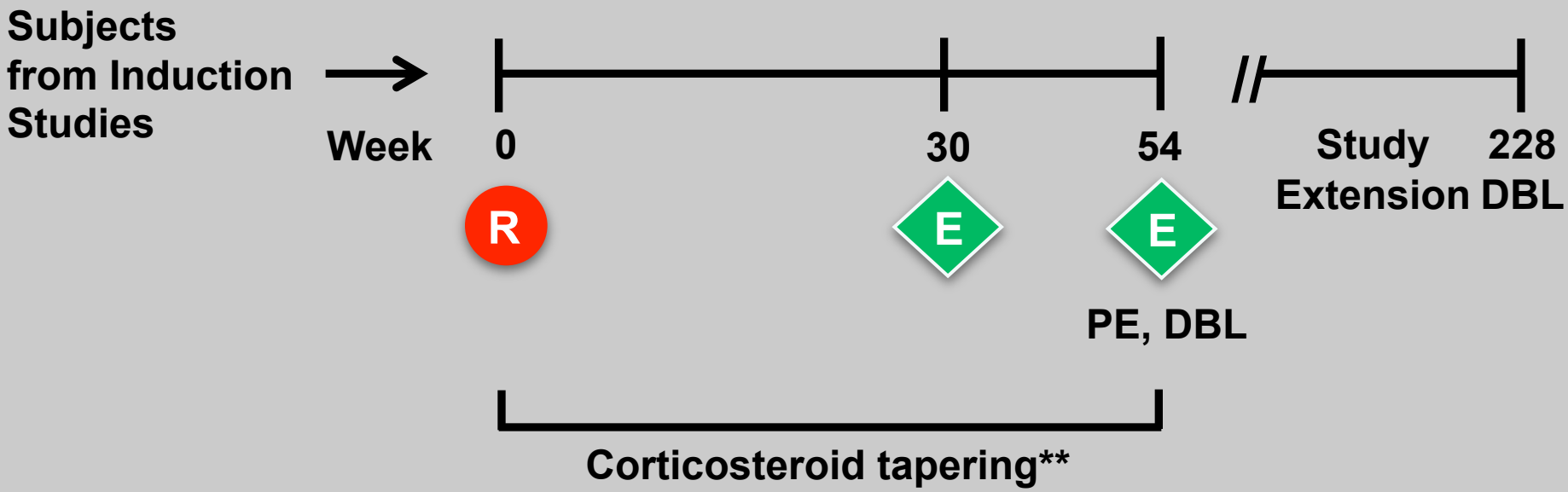
Sandborn WJ et al. Gastroenterology 2013

PURSUIT-Maintenance: Treatment Groups



Sandborn WJ et al. Gastroenterology 2013

PURSUIT-Maintenance: Study Schema



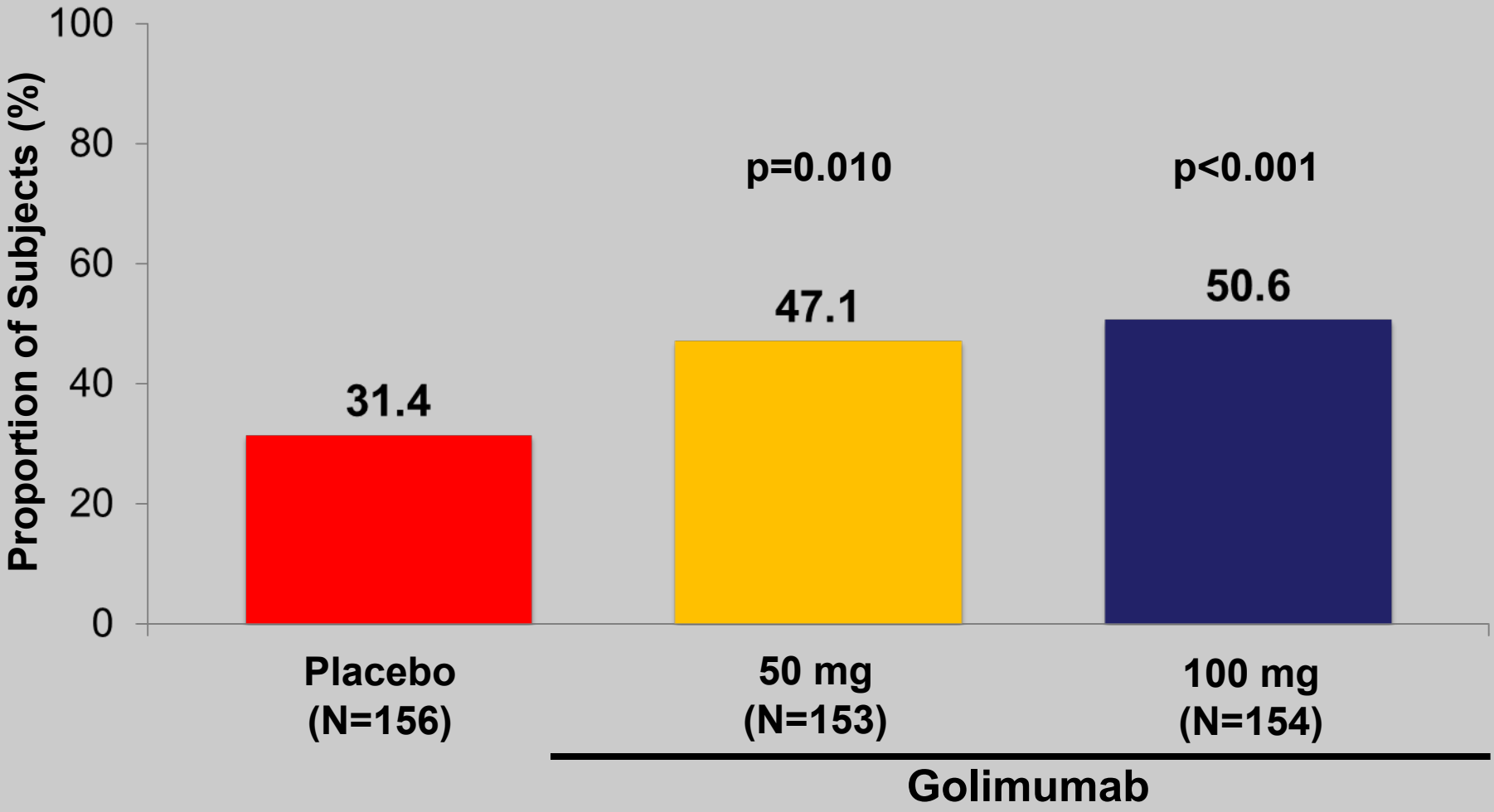
R =Randomization* E =Efficacy evaluation by Mayo score

PE=Primary Endpoint DBL=Database lock

Subjects in clinical response to golimumab induction dosing
****Subjects in clinical response***

Sandborn WJ et al. Gastroenterology 2013

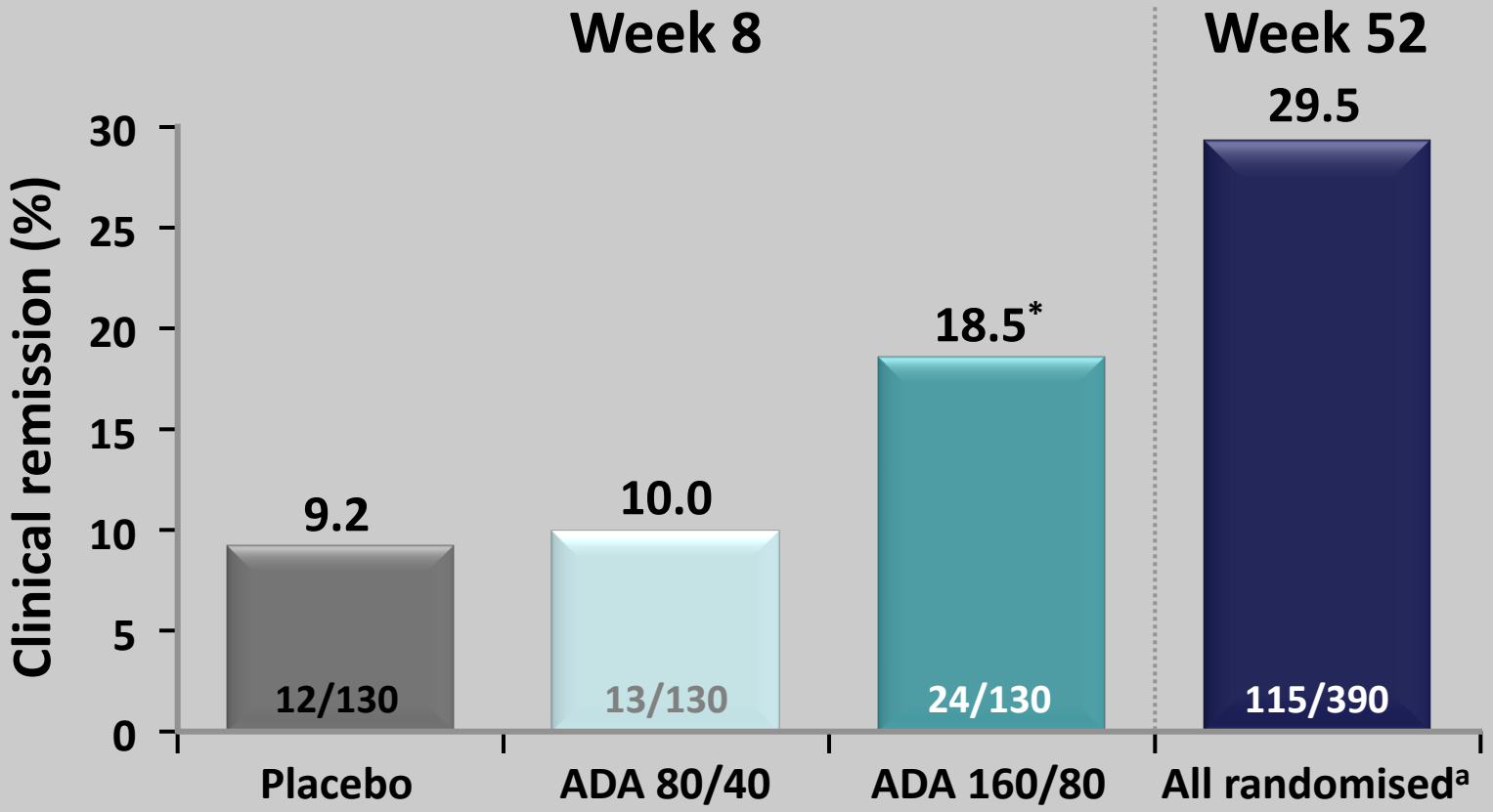
PURSUIT-Maintenance: Clinical Response* Through Week 54 Among Subjects in Clinical Response to Golimumab Induction



**Defined as a decrease from Week 0 of an induction study in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1*

Sandborn WJ et al. Gastroenterology 2013

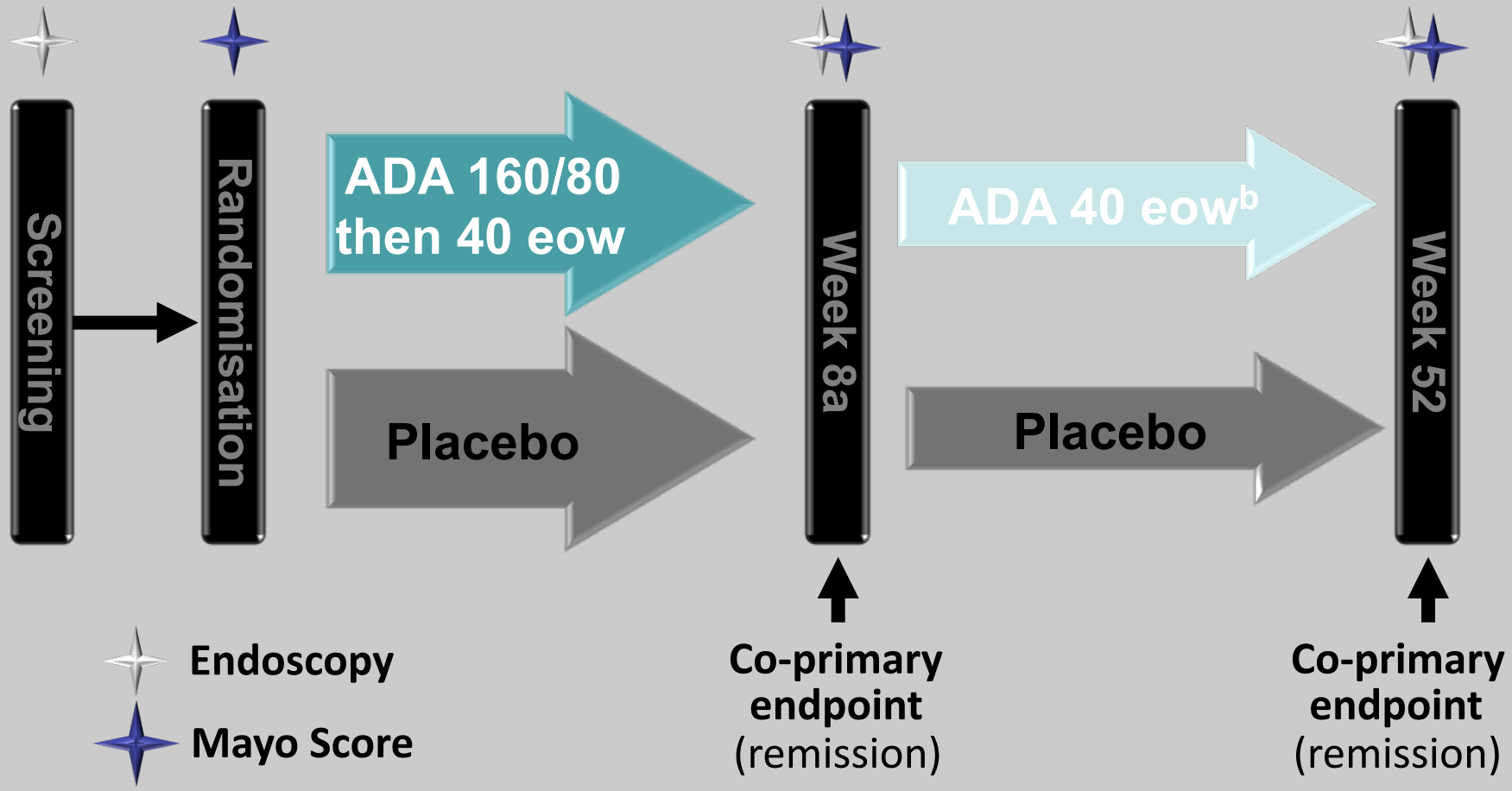
Adalimumab: ULTRA-1 induction and open-label maintenance: clinical remission at Week 8 and 52



*p=0.031 vs placebo
Non-responder imputation (NRI) analyses, Week 8; mNRI analyses, Week 52
[a]mNRI (modified NRI): did not count patients who dose escalated (and were in remission) as failures (*post-hoc* analyses)
Clinical remission: Mayo score ≤2 with no individual subscore >1

Reinisch W, *et al. J Crohn's Colitis* 2011;5:S10:A16
Reinisch W, *et al*. Gut 2011;60:780–7

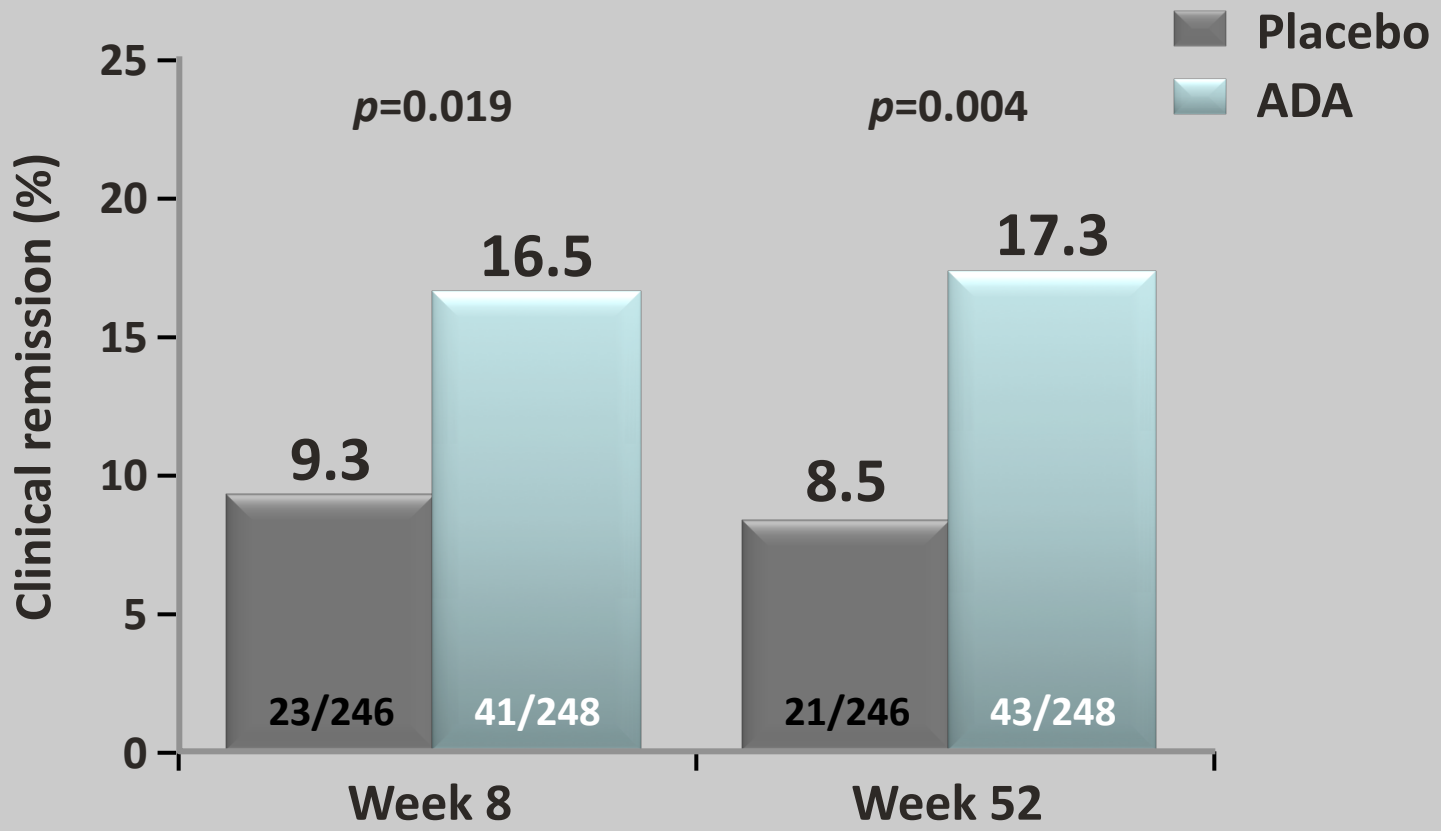
ULTRA-2: study design



a. Patients with satisfactory clinical response begin corticosteroid taper at or after Week 8
b. Patients demonstrating inadequate response could switch to open-label eow at Week 12
Dose escalation to ADA 40 mg weekly permitted for inadequate response on OL administration
eow: every other week

Sandborn W, *et al. Gastroenterology* 2012;142:257–65

ULTRA-2: clinical remission at Week 8 and Week 52, all patients



ITT analysis set: non-responder imputation (i.e missing data or switch to OL imputed as not achieving remission)
Clinical remission: Mayo score ≤2 with no individual subscore >1

Sandborn W, *et al. Gastroenterology* 2012;142:257–65

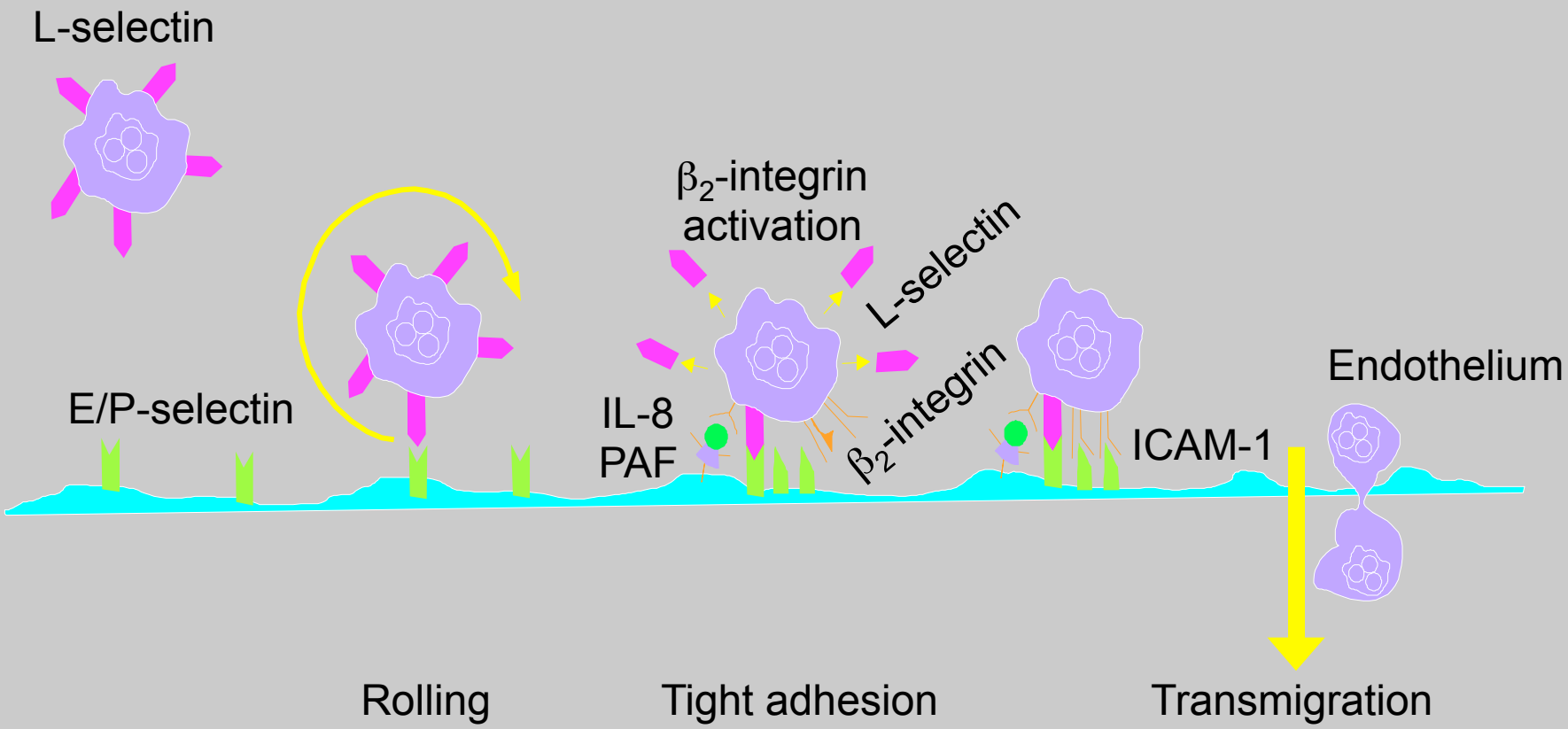
Infection and TNF Antagonists

- TREAT registry n > 6,000, f/u > 5yrs
- Factors independently associated with serious infections (Descending order of risk) :
  - Disease activity mod-severe (HR = 2.24, 95% CI = 1.57, 3.19; P < 0.001),
  - Narcotic analgesic treatment (HR = 1.98, 95% CI = 1.44, 2.73; P < 0.001)
  - Prednisone therapy (HR = 1.57, 95% CI = 1.17, 2.10; P = 0.002)
  - Infliximab treatment (HR = 1.43, 95% CI = 1.11, 1.84; P = 0.006).

Lichtenstein GR. Am J Gastroenterol. 2012 Sep;107(9):1409-22.

Selective Leukocyte Adhesion Molecule Inhibitors

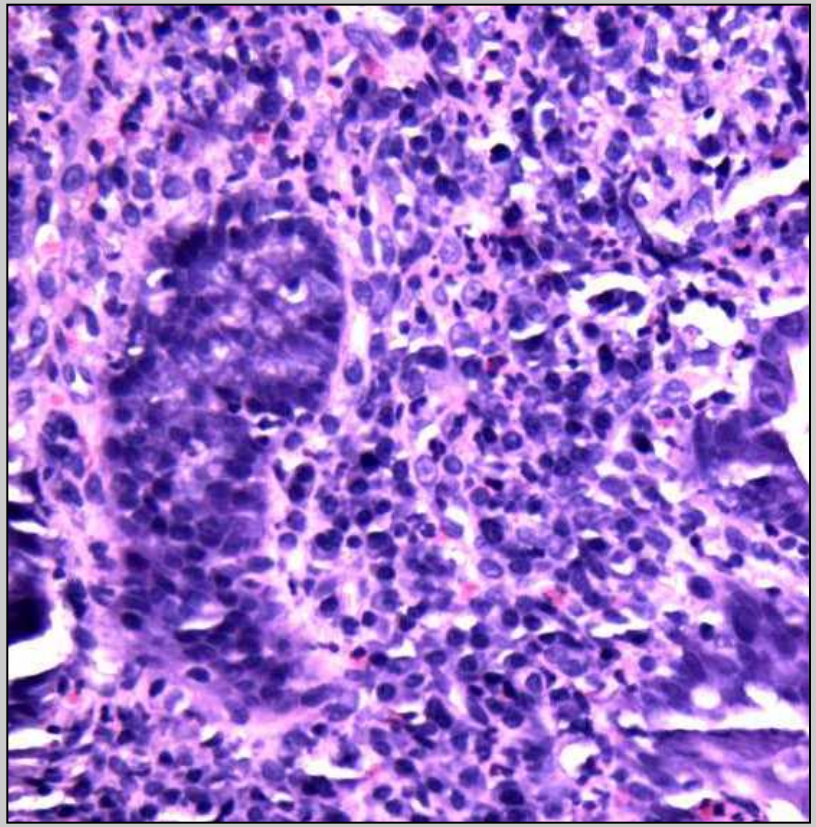
Recruitment of Neutrophils Into Inflamed Tissue



Van Deventer SJ. *Gut*

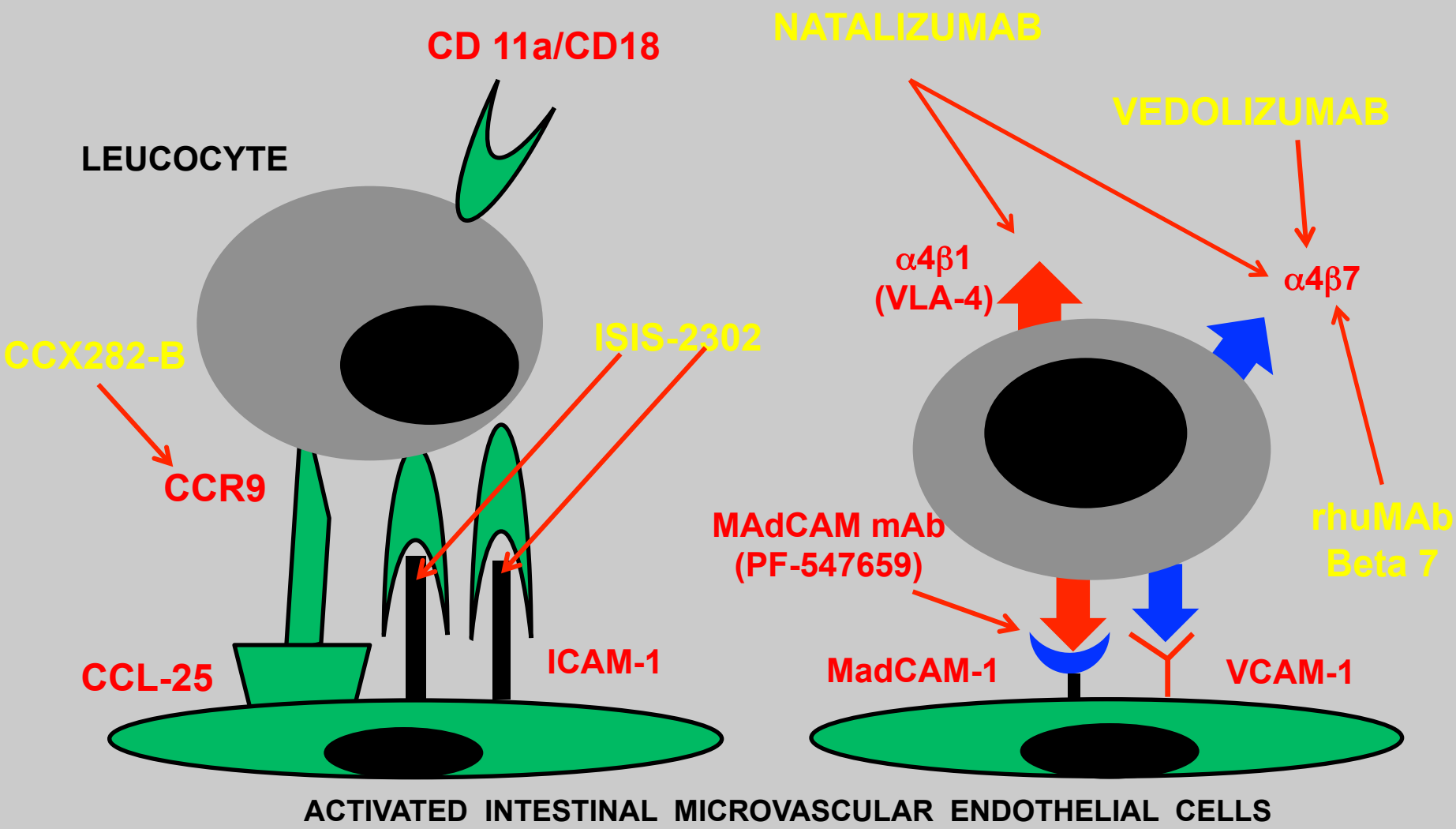
Consequences of Leukocyte Entry

- Cellular immunity
- Humoral immunity
- Cytokine\chemokine expression
- Phagocytic activity
- Antigen presentation



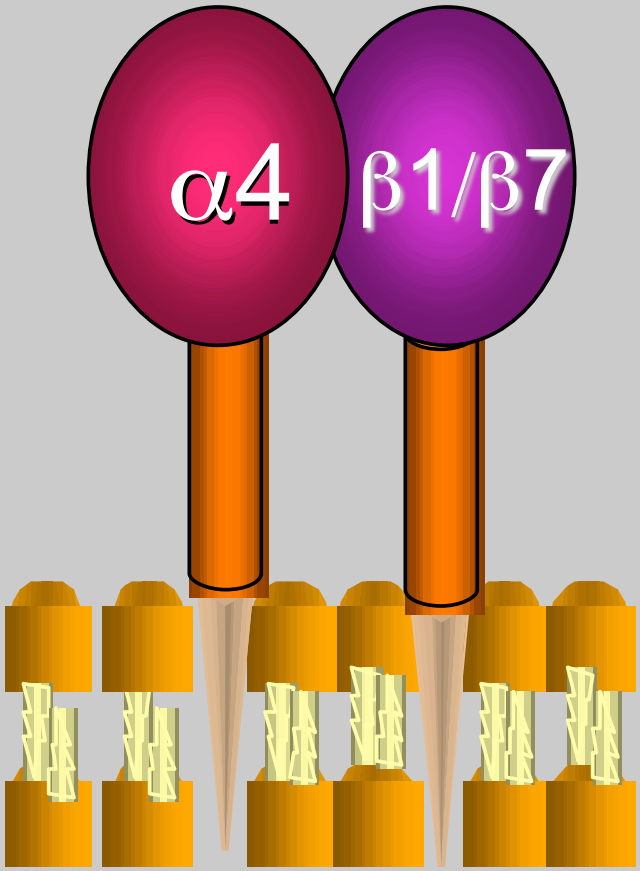
Frohman EM, et al. *J Clin Immunol.* 1989;9:1-9.

Therapeutic Targets



Adapted from Danese S Gut 2011;60:998-1008

Endothelial and Leukocyte Adhesion: α4 Integrins



- Leukocyte membrane glycoproteins
- β1 and β7 subunits
- Interact with endothelial ligands VCAM-1, fibronectin, and MAdCAM-1
- Mediate leukocyte adhesion and trafficking

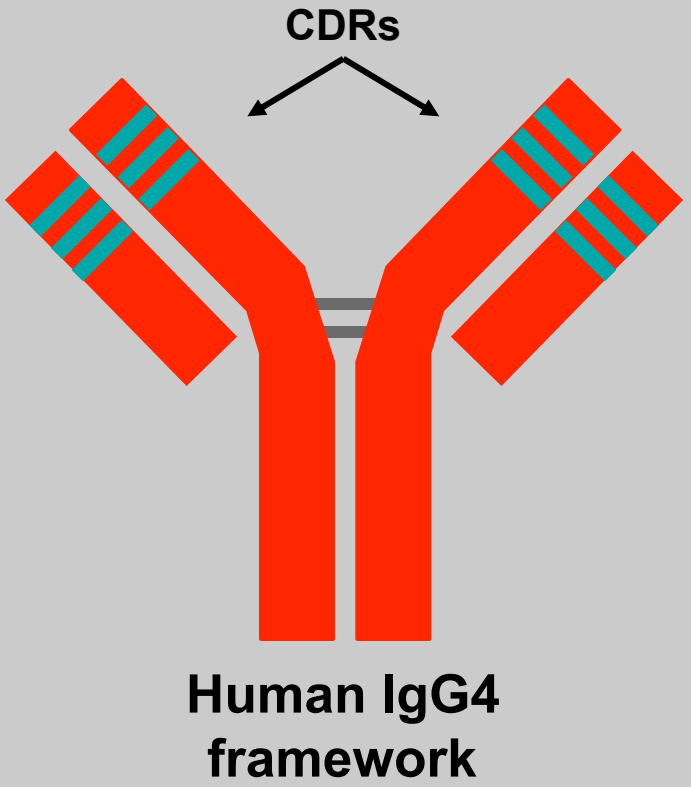
Springer TA. *Cell* 1994;76:301-314. Butcher EC et al. *Science* 1996;272:60-66

Rationale for α4 Integrins as Therapeutic Targets

- Increased VCAM-1 and MAdCAM-1 expression in mucosa of inflammatory bowel disease (IBD) patients
- Inflamed intestinal mucosa from IBD patients displays increased α4-dependent adhesiveness to leukocytes in vitro
- Human and animal studies suggest the α4β7 MAdCAM-1 interaction mediates leukocyte homing to the intestine
- Anti-α4 and anti-α4β7 antibodies ameliorate spontaneous colitis in the Cotton-top Tamarin animal model

Natalizumab: A Humanized Monoclonal Antibody against α_4-Integrins

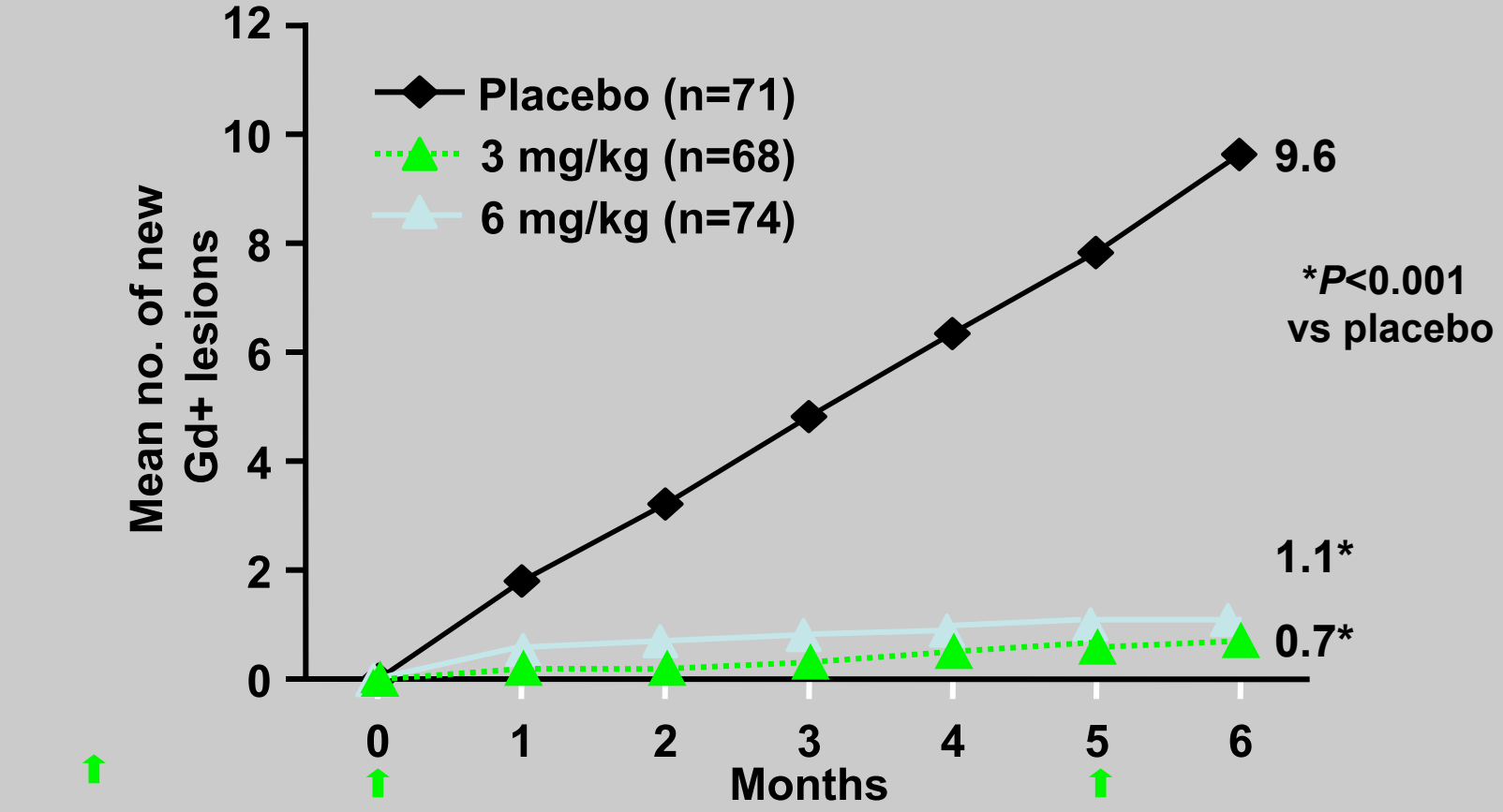
- α_4-Integrin antagonist
- CDR grafted from murine antibody
- Human IgG4 subclass framework
- Non-complement fixing



CDRs, complementarity-determining regions.

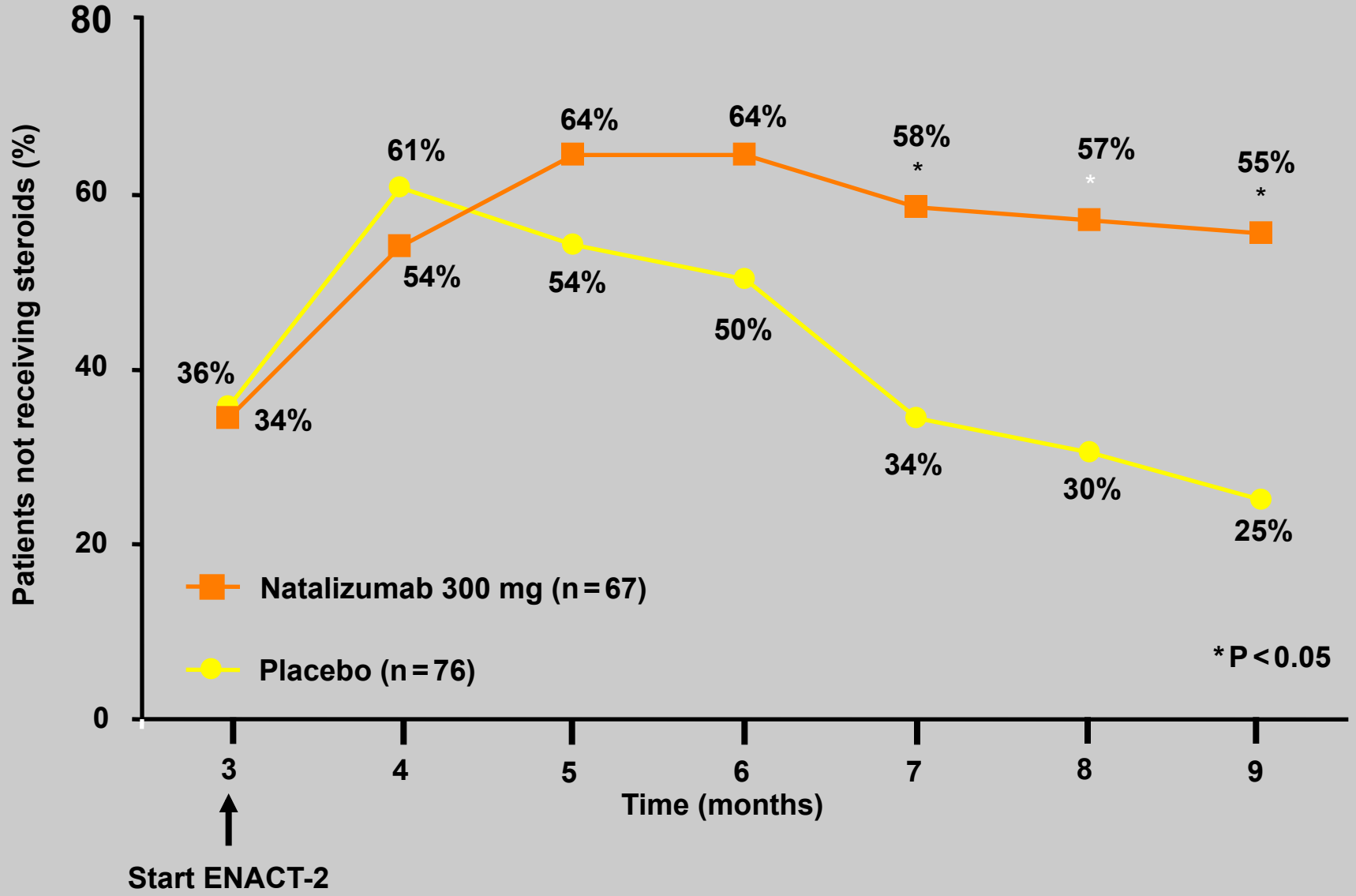
Sheremata WA, et al. *Neurology.* 1999;52:1072-1074.

Cumulative Number of New Gd+ Lesions *Miller et al., 2003 (1 Year)*



Miller DH, et al. *N Engl J Med*. 2003;348:15-23.

ENACT-2: Patients Removed from Concurrent Steroids



Sandborn WJ. et al. (ENACT-2) *N Engl J Med*. 2005;353(18):1912-25.

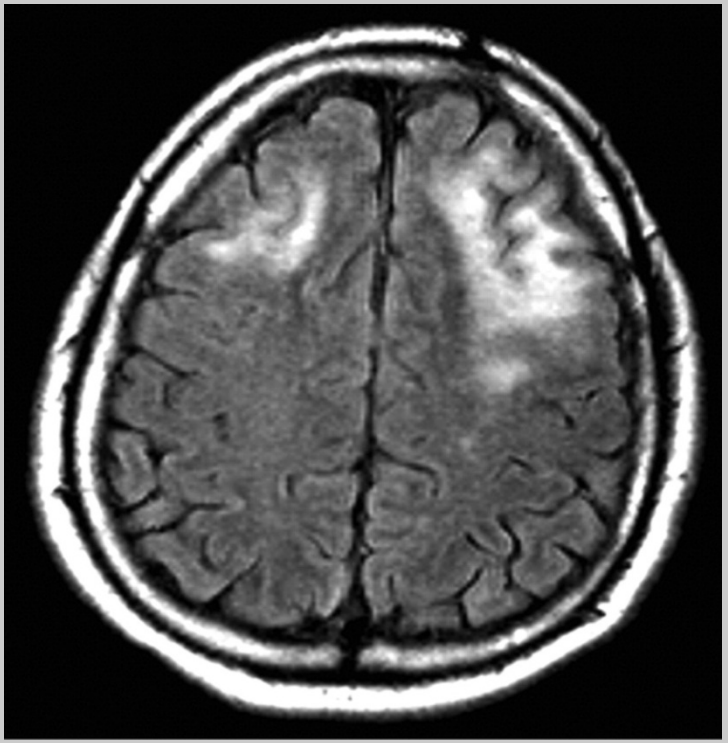
ENACT-2: ITT Safety and Tolerability Profile

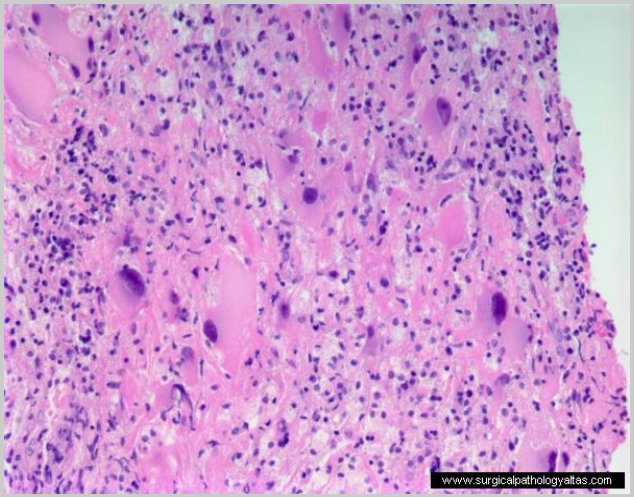
	Placebo (n = 214)	Natalizumab (n = 214)
Patients with adverse events	203 (95%)	192 (90%)
Serious adverse events	21 (10%)	19 (9%)
Discontinuations due to adverse events	53 (25%)	26 (12%)
Drug-related adverse events	53 (25%)	40 (19%)
Frequently occurring drug-related AEs		
Headache	16 (7%)	13 (6%)
Fatigue	4 (2%)	7 (3%)
Nausea	8 (4%)	5 (2%)
Patients with serious infections	4 (2%)	5 (2%)
Patients with malignancies (both were basal cell carcinomas)	1 (1%)	1 (1%)
Acute infusion reactions		
As % of patients	16 (7%)	14 (7%)
As % of infusions	1.6%	1.8%
Immunogenicity (primary analysis population)		7.2%

Sandborn WJ. et al. (ENACT-2) *N Engl J Med*. 2005;353(18):1912-25.

PML

- JCV- human papova virus
- Latent in renal tubuloepithelium; 60% of individuals
- Severe CNS disease in highly immunosuppressed patients (HIV \combination chemotherapy)
- Very high risk with natalizumab therapy (1:160 to 1:10,000 dependent on risk factors)
- “chilling” effect on anti-adhesion molecule Rx





Natalizumab and PML

- Diagnosis
  - Clinical impression
  - Brain MRI
  - CSF analysis for JCV DNA by PCR (has replaced brain biopsy)
  - Brain biopsy (gold standard)
- Safety study demonstrated risk of PML at 1:1,000 (95% CI 1:200 to 1:2,800) after a mean of 18 months of treatment in clinical trials
- Approved for multiple sclerosis and Crohn's disease
- Restricted to patients for whom anti-TNF therapy failed
- Mandatory participation in the TOUCH risk management program
- ~ 180 additional cases reported in patients with multiple sclerosis, 100,000 patients under treatment
- Plasmapheresis is of benefit
- New antibody test highly accurate in identifying patients with prior exposure

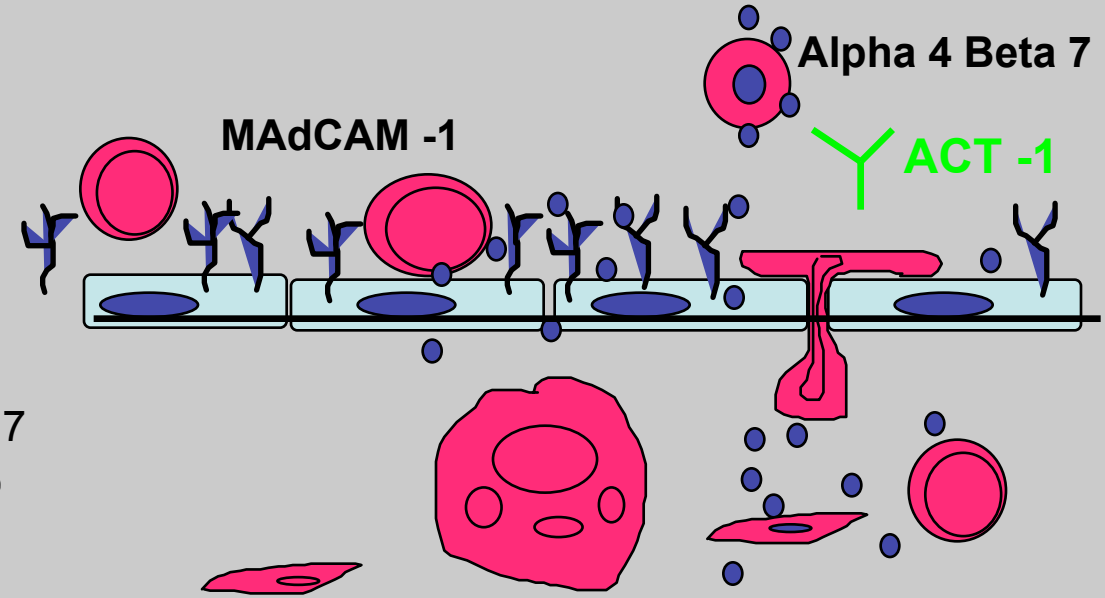
PML Risk Reduction by JCV Serology

- ~40 % of patients do not acquire the virus
- No virus = No PML
- PCR of peripheral blood or urine not useful – low positive predictive value
- ELISA for JCV antibody detection highly sensitive and specific
- False-negative rate of 2.5 % (one sided UCL-95 of 4.4 %)
- All patients with PML were antibody positive
- Useful for risk stratification

Trampe A.K. et al *Neurology* 2012;78 (22); Gorelik L. et al *Ann Neur* 2010; 68(3)

Vedolizumab:Background

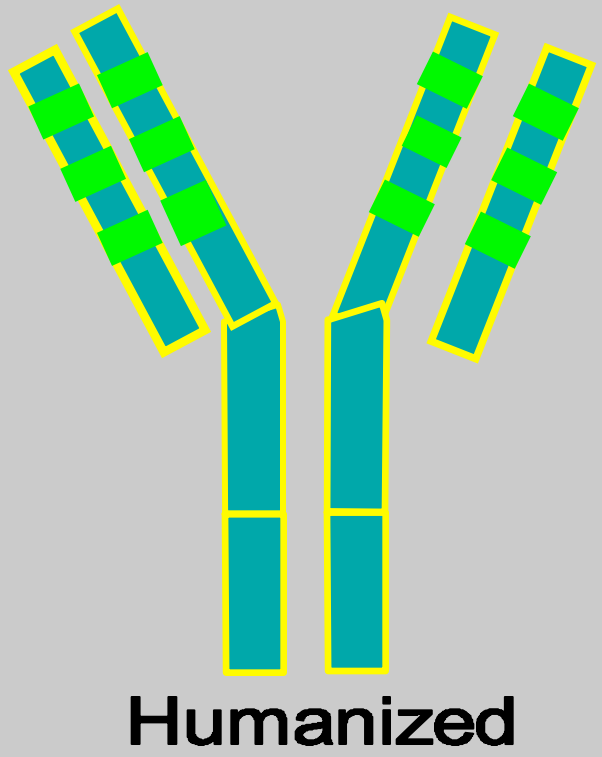
- Ligand for $\alpha_4\beta_7$ is MAdCAM
- Animal models show that ACT-1 selectively blocks trafficking of $\alpha_4\beta_7$ positive lymphocytes to the gut
- Raises possibility of gut specific immune modulation
- Striking benefit in cotton-top tamarin model



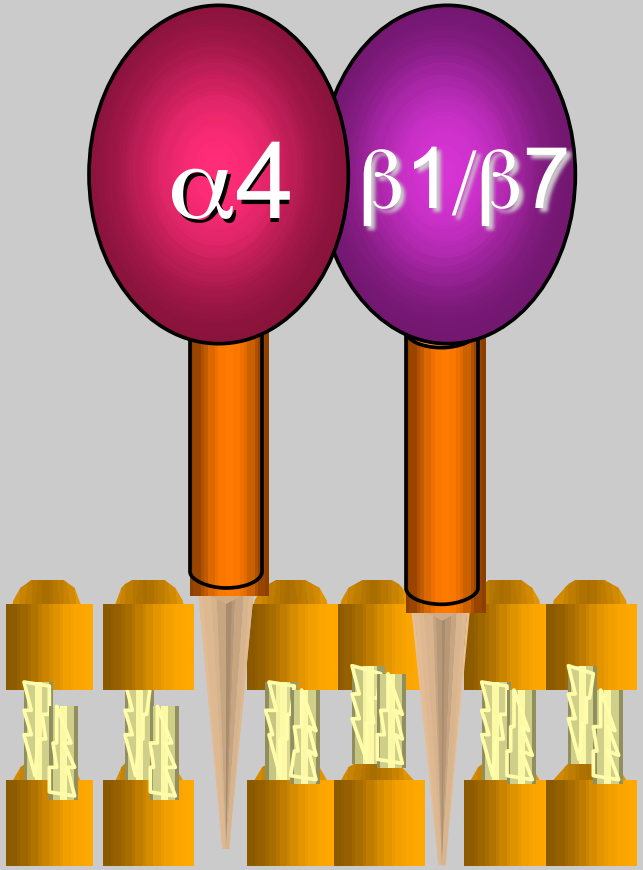
Hesterberg PE et al. *Gastroenterology* 1996;111:1373-80
Podolsky et al. *JCI* 1993;92:372-80

Background II

- MLN-02 was created by grafting the complementarity determining regions of ACT-1 into a human IgG1 framework
- Excellent safety/tolerability in Phase I studies
- Clinical trial programs (Millennium) in both ulcerative colitis and Crohn's disease



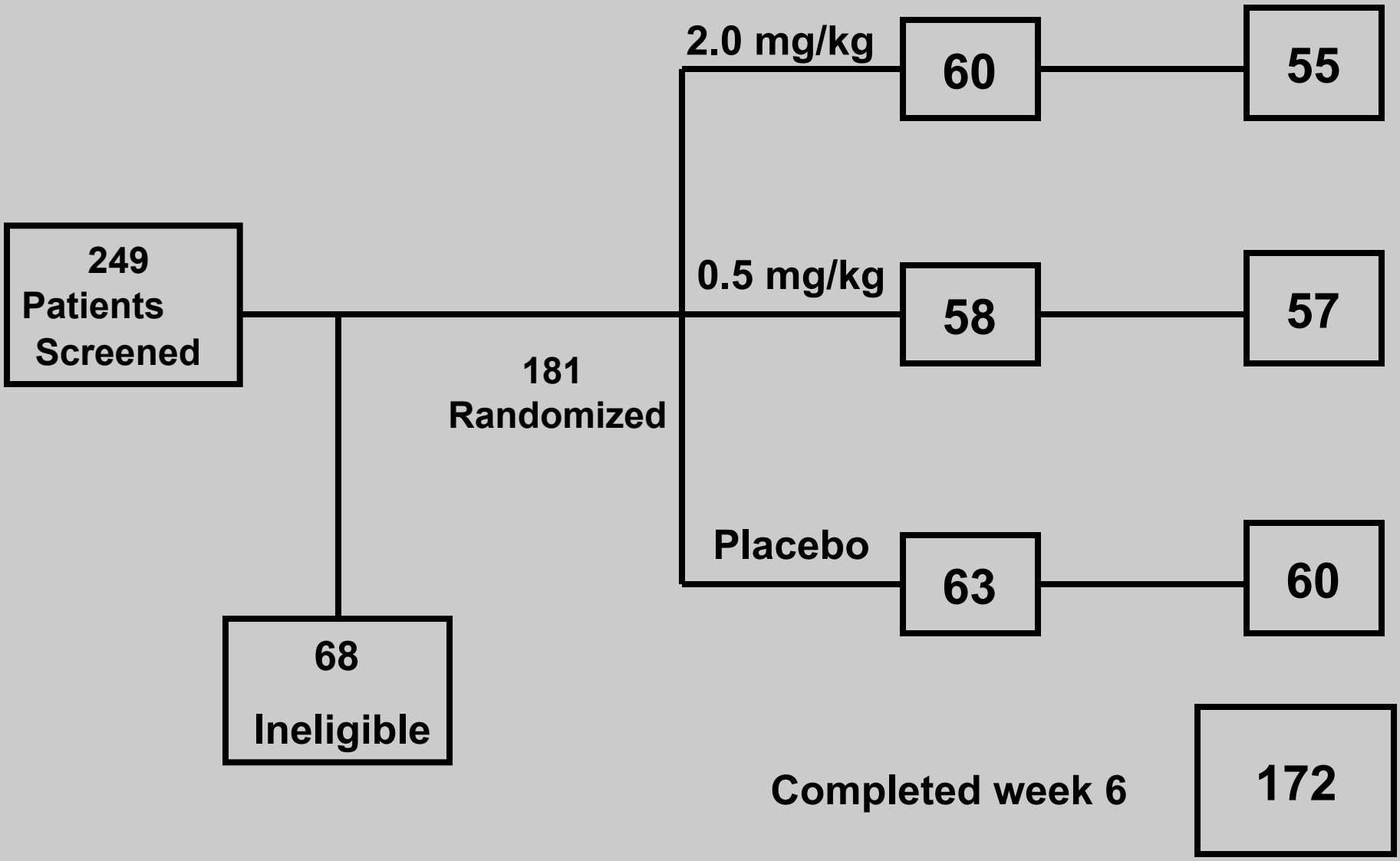
Endothelial and Leukocyte Adhesion: α4 Integrins



- Leukocyte membrane glycoproteins
- β1 and β7 subunits
- Interact with endothelial ligands VCAM-1, fibronectin, and MAdCAM-1
- Mediate leukocyte adhesion and trafficking

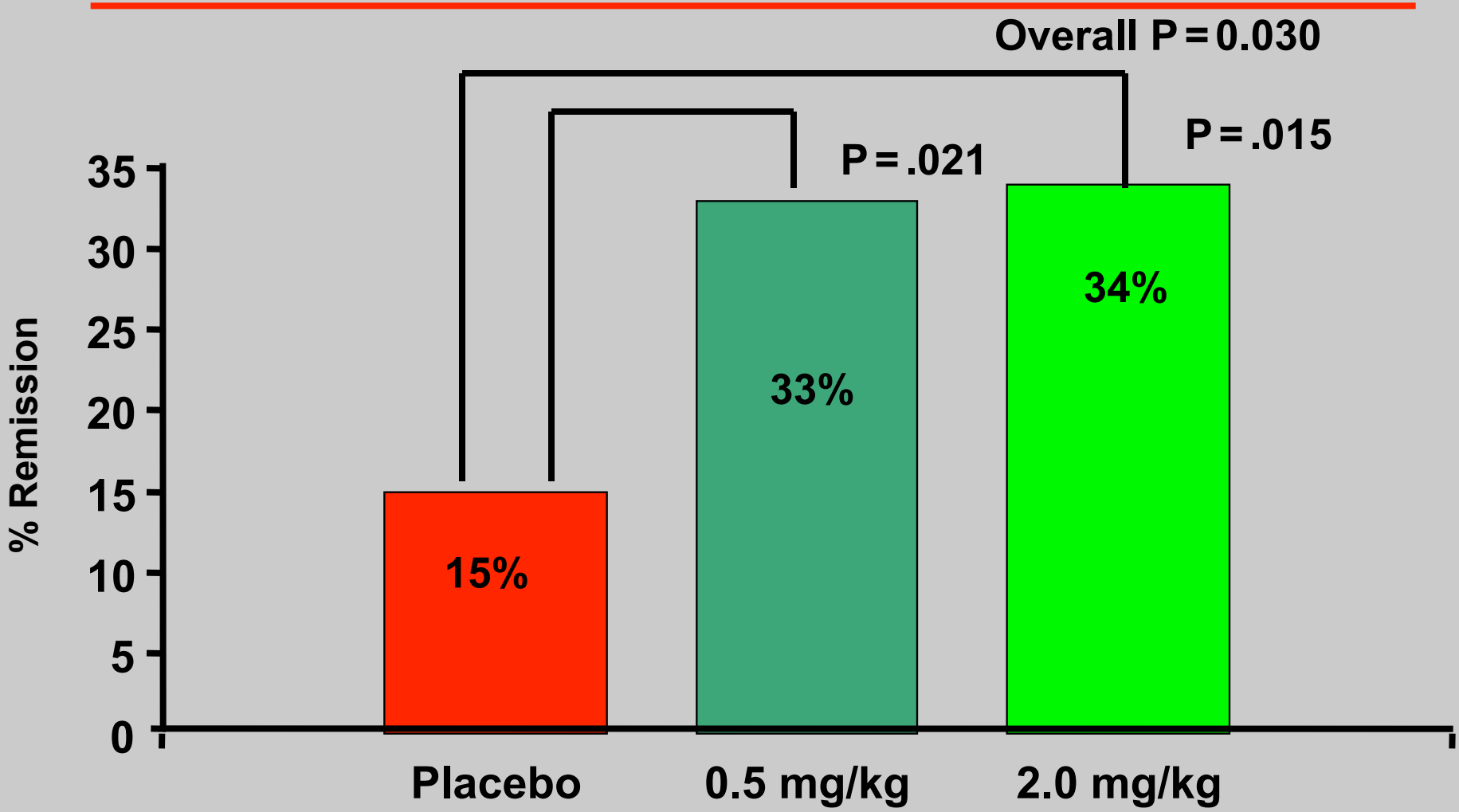
Springer TA. *Cell* 1994;76:301-314. Butcher EC et al. *Science* 1996;272:60-66

MLN-02 in UC: Design of the Trial



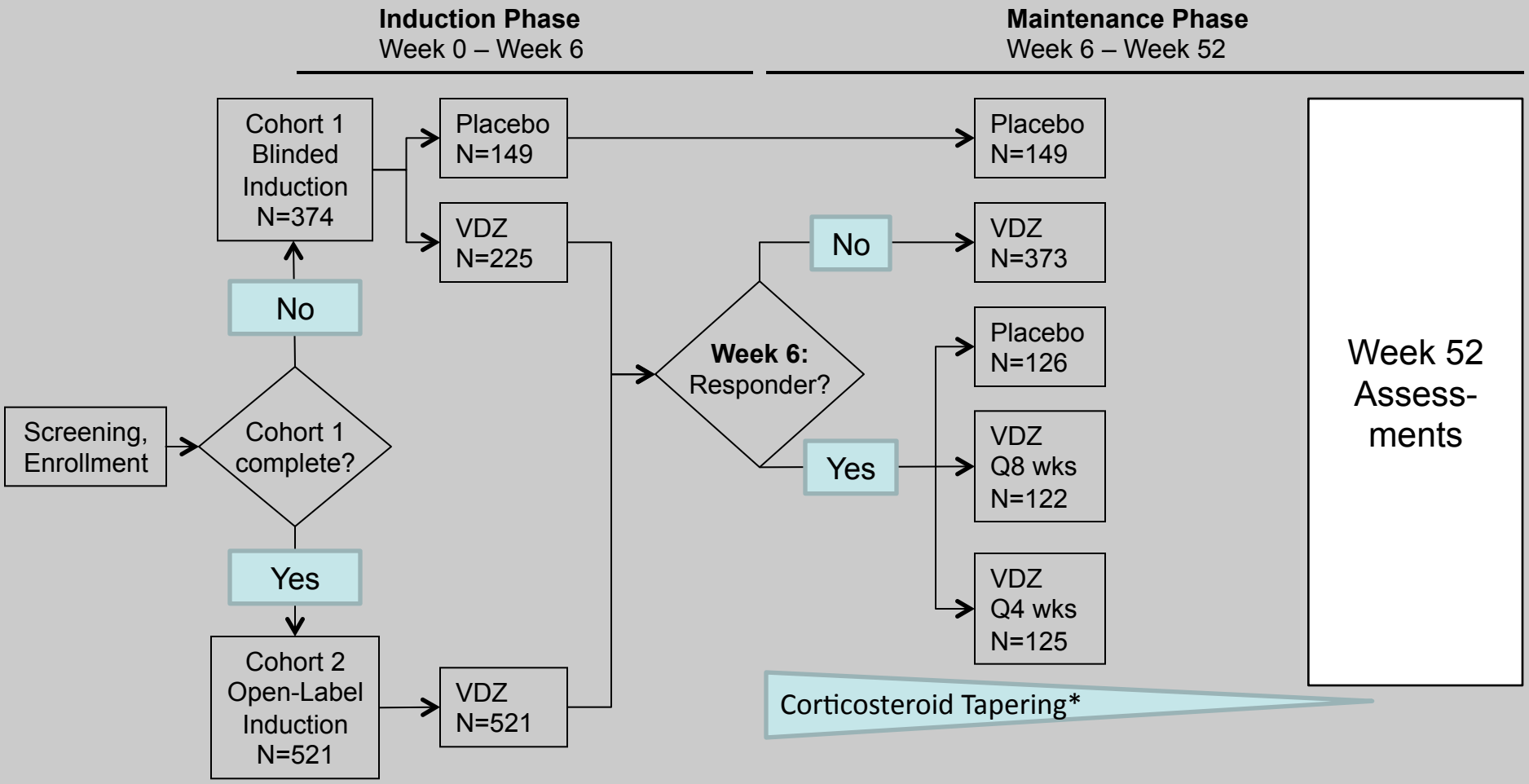
Feagan BG. et al *N Engl J Med.* 2005;352(24):2499-507.

Clinical Remission
Week 6



Feagan BG. et al *N Engl J Med.* 2005;352(24):2499-507.

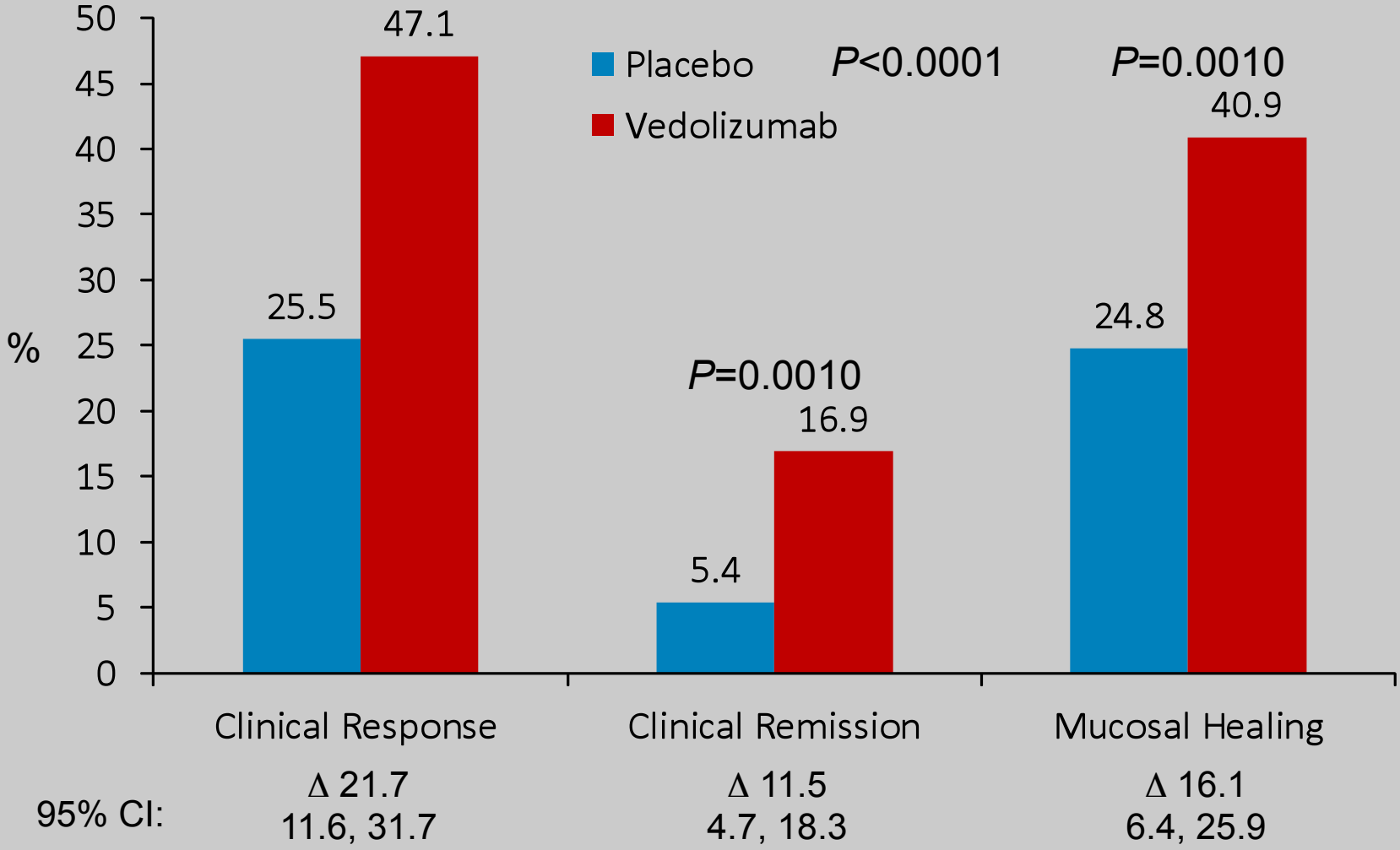
Vedolizumab Phase III: Study Design



*Responders began tapering regimen at 6 weeks; others, as soon as a clinical response was achieved.

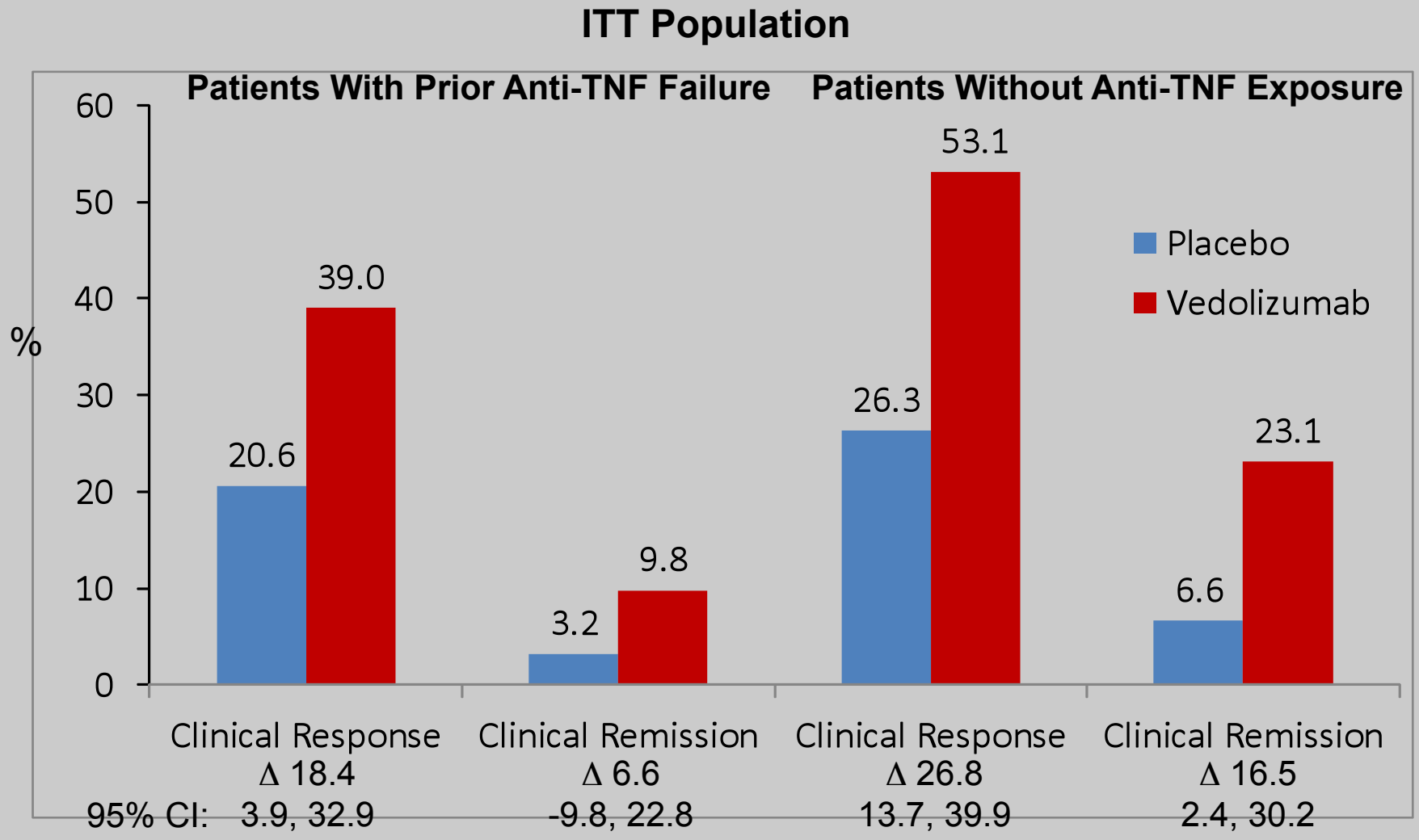
Feagan, B.G. et al New Engl J Med 2013

Clinical Response, Clinical Remission, Mucosal Healing at 6 Weeks, ITT Population



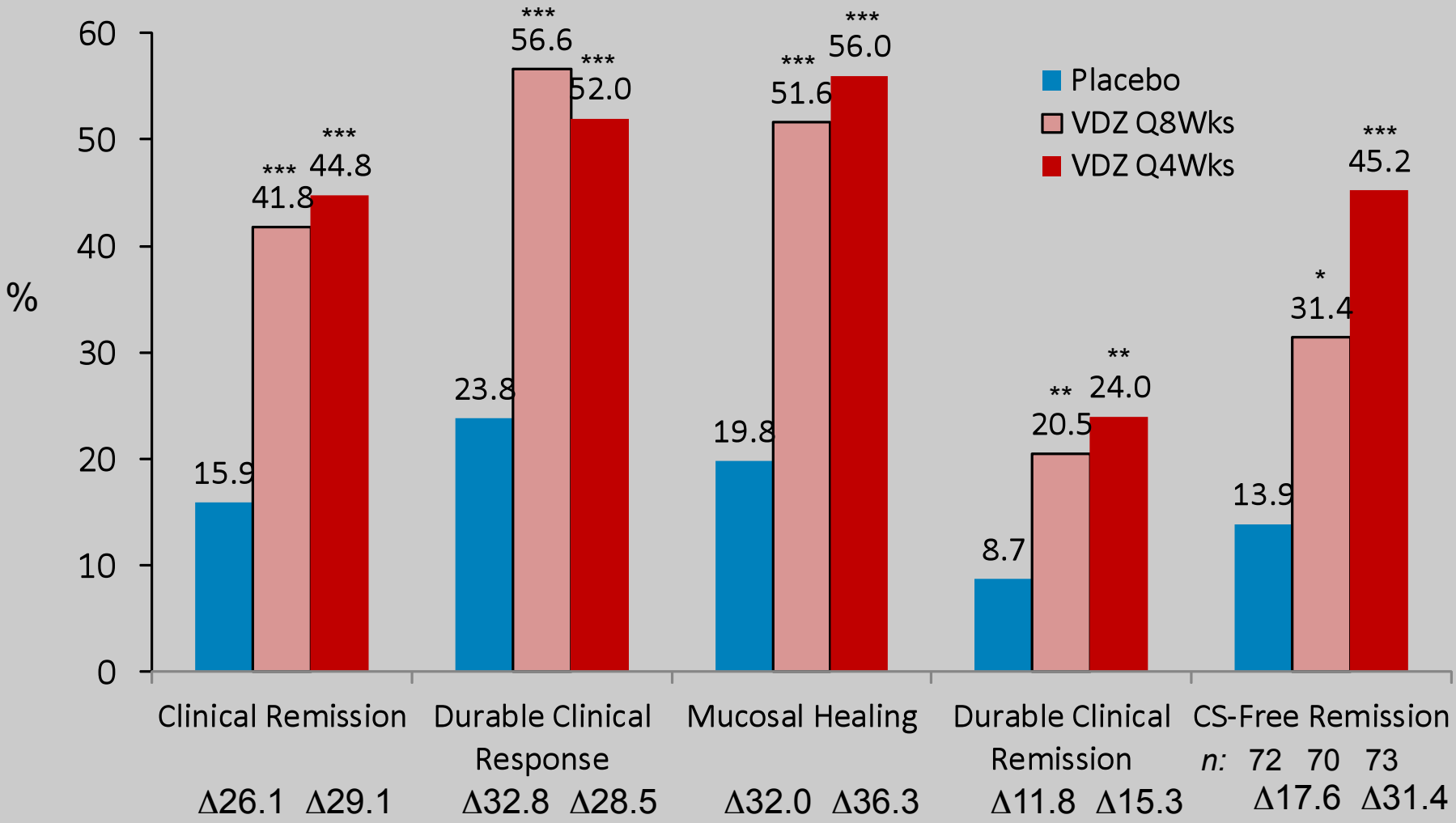
Feagan BG et al New Engl J Med 2013

Clinical Response and Remission at 6 Weeks: Prior Anti-TNFα Failure vs No Anti-TNFα Exposure



Feagan BG et al New Engl J Med 2013

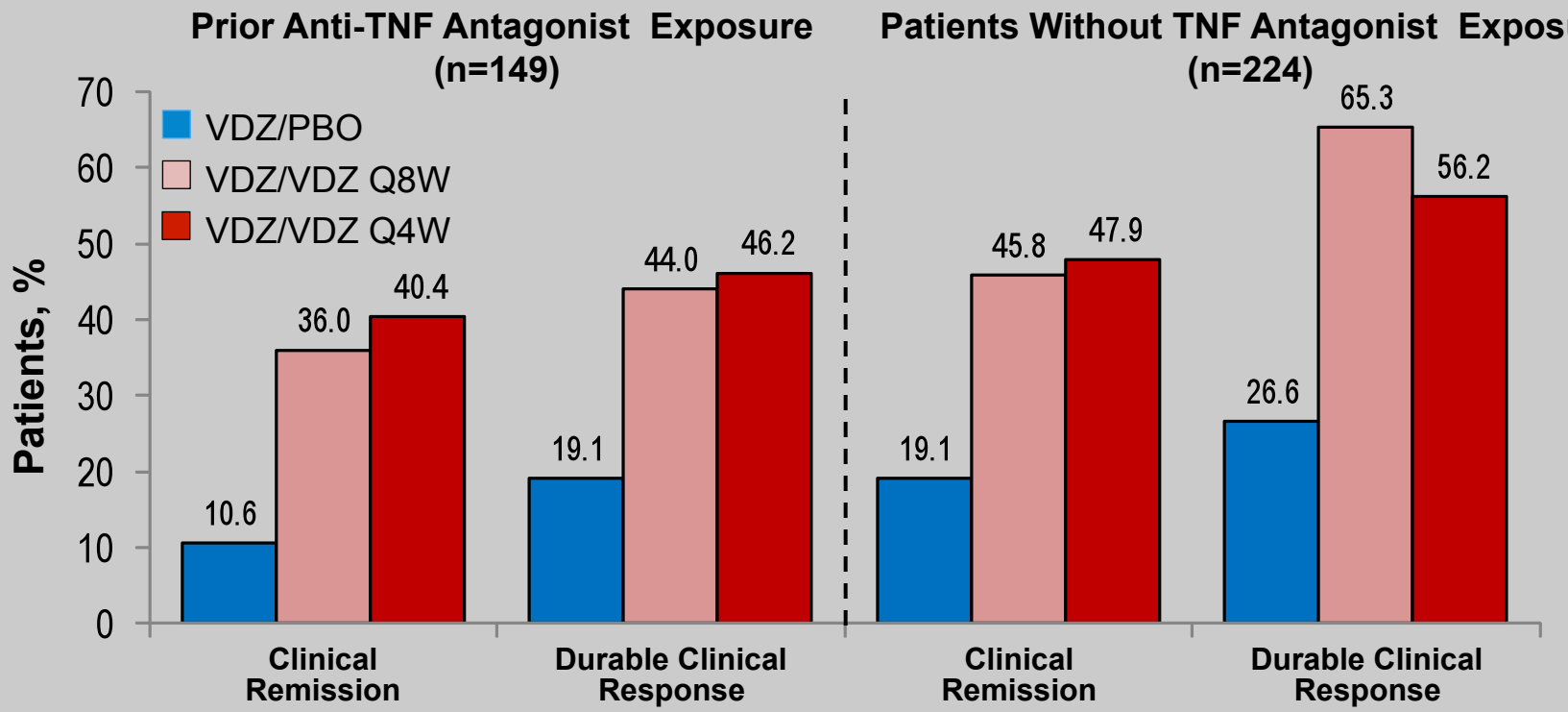
Primary and Secondary Outcomes Through 52 Weeks, ITT Population



*P<0.05. **P<0.01. ***P<0.0001

Feagan BG et al New Engl J Med 2013

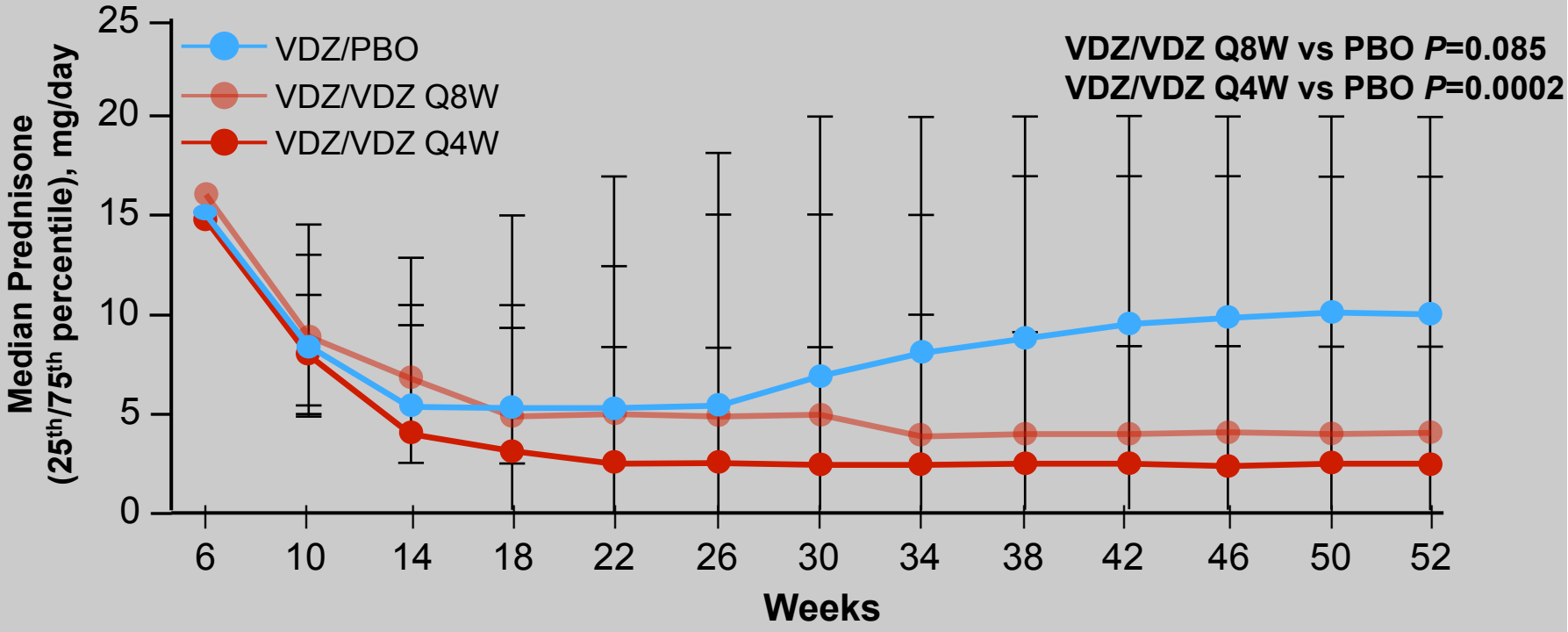
Clinical Remission, Durable Clinical Response at 52 Weeks by Prior TNF Antagonist Exposure



Mean Δ% vs VDZ/PBO (95% CI)				
VDZ/VDZ Q8W:	25.4 (5.1, 43.8)	24.9 (7.1, 42.6)	26.8 (12.4, 41.2)	38.7 (24.0, 53.4)
VDZ/VDZ Q4W:	29.7 (10.3, 47.7)	27.0 (9.4, 44.6)	29.0 (14.6, 43.3)	29.6 (14.6, 44.6)

Feagan BG et al New Engl J Med 2013

Corticosteroid Use From Week 6*



Feagan BG et al New Engl J Med 2013

Comparison of AEs of Special Interest Between Vedolizumab and Placebo in Studies C13006 and C13007

Primary System Organ Class High Level Term	PBO (N=576)		VDZ (N=1434)	
	Events, No.	Events/ 100 Pt-Y	Events, No.	Events/ 100 Pt-Y
Infections and infestations	**379**	**108.5**	**1086**	**109.8**
Upper respiratory tract infections	152	43.5	480	48.5
Abdominal and GI infections	38	10.9	98	9.9
Fungal infections not elsewhere classified (NEC)	5	1.4	22	2.2
Sepsis, bacteraemia, viraemia, and fungaemia NEC	2	0. 6	6	0.6
Herpes viral infections	20	5.7	39	3.9
Clostridia infections	1	0. 3	5	0.5
GI disorders	**534**	**152.9**	**1352**	**136.7**
GI inflammatory disorders NEC	75	21.5	197	19.9
GI and abdominal pains (excl oral and throat)	91	26.1	228	23.1
General disorders and administration site conditions	**195**	**55.8**	**515**	**52.1**
Infusion Site Reactions	8	2.3	12	1.2

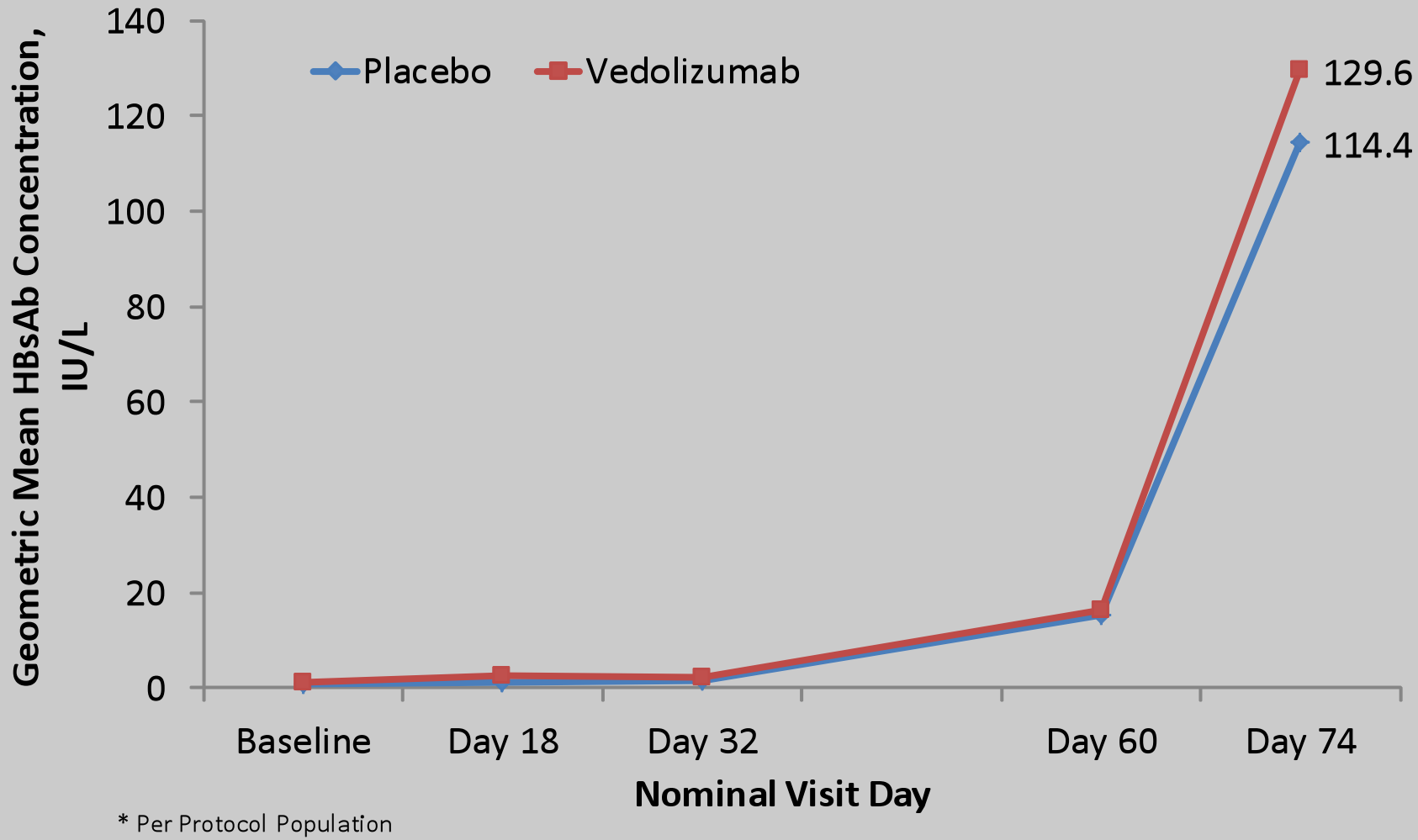
Exposure-Adjusted Adverse Events Affecting >5% of Patients Through Week 52

Preferred Term	PBO Rate (N=275)	VDZ Rate (N=620)	Relative Risk	95% CI
Headache	0.168	0.262	1.6039	0.9021, 2.8519
Colitis ulcerative	0.273	0.206	0.7543	0.5448, 1.0444
Nasopharyngitis	0.137	0.187	1.3692	0.8677, 2.1605
Upper respiratory tract infection	0.132	0.125	0.9432	0.5530, 1.6088
Arthralgia	0.115	0.113	0.9825	0.6069, 1.5907
Nausea	0.101	0.095	0.9398	0.5166, 1.7099
Abdominal pain	0.044	0.075	1.6900	0.8253, 3.4605
Anaemia	0.071	0.072	1.0317	0.5756, 1.8492
Fatigue	0.044	0.069	1.5721	0.7380, 3.3490
Cough	0.062	0.066	1.0668	0.5663, 2.0093
Influenza	0.031	0.057	1.8528	0.7463, 4.5996
Any serious AE	**0.234**	**0.179**	**0.8014**	**0.5083, 1.2636**
Any infection	**0.812**	**0.804**	**0.9932**	**0.7573, 1.3027**

Safety: Is Vedolizumab Gut Selective?

- No peripheral blood lymphocytosis
- No protective effect in primate model of MS (EAE)
- No inversion of CD4\CD8 ratio in CSF of humans
- Clinical data – no cases of PML observed
- Preservation of systemic humoral responses to T cell dependent antigens with modest impairment to oral antigen (vaccine study)

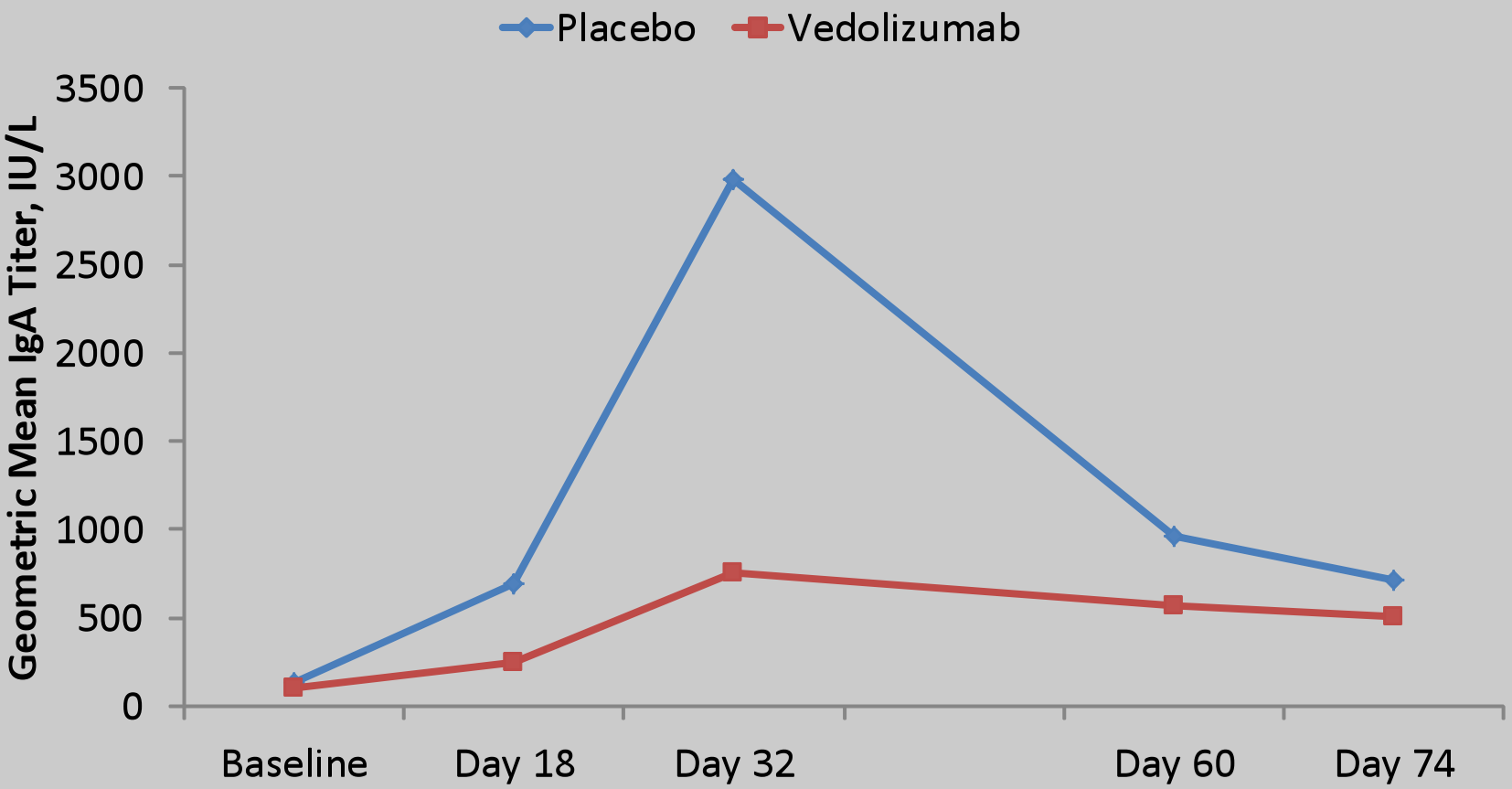
Hepatitis B Surface Antibody (HbsAb) Concentration Through Day 74*



* Per Protocol Population

Parikh A. et al. ECCO 2013

Serum IgA Response to Oral Cholera Vaccine Through Day 74*

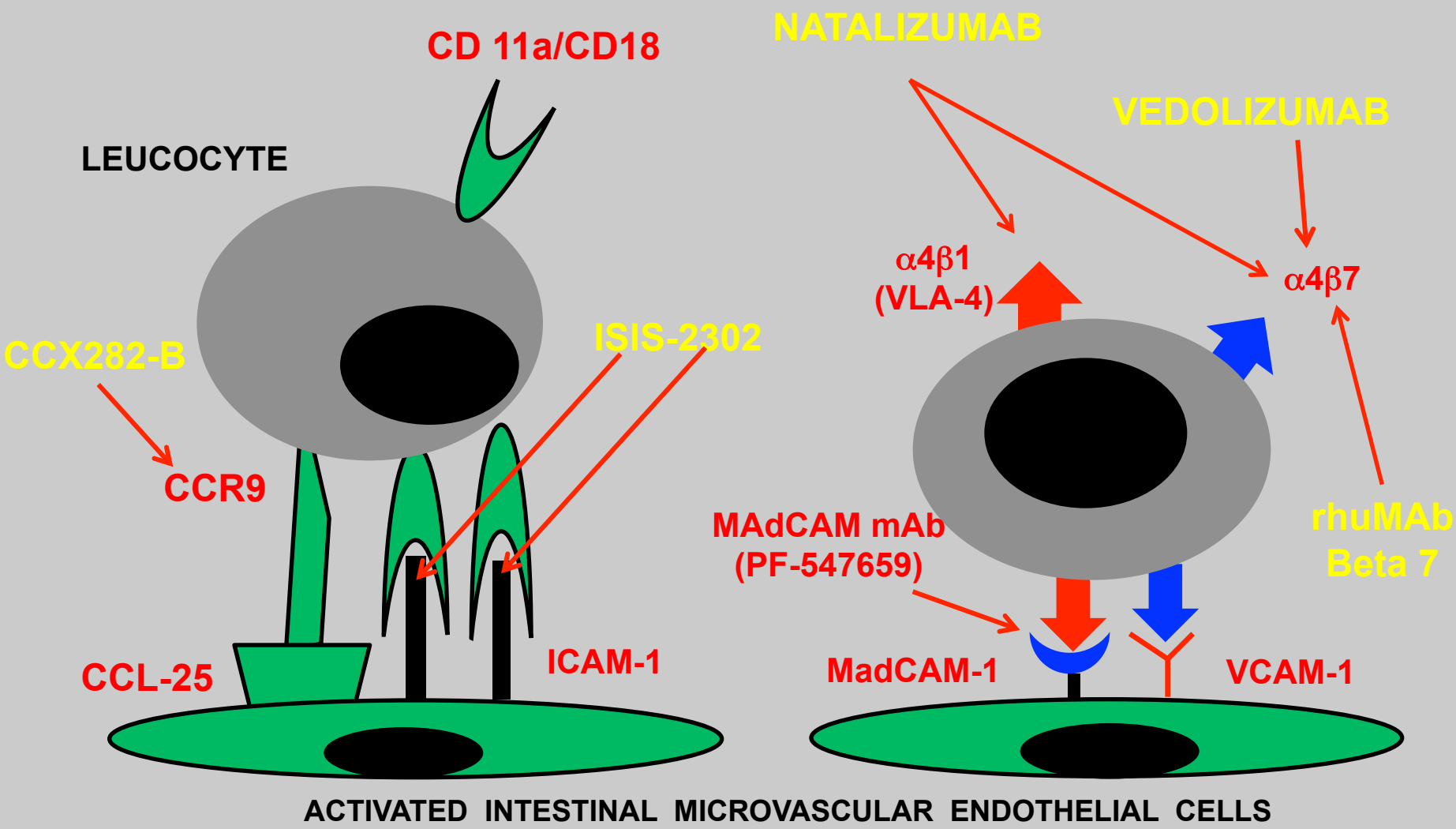


% responders (95% CI):	PBO	50.0 (37.6, 62.4)	83.9 (74.7, 93.0)	74.2 (63.3, 85.1)	59.7 (47.5, 71.9)
	VDZ	30.2 (18.8, 41.5)	63.5 (51.6, 75.4)	57.1 (44.9, 69.4)	50.8 (38.4, 63.1)

*Dukoral Population

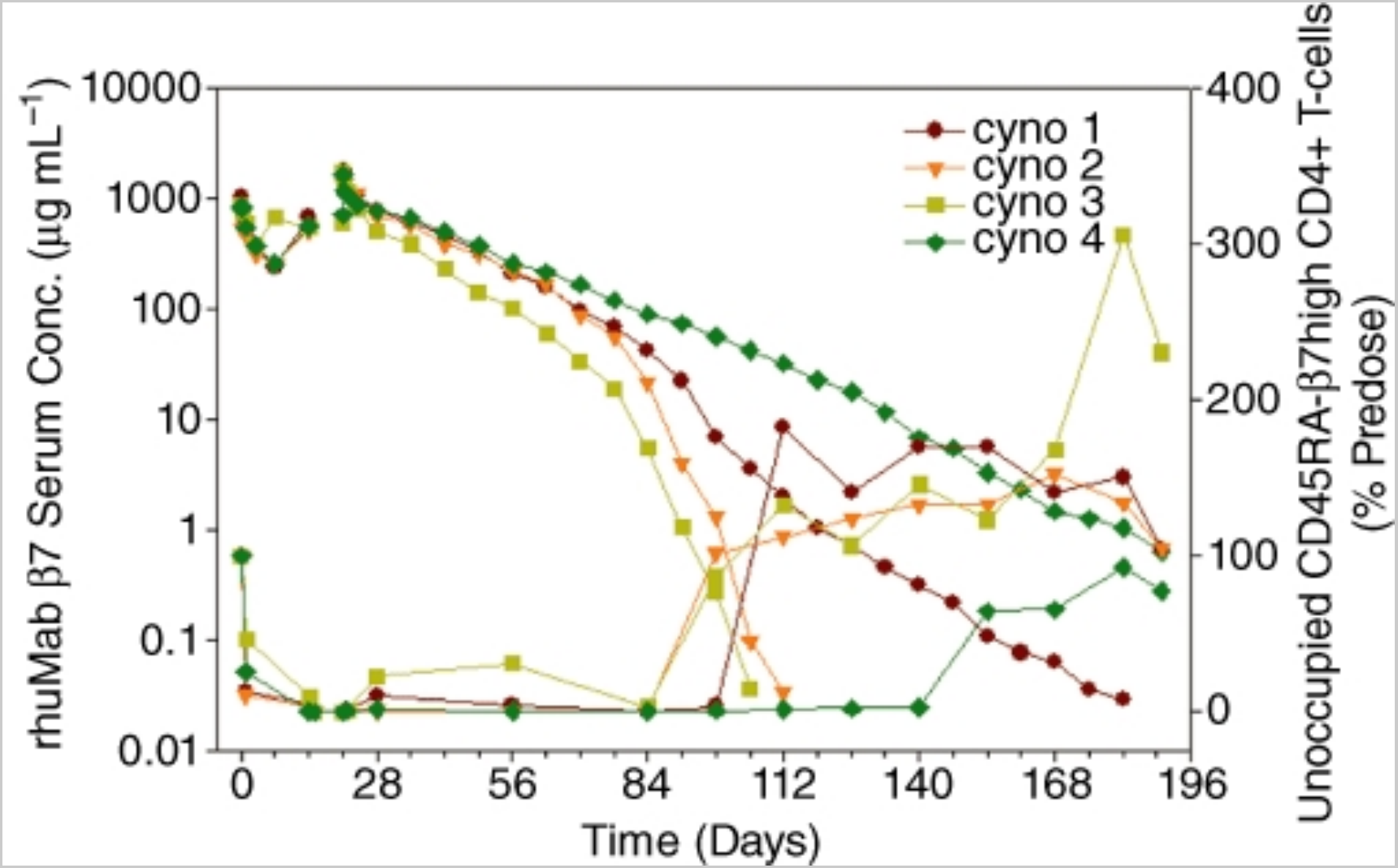
Parikh A. et al. ECCO 2013

Therapeutic Targets



Adapted from Danese S Gut 2011;60:998-1008

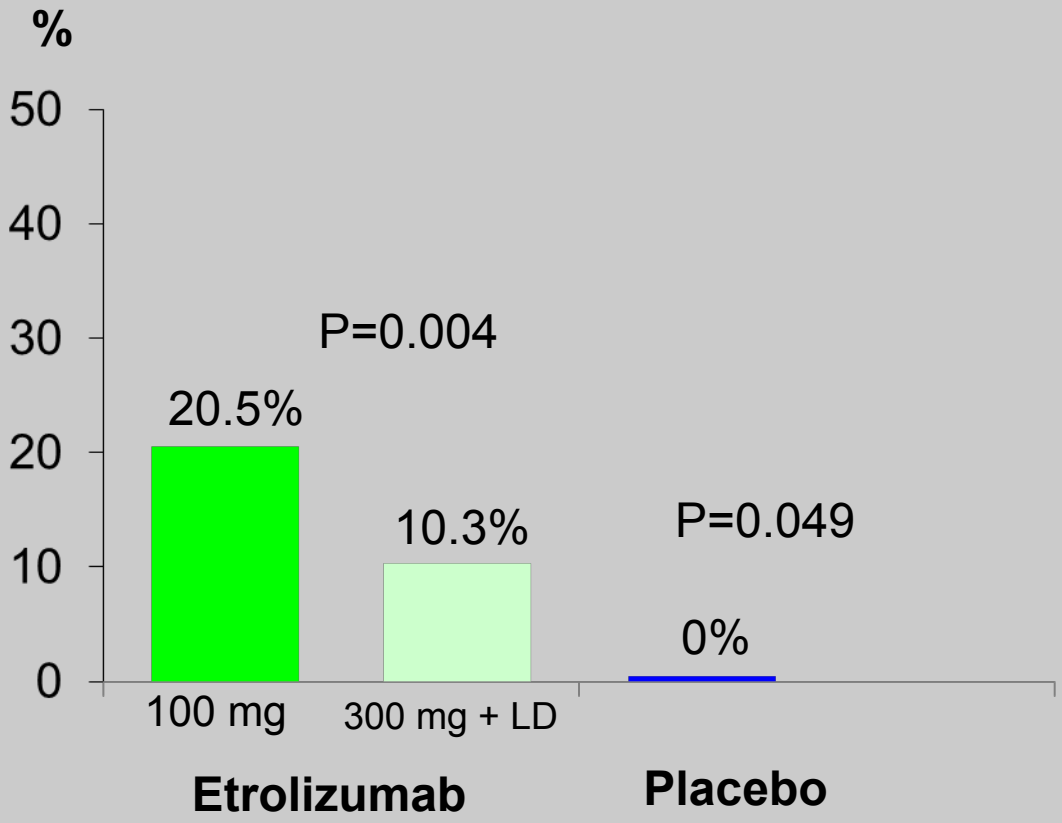
Humanized Antibody to Beta -7 [Rhumbeta7]



Stefanich E.G. et al Br J Pharmacol 2011 162 (8) :1855-70

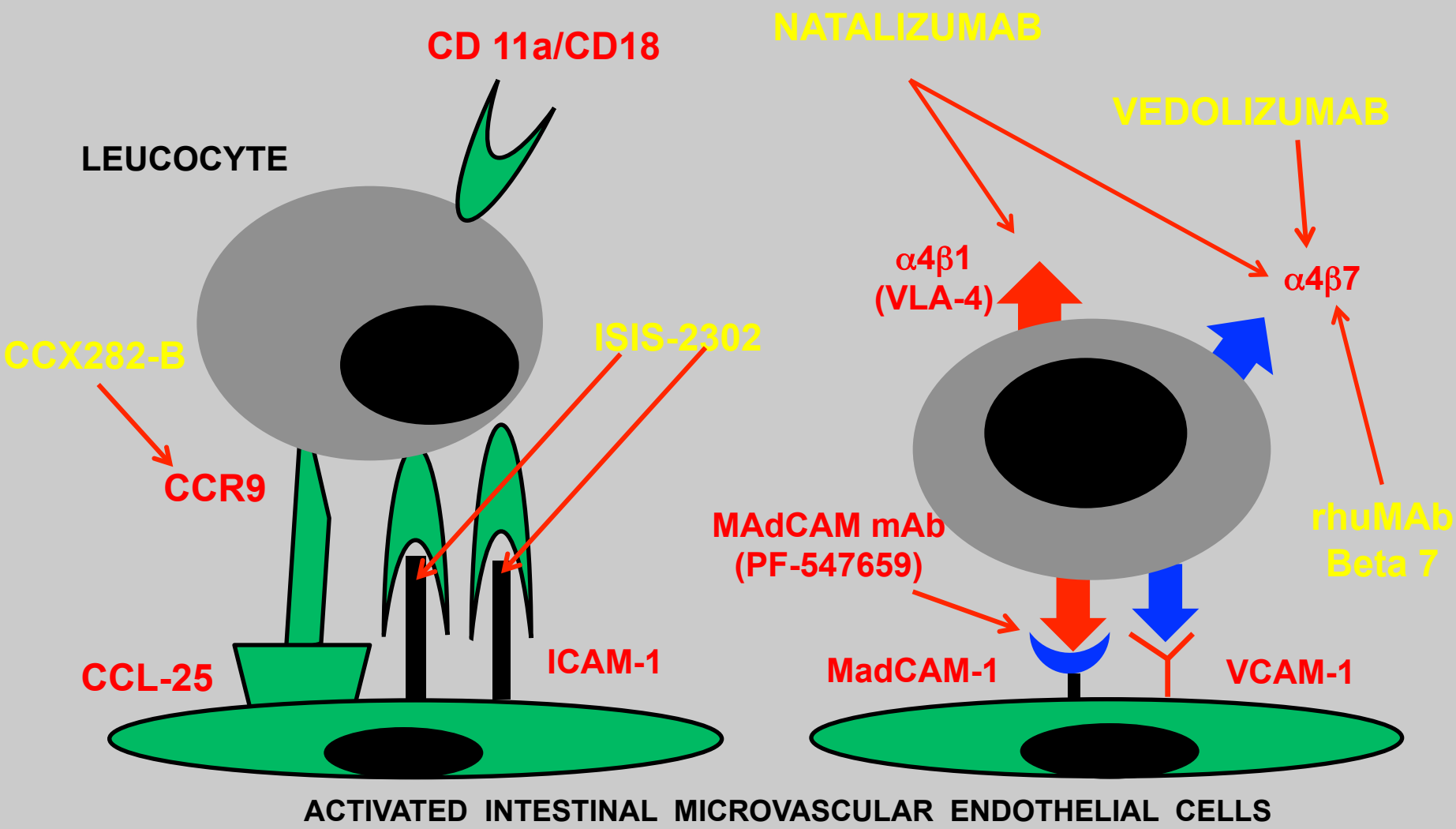
Etrolizumab vs Placebo – Eucalyptus Phase II Randomized Induction Study in Active UC – Clinical Remission at Wk 10

- Humanized monoclonal antibody to the B7 subunit of the heterodimeric integrins $\alpha4\beta7$ and $\alpha E\beta7$ in patients with mod-sev active UC
- N=124
- Randomized to 2 dose groups vs placebo



Vermiere S. et al. DDW 2013 Late Breaking Abstract.

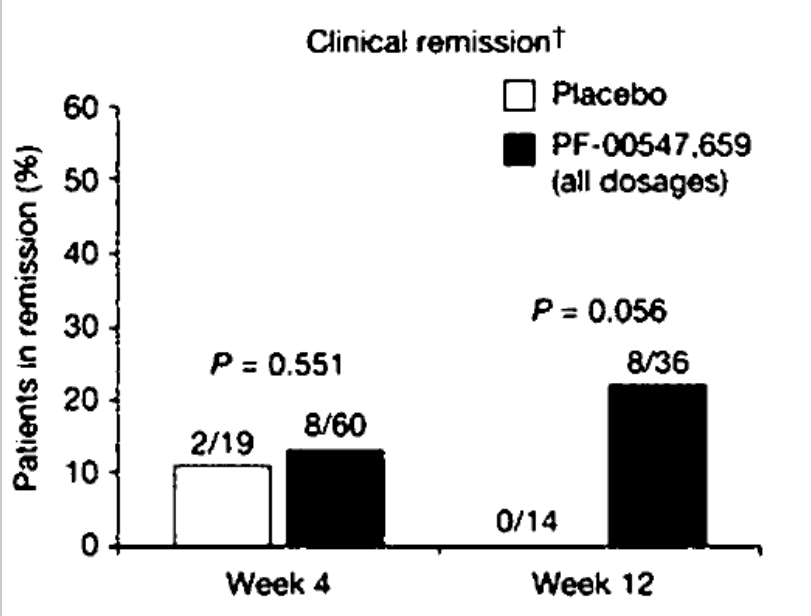
Therapeutic Targets

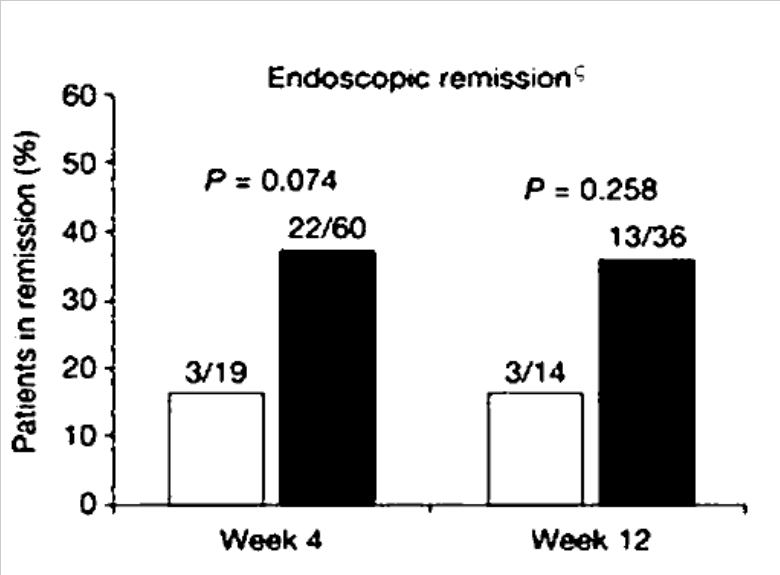


Adapted from Danese S Gut 2011;60:998-1008

Anti-Madcam Antibody for Active UC

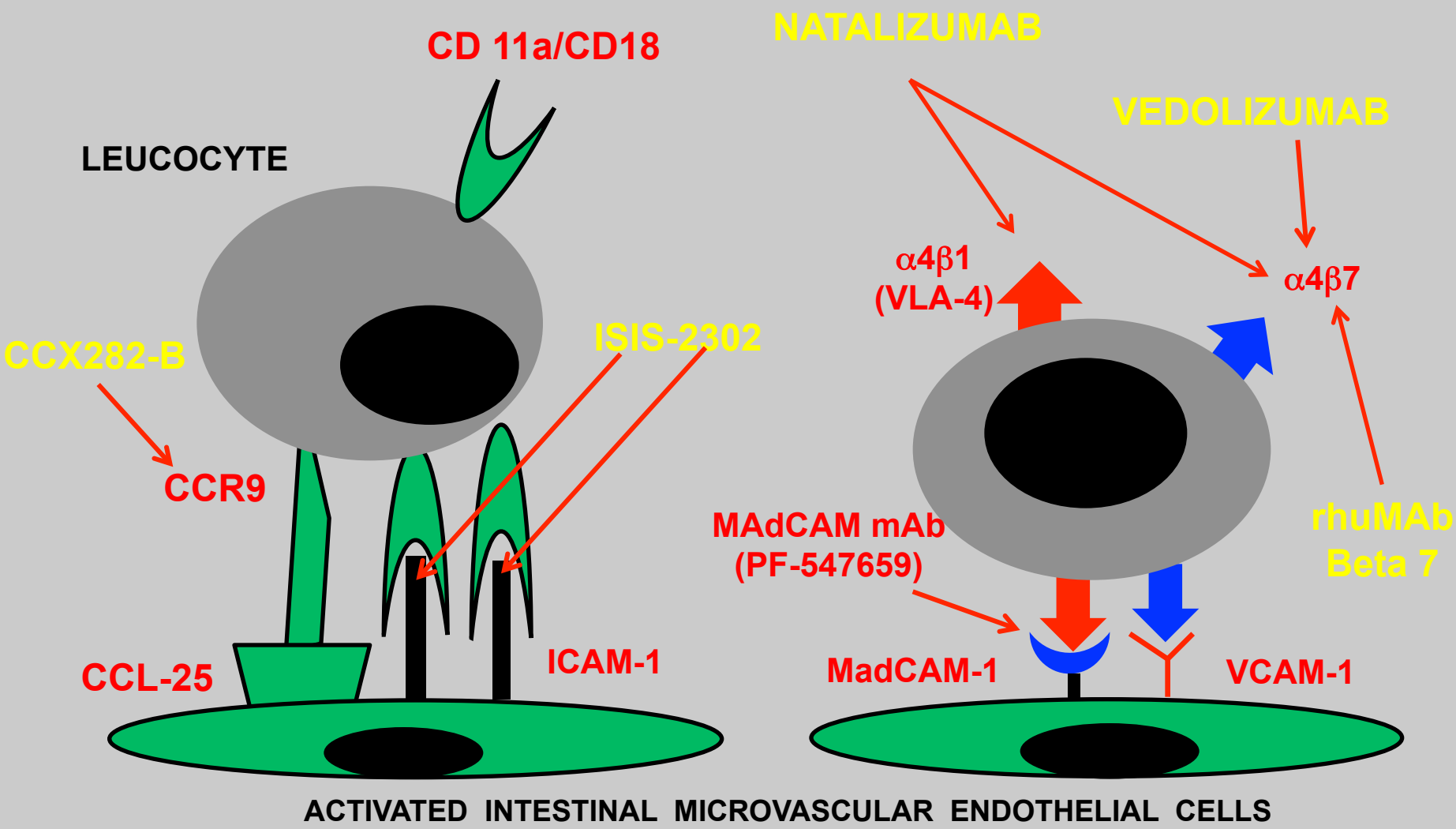
- Placebo controlled dose escalation RCT
- 3 doses against placebo
- Pooled analysis
- Total n=80





Vermiere S. et al. Gut 2011;60:1068-1075

Therapeutic Targets



Adapted from Danese S Gut 2011;60:998-1008

Conclusions