Evaluation of treatment effect in adult UC and CD

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Disclosures

- Dr Travis has been adviser to, in receipt of educational or research grants from, or invited lecturer for Abbott/AbbVie; Asahi; Boehringer Ingelheim; BMS; Cosmo; Elan; Ferring; FPRT Bio; Genentech/Roche; Genzyme; Glenmark; GW Pharmaceuticals; Lilly; Merck; Novartis; Novo Nordisk; Ocera; Pfizer; Shire; Santarus; SigmoidPharma; Synthon; Takeda; Tillotts; Topivert; Trino Therapeutics with Wellcome Trust; UCB Pharma; Vertex; VHsquared; Vifor; Warner Chilcott
- All advisory boards were suspended Q1 2012-14 while President of ECCO

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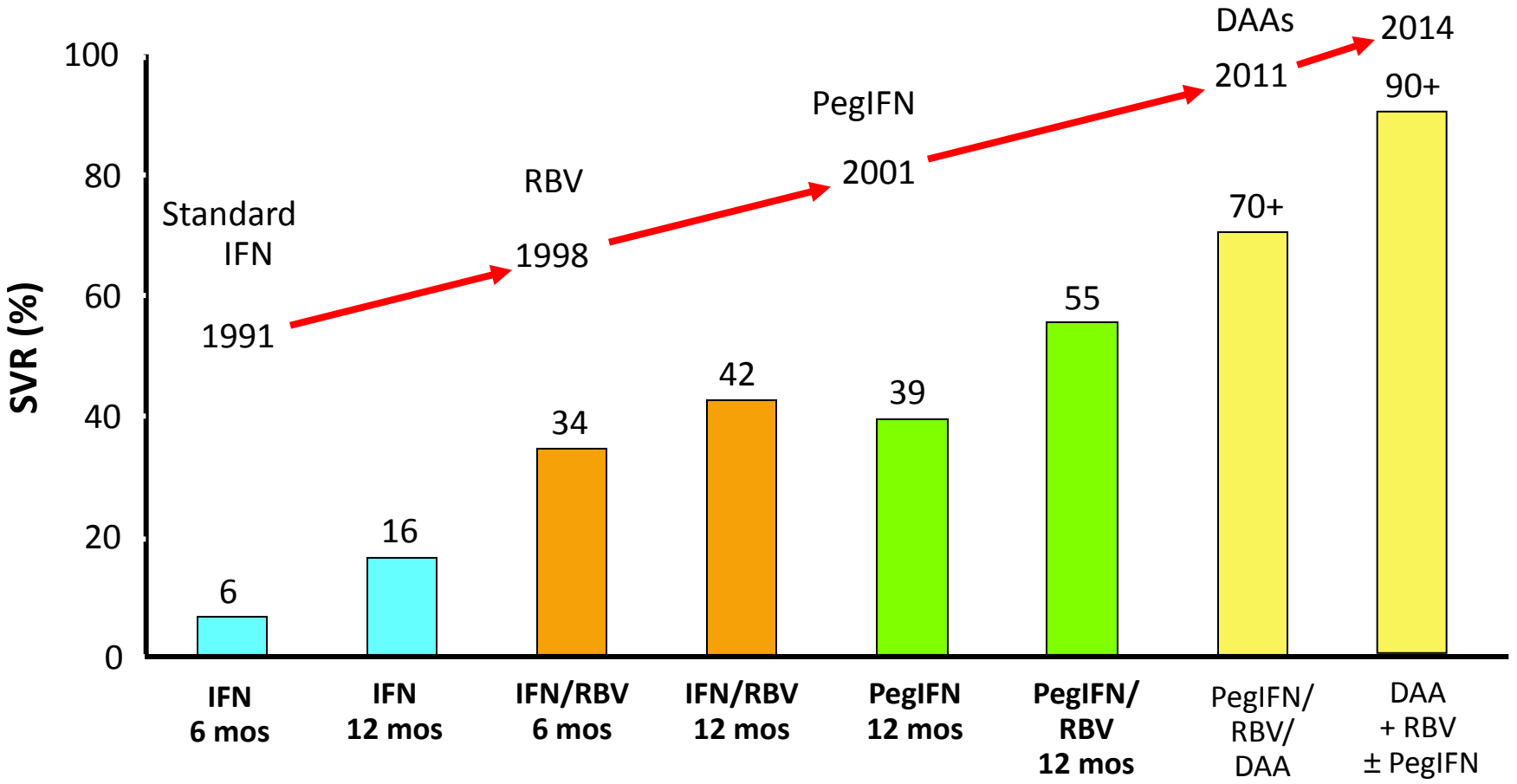
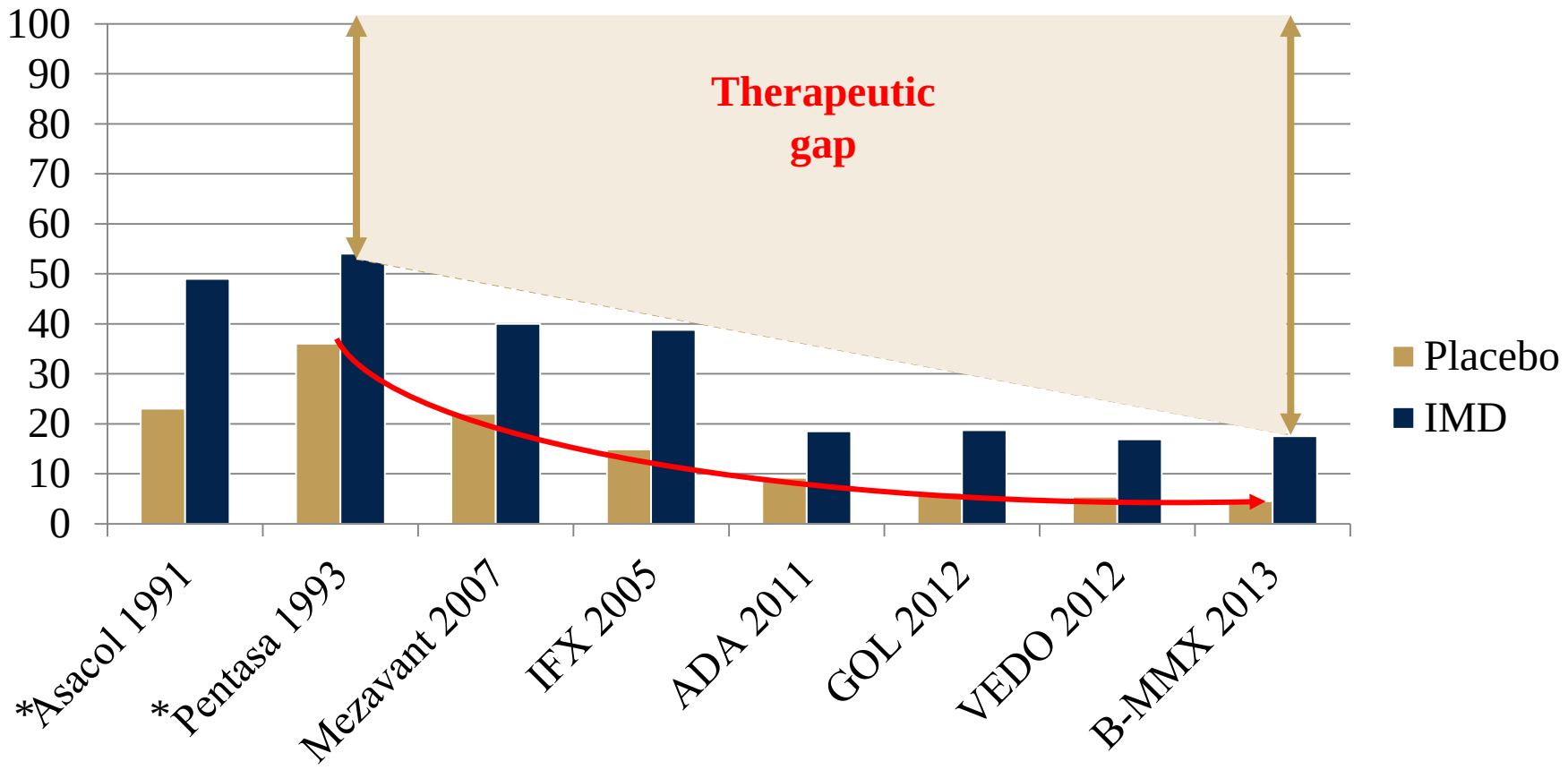
The Good News: Treatment of Hepatitis C



Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.

Impact of robust endpoints for UC: the gap widens



*: response; remainder = remission (criteria for inclusion, definitions and analyses differed)

Studies:

Sninsky *Ann Int Med* 1991; Hanauer *Am J Gastro* 1993; Kamm *Gastro* 2007; Rutgeerts *NEJM* 2005; Reinisch *Gut* 2012; Sandborn *DDW* 212; Feagan *DDW* 2012; Travis *Gut* 2013

Characteristics of ideal outcome measures

- Distinguish effective from ineffective therapies
  - Reproducible
  - Distinguish between different levels of disease activity
  - Responsive to change
  - Predict long term outcomes
  - Congruent with goals of therapy

Goals of Therapy: A clinical trials' perspective

- Avoid adverse drug effects
  - Safety
- Make the patient feel better
  - Improve symptoms and QoL (subjective)
- Address the pathologic process
  - Reduce/eliminate inflammation (objective)
- Short and long term control of disease (timeframe)
  - Induction
  - Maintenance (continuous clinical response vs single time point)
- Prevent complications of the disease
  - Alter the natural history

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Challenges in measuring disease activity in IBD

- How to capture “activity” in a single measure?
  - Heterogeneity of symptoms
    - Varies in both UC and CD
    - Varies by biological severity of disease
    - Varies by disease location (perianal vs ileal, proctitis vs pancolitis etc)
    - Varies by manifestation (intestinal/extra-intestinal)
- Historical solution: “disease activity indices”

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UC: Considerations

- **Placebo remission rate**
  - The more robust, the lower it gets
- **International opinion**
  - STRIDE
- **Choice of goals**
  - Separating the indices: clinical/endo/histo/QoL
- **Exploratory endpoints**
  - Continuous clinical response/durable remission
- **Predictors of the long term**
  - Endo/histo
- **Independent evaluation**
  - Central reading
- **Responsiveness**
  - Scales of indices
- **Quality of life outcome**
  - IBDQ/CCQ

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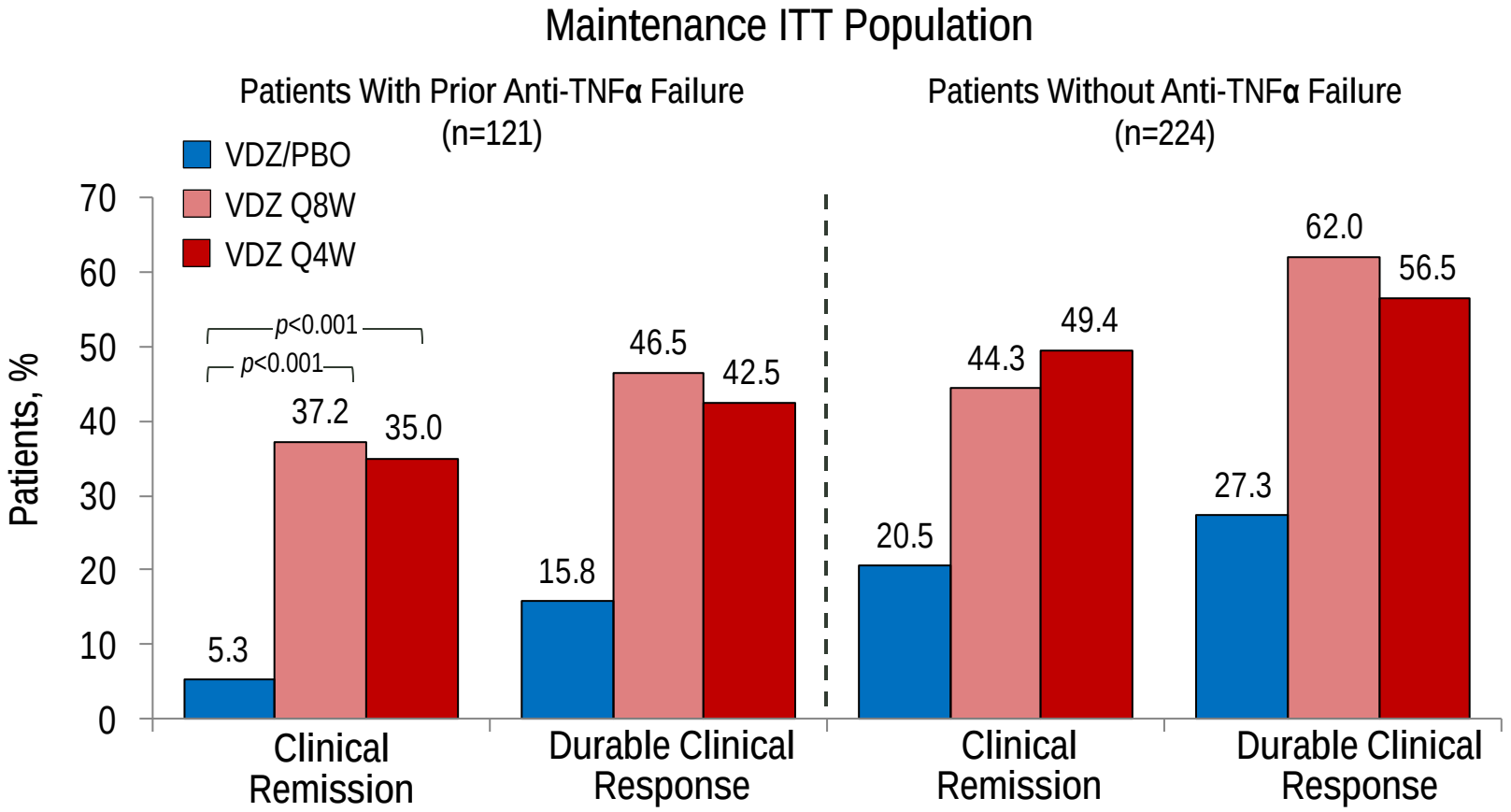
Endpoints in recent UC trials

Trial	Primary endpoint	Main Secondary	Exploratory
ADA *Gut* 2011	Remission w6 (MCS≤2, no SS >1)	Response (δMCS 3, all SS ≥1-0)	
VDZ *NEJM* 2013	Response w6/remission w52	Remission w8, w52, steroid-free, IBDQ	Durable response w6+w52; durable remission
BMMX *Gut* 2013	Remission (SF+RB=0 + full colonoscopy	Response, histopath (Saverymuttu)	
GLM *Gastro* 2014	Response w6 (MCS)	Remission w6; mucosal healing; IBDQ	Continuous clinical response
ETRO *Lancet* 2014	Remission w10, (MCS≤2, no SS >1)	Remission (Endo0 + RB0) at w6 and w10, histo (Geboes)	Change in baseline mucosal healing; histo (Geboes), biomarkers
IFX/AZA/both *Gastro* 2014	Steroid-free remission w16	Mucosal healing	
TRALO *Gut* 2015	Response w8	Remission w8, mucosal healing, histo (Riley)	

GEMINI I: Vedolizumab in UC
Outcomes at week 52 by prior anti-TNFα failure

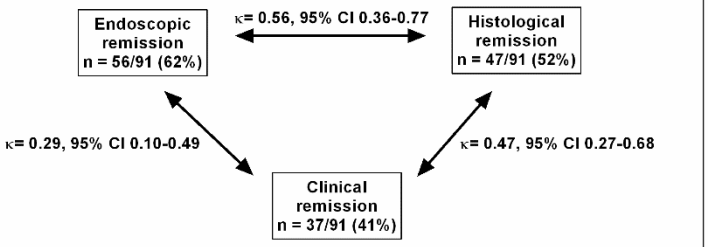


Mean Δ% (95% CI)				
VDZ Q8W:	31.9 (15.8, 48.0)	30.7 (11.8, 49.6)	23.8 (10.0, 37.7)	34.8 (20.6, 48.9)
VDZ Q4W:	29.7 (13.3, 46.1)	26.7 (7.5, 45.9)	29.0 (15.4, 42.5)	29.2 (15.1, 43.3)

VDZ, vedolizumab PBO, placebo;
TNF, tumor necrosis factor.

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

Predictive value of histopathology in UC remission



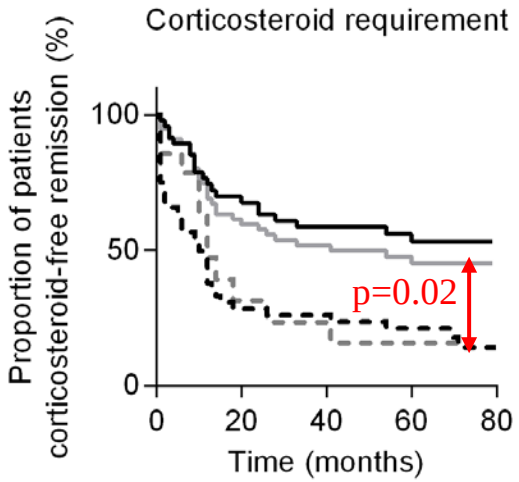
Measure of remission	Concordance with other measures of remission (%)		
	Clinical	Endoscopic	Histological
Clinical (n=37)	100% (n=37)	81% (n=30)	81% (n=30)
Endoscopic (n=56)	54% (n=30)	100% (n=56)	75% (n=42)
Histological (n=47)	64% (n=30)	89% (n=42)	100% (n=47)

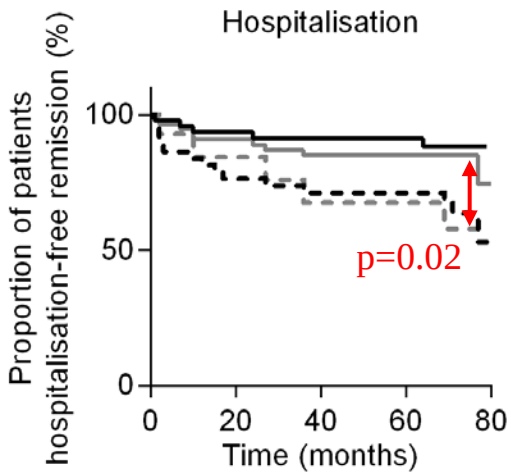
Gut Online First, published on May 18, 2015 as 10.1136/gutjnl-2015-309598
Inflammatory bowel disease

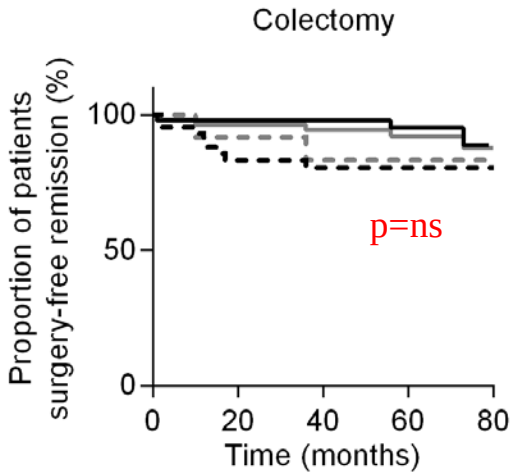
ORIGINAL ARTICLE

Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalisation over 6 years of follow-up

Robert V Bryant, Daniel C Burger, Joseph Delo, Alissa J Walsh, Sally Thomas, Axel von Herbay, Otto C Buchel, Lydia White, Oliver Brain, Satish Keshav, Bryan F Warren, Simon P L Travis







Median follow up 72m (IQR 54-75)

- Histological 'complete' remission^
- Histological activity
- Endoscopic remission
- Endoscopic remission AND histological activity

CD: Considerations

- **Shortcomings of CDAI and HBI**
  - Change driven by subjective GWB
- **Other scoring systems**
  - CDEIS vs SES-CD
  - Rutgeerts'
  - MaRIA, Lémann
- **International opinion**
  - STRIDE
- **Independent evaluation**
  - Endoscopy
  - Biomarker (CRP, fC etc)
- **Exploratory endpoints**
  - PROs
- **Predictors of the long term**
  - Mucosal healing
  - MRI
- **Quality of life outcome**
  - IBDQ/CCQ

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Endpoints in recent CD trials

Trial	Primary endpoint	Main Secondary	Exploratory
UST *NEJM* 2012	Response w6 (CDAI δ-100)	Remission w6 (CDAI<150) Response w4, Rem w22	
ADA *Gastro* 2012 (EXTEND)	Mucosal healing w12	Mucosal healing w52	Deep remission (CDAI<150 and m. healing)
VDZ *NEJM* 2013	Two: CDAI<150 w6 and w52; Response CDAI δ-100	δCRP w6; steroid-free remission	Durable clinical remission (w6-52 >80% CDAI <150)
TOFA *CGH* 2014	Response w4 (CDAI δ-70)	Remission w4;	PRO and patient app; δCRP; faecal calpro
MGSN *NEJM* 2015	Remission: CDAI<150 by d15, sustained to d28	Response CDAI δ-100 at d28	

FDA analysis of CDAI

- FDA Abstract DDW 2014:

Su1083

Can Crohn's Disease Activity Index Differentiate Clinical Remission Induced by Placebo Versus Biologics Treatment? - Analyses of Six Clinical Trials for Crohn's Disease

Yoonhee Kim, Andrew E. Mulberg, Jessica J. Lee, Klaus Gottlieb, Freda Cooner, Sue Chih H. Lee, Li Zhang, Insook Kim

- Response (δCDAI) to placebo and active treatment compared

	Placebo (6 trials)	Active treatment (6 trials)
Mean baseline CDAI	294 - 313	295 - 312
Rate of remission	8.2% - 30.3%	22.2% - 39.6%
Average decrease in CDAI (remitters)	167	186

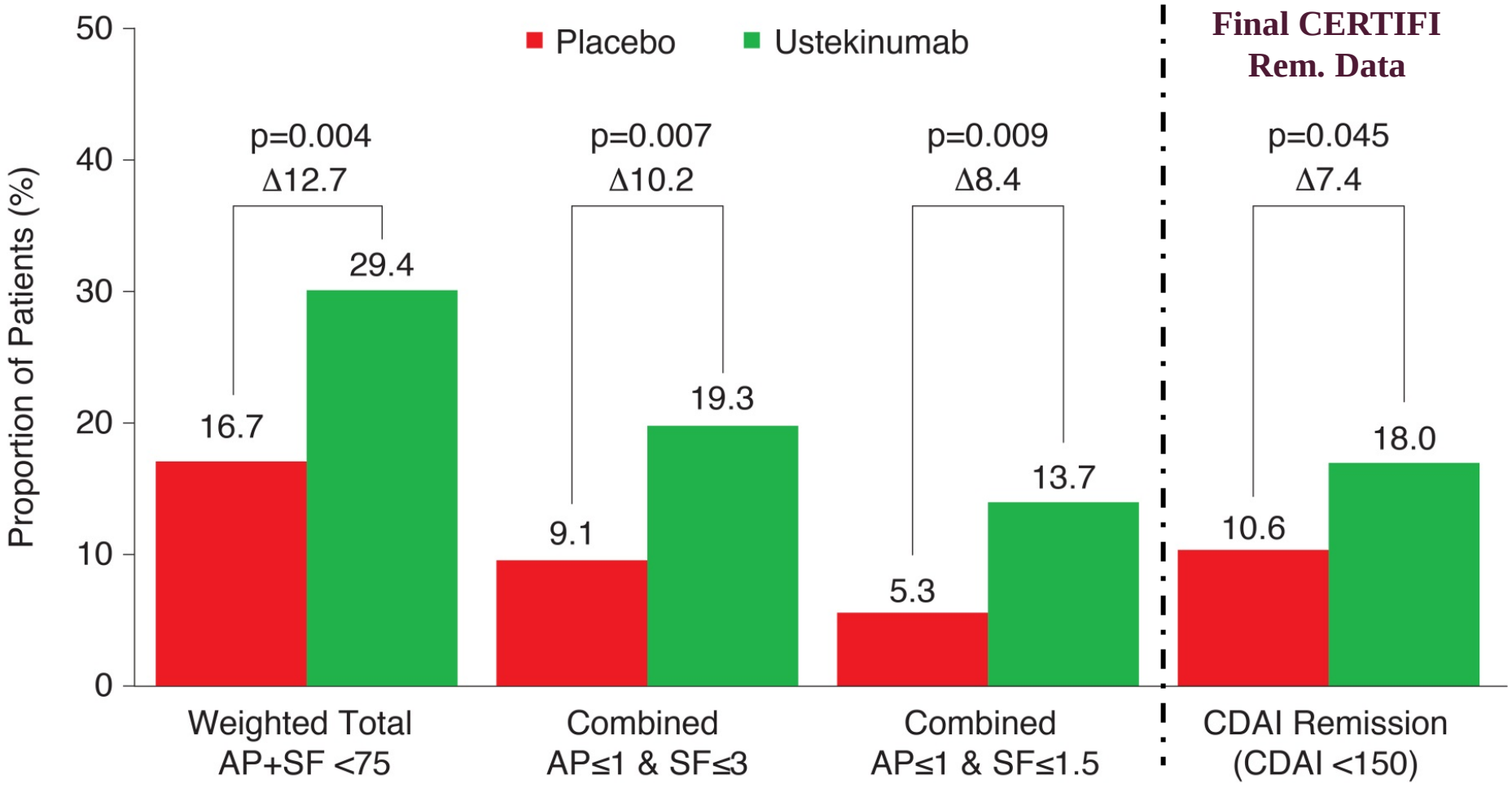
- δCDAI driven by GWB (40%), Abdo Pain (25%) and Stool Freq 22%)
- Relative contribution not different between pbo and active ttmt
- **Conclusion** δGWB contributes most to improvement, especially with high placebo remission rates. Better measures needed to discriminate placebo response from active treatment

Likely FDA recommended CD Endpoints

Co-Primary Endpoint (technically nested co-primary endpoints)

1. **Sign & symptom-based responder definition**
   - **2-component signs/symptoms score: abdominal pain and liquid/soft stool**
     - Bristol Stool Scale (BSS) to provide a definition of stool consistency
     - 10-point ordinal scale to score abdominal pain
   - **Responder definition** (a co-primary in itself)
     - A daily abdominal pain score of 0 or 1/10 for each of the 7 days prior to the assessment time point visit; **AND**
     - Total number of liquid/very soft stools (BSS score 6 or 7) for the 7 days prior to the assessment time point being ≤ 10
2. **Endoscopic responder definition**
   - Based on SES-CD

Candidate PRO-2 remission definitions in combined Ustekinumab vs. Placebo at week 8 of CERTIFI



Conclusions

- Independent assessment of biological disease activity is essential
  - Should not be optional (central reading, histopathology, biomarkers…)
- Continuous clinical response matters for patients
  - A period of disease without flares ('period' needs definition – eg ≥12 months)
  - Confirmed or monitored by biomarker/endoscopy (PROs alone are not enough)
- UC
  - Separate indices for symptoms/endoscopy/QoL
  - Favour SCCAI (symptoms); UCEIS (endoscopy); histopath (Nancy); CCQ (QoL)
- CD
  - Align with FDA?
  - PRO and independent assessment?
- Concordance between EMA and FDA would help
  - Patients, comparisons between trials, trialists and sponsors

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