USTEKINUMAB IN IBD:
FROM THE EXPERIENCE IN CD TOWARDS THE LABEL IN UC

Real-life experience with Ustekinumab in Crohn's disease

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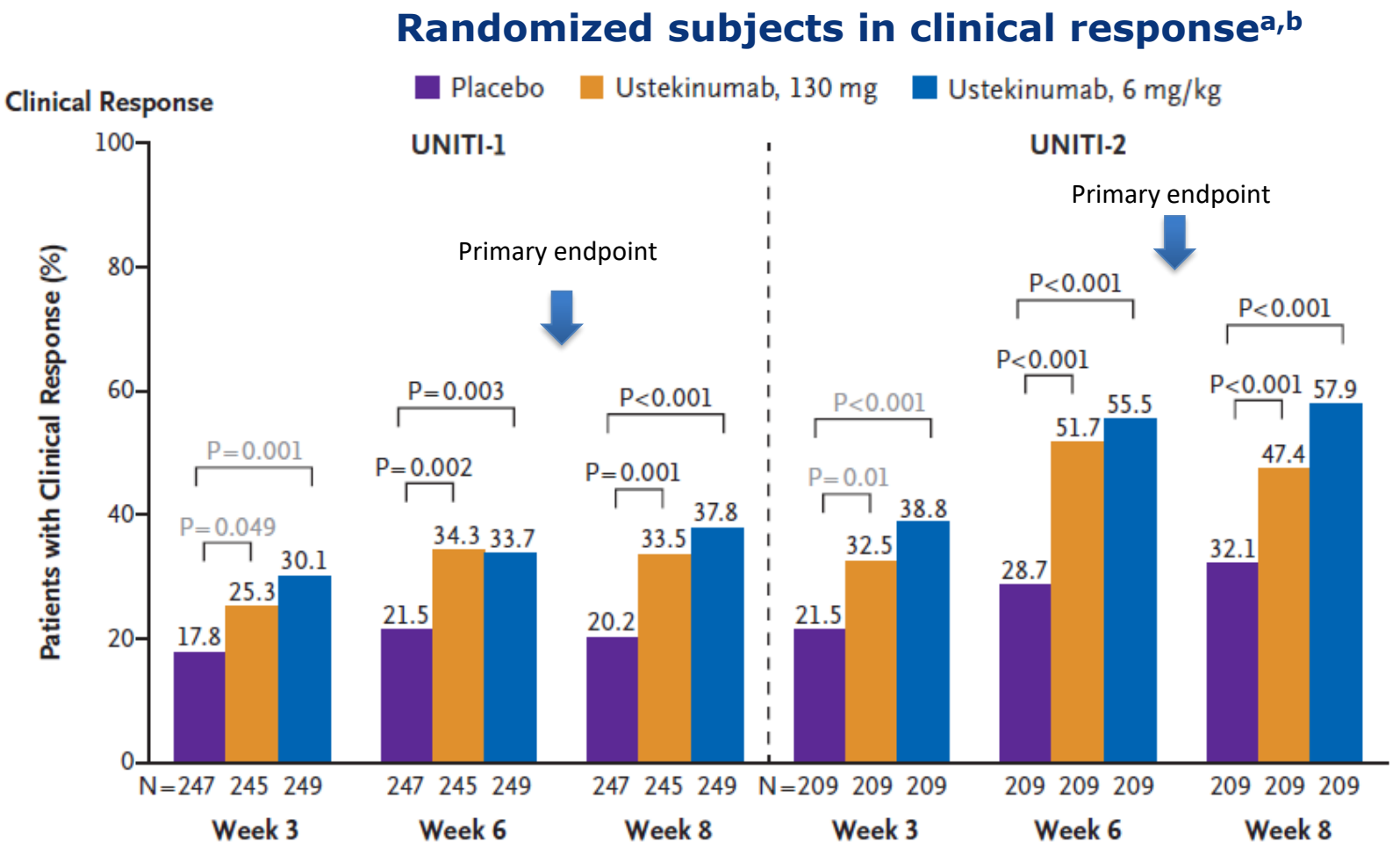
Benefits of real-life data:

- Information collected on drug effectiveness in a practical, real-life setting
- Data obtained from sources beyond what is normally collected in a clinical trial
- Diverse study population
- Useful to understand and move outcomes from clinical trial into clinical practice

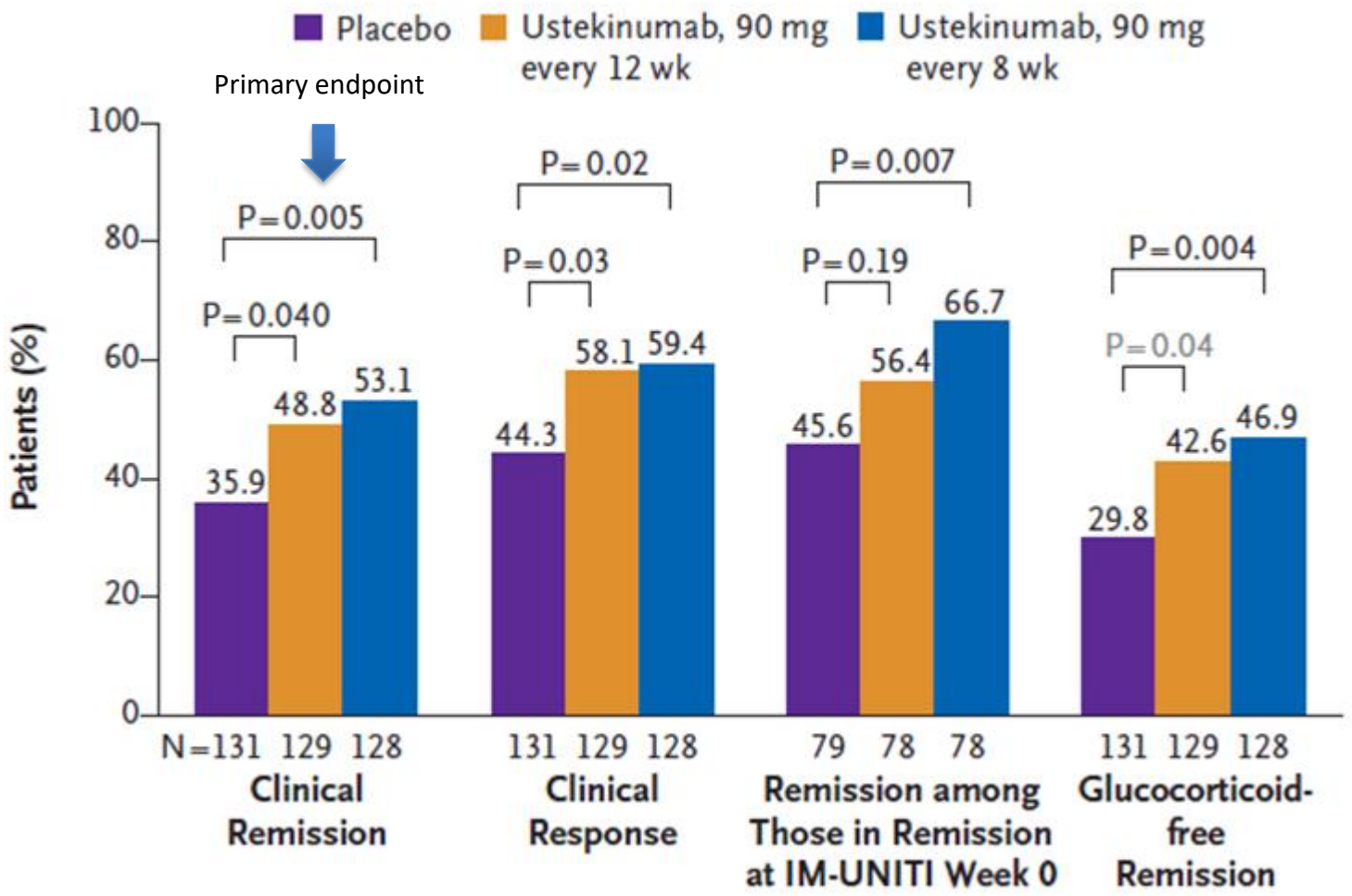
Primary Endpoint: Clinical Response at Week 6



[a]Subjects who had a prohibited Crohn's disease–related surgery or had prohibited concomitant medication changes are considered not to be in clinical response, regardless of their CDAI score.
[b]Subjects who had insufficient data to calculate the CDAI score are considered not to be in clinical response.
* Weight-tiered-based dosing reflecting approximately 6 mg/ kg Ustekinumab IV

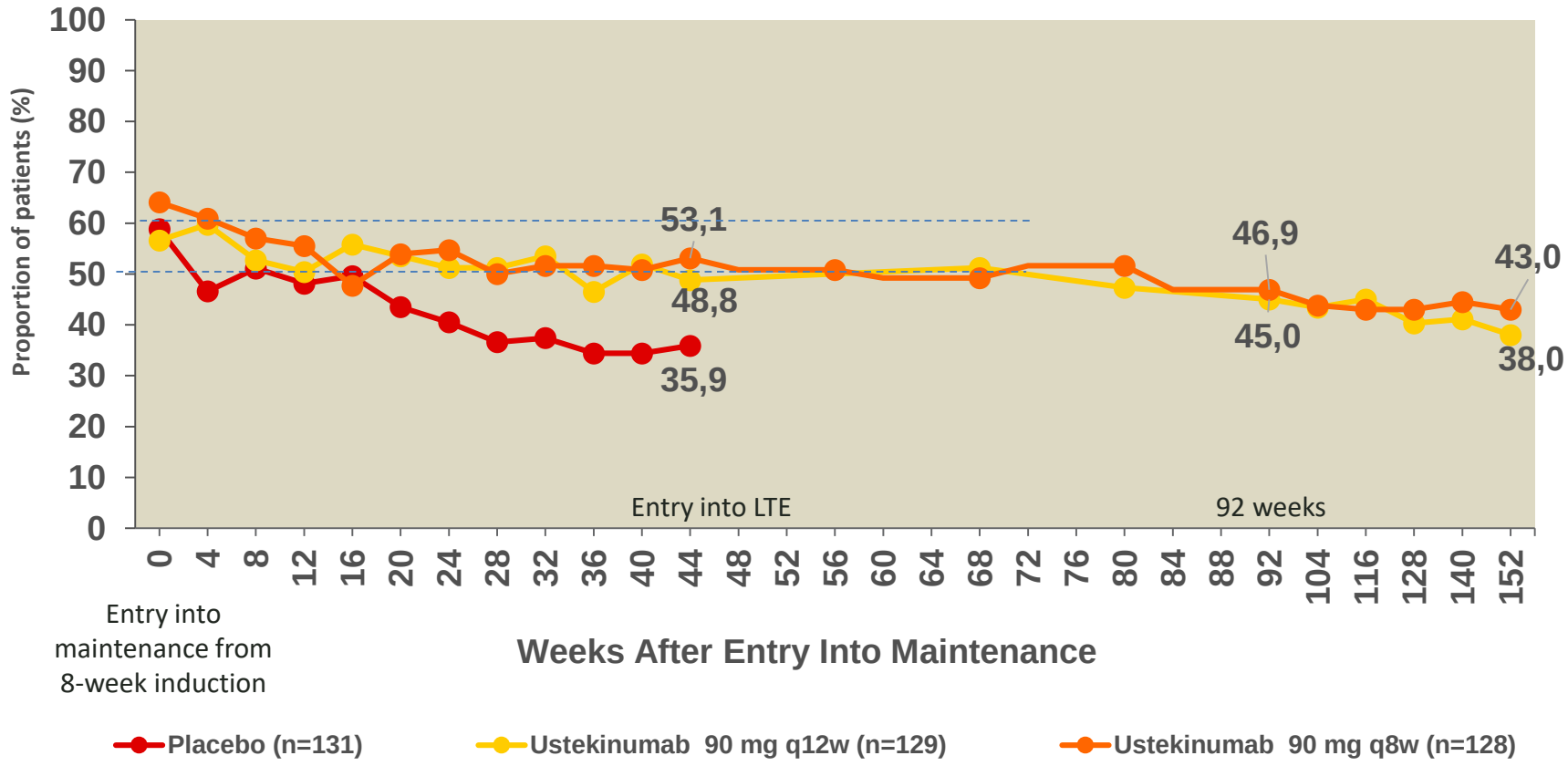
Feagan B. et al., N Engl J Med 2016

IMUNITI Week 44



Feagan B. et al., N Engl J Med 2016.

Clinical Remission of Patients Responding to UST Induction Through Week 152 (**ITT***)



Rate of remission at 3 years in patients who responded to IV induction is ~80% of that seen at 1 year

*Intent-to-treat analysis of IM-UNITI primary population from Week 0; UST: Stelara

Adapted from Sandborn et al. UEGW 2018 #OP306.
Sandborn et al. Aliment Pharmacol Ther 2018

Patients Enrolled in Randomized Controlled Trials Do Not Represent the IBD Patient Population

Clinical trials	Clinical practice
Defined population	Heterogeneous population
Prescribed treatment regimen	Variable treatment regimen with optimisation
Follow-up regimented with schedule	Follow-up not fixed
Uniform primary endpoint	Variable outcomes
Efficacy	Effectiveness

The IBD population: clinical trial versus clinical practice

Retrospective study of patients with moderate-severe IBD at a US tertiary referral centre (n=206)

31% of patients were not eligible for participation in a clinical trial of biologic therapy*

Reasons for exclusion in CD

- **Strictures or abscesses** (62%)
- **Recent exposure or nonresponse to anti-TNF** (51%)
- **High-dose steroids** (18%)
- **Comorbidities** (26%)

Reasons for exclusion in UC

- **Current rectal therapy use** (57%)
- **Steroid and immunomodulator naïve** (45%)
- **Newly diagnosed** (17%)
- **Colectomy likely** (15%)

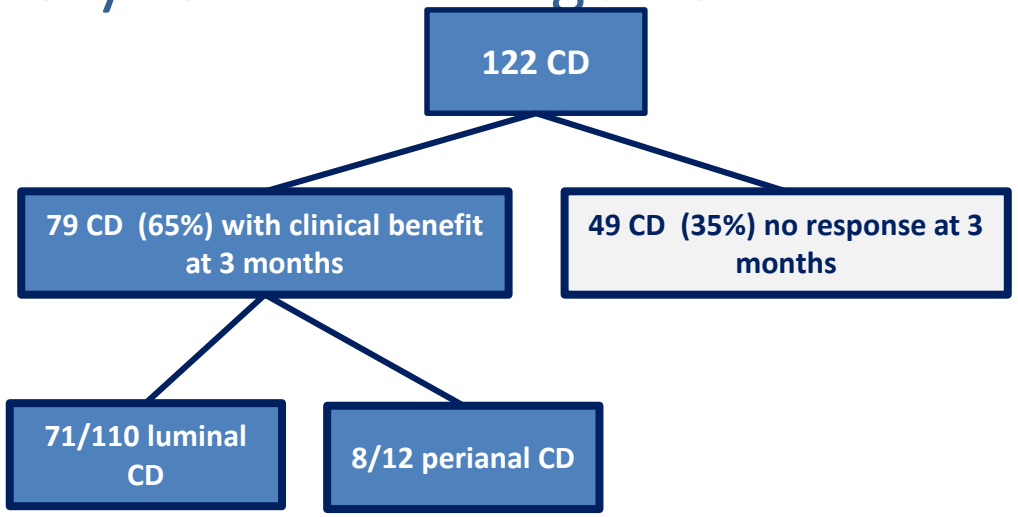
Non-eligible CD patients had a significantly lower response rate to biologics than eligible CD patients (60% vs 89%, *p*=0.03) **4–12 weeks after initial visit**

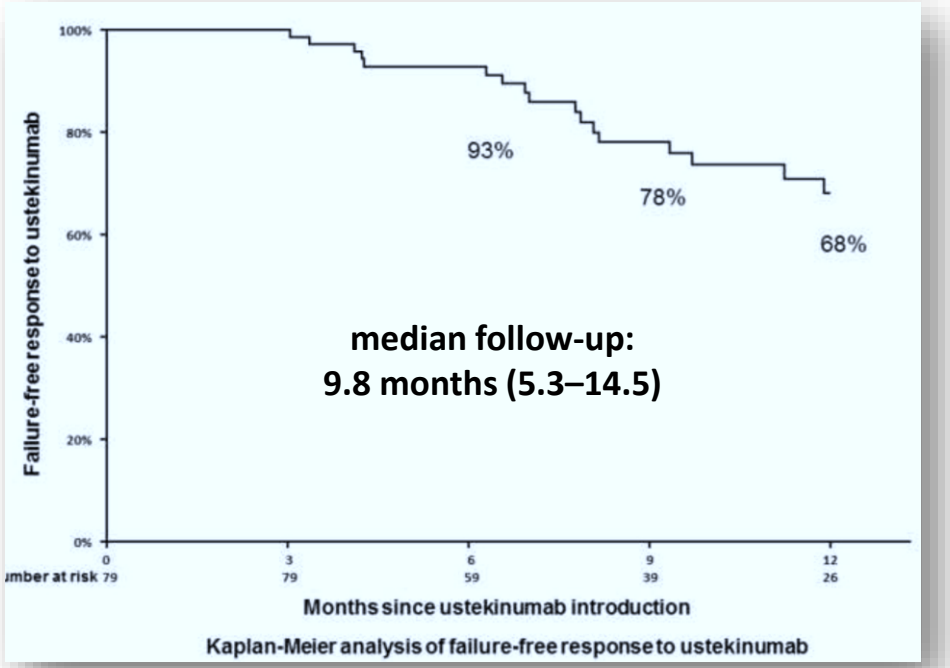
***Inclusion criteria based on those published for 9 trials of biologic therapy: ACCENT I, CLASSIC I, CHARM, PRECISE I, ENCORE, ENACT, SONIC, ACT 1, ACT 2**

Ha C, *et al. Clin Gastroenterol Hepatol* 2012.

Ustekinumab Provides Clinical Benefit for Two-Thirds of Patients With Crohn's Disease Refractory to Anti-TNF Agents

Characteristics	Patients (n=122)
Gender (female) - %	71
Age (years) – median	33.8
Disease Duration (years) – median	11.5
Previous intestinal resection - %	62
Abnormal CRP %	69
Reason for Ustekinumab introduction - % Luminal disease Perianal disease	 90 10
Concomitant corticosteroid – %	16
Concomitant immunosuppressants - %	15
Previous immunosuppressants - %	98
Previous failed anti-TNFs - % 1 TNF antagonist 2 TNF antagonists 3 TNF antagonists	 100 92 37

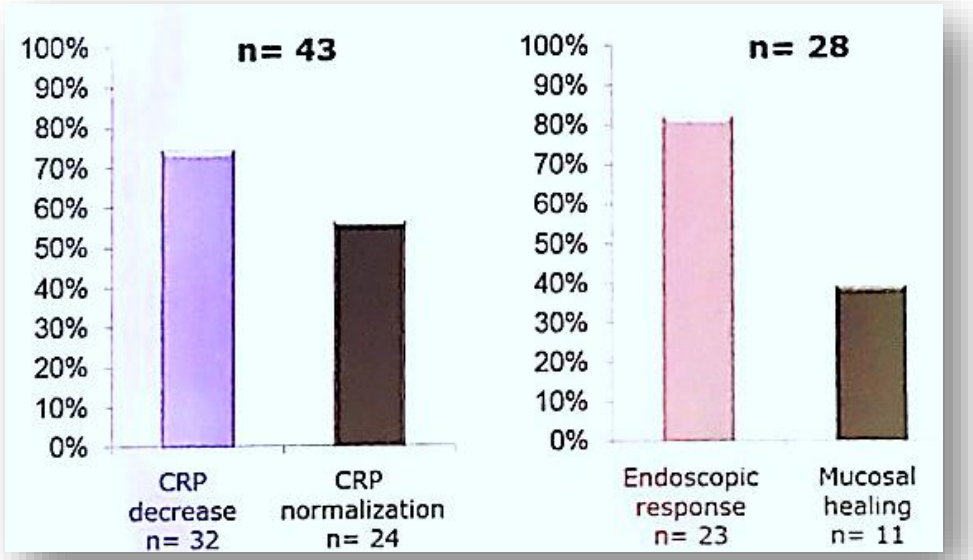


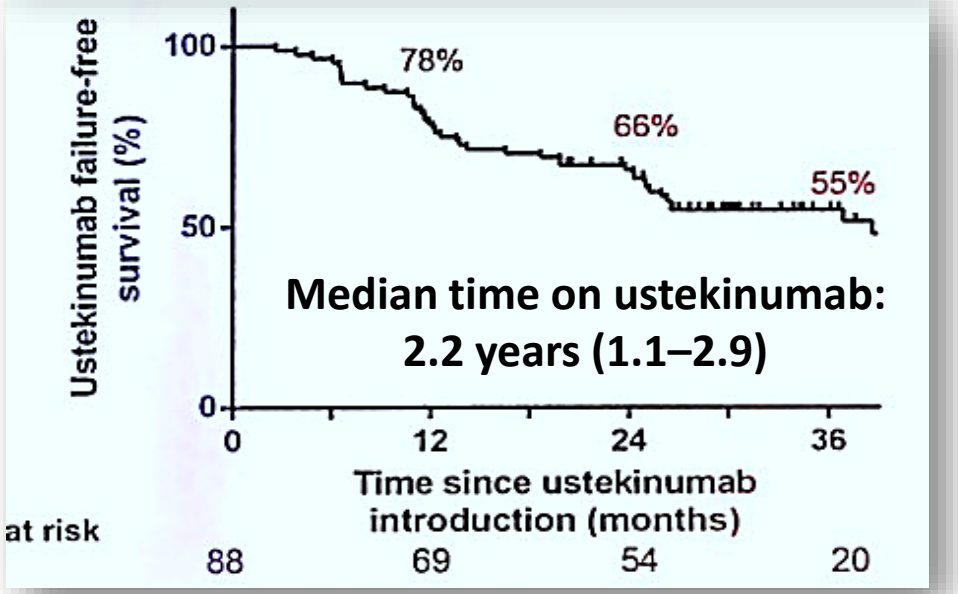


Wils P, et al. Clin Gastroenterol Hepatol 2016

Long Term Efficacy And Safety Of Ustekinumab In Refractory Crohn's Disease Patients

Characteristics	Patients (n=88)
Gender (female) - %	73
Age (years) – median	32.5
Disease Duration (years) – median	11.8
Previous intestinal resection - %	64
Abnormal CRP %	69
Reason for Ustekinumab introduction - % Luminal disease Perianal disease	 90 10
Concomitant corticosteroid – %	15
Concomitant immunosuppressants - %	15
Previous immunosuppressants - %	98
Previous failed anti-TNFs - % Infliximab Adalimumab Certolizumab	100 97 90 35

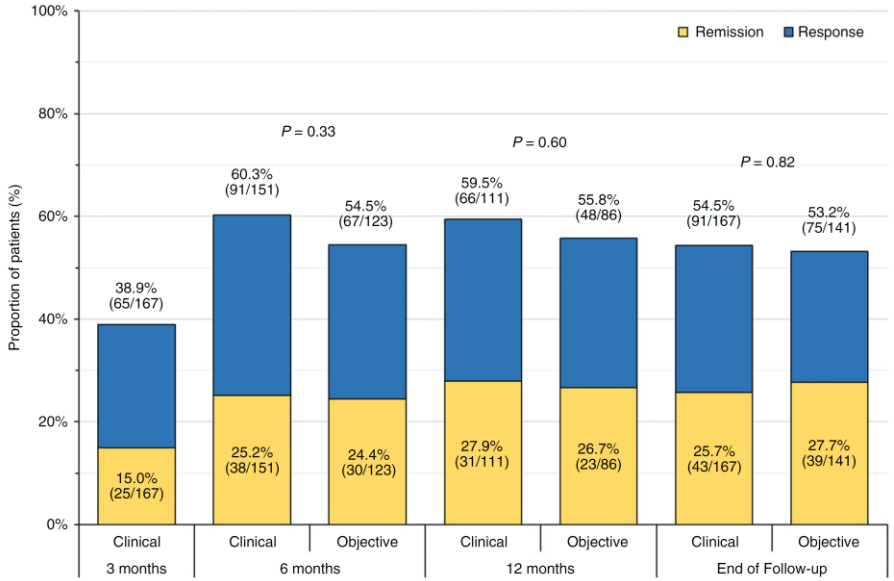


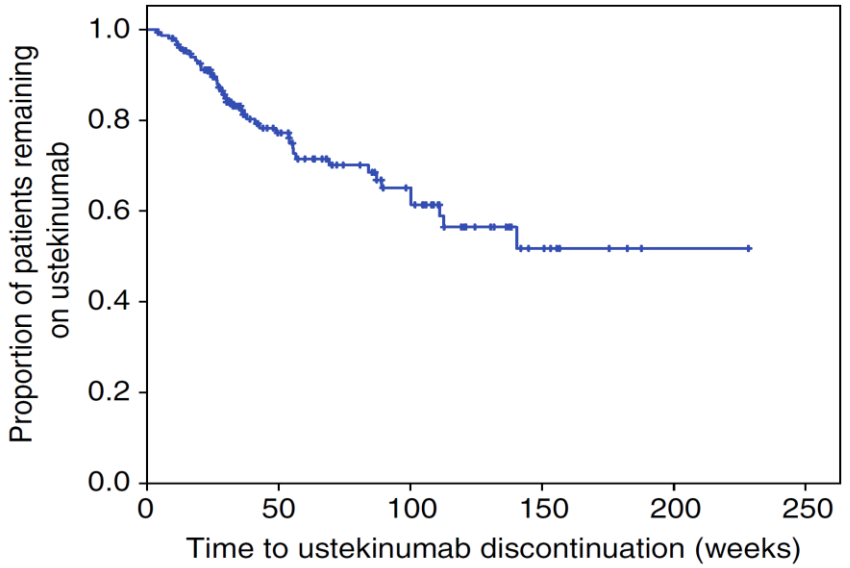


Wils P, et al. UEGW 2017

Clinical and objective outcomes with Ustekinumab in medically-refractory Crohn's disease

Characteristics	Patients (n=167)
Gender (female) - %	56
Age (years) – median	44.6
Disease Duration (years) – median	14.3
Previous intestinal resection - %	66.5
Median CRP (mg/L)	7.8
Median HBI	8
Concomitant corticosteroid – %	43.1
Concomitant immunosuppressants - %	43.7
Previous immunosuppressants - %	75.4
Previous failed anti-TNFs - % 1 TNF antagonist 2 TNF antagonists 3 TNF antagonists	95.2 25.1 55.7 14.4
Median follow-up (weeks)	45.6





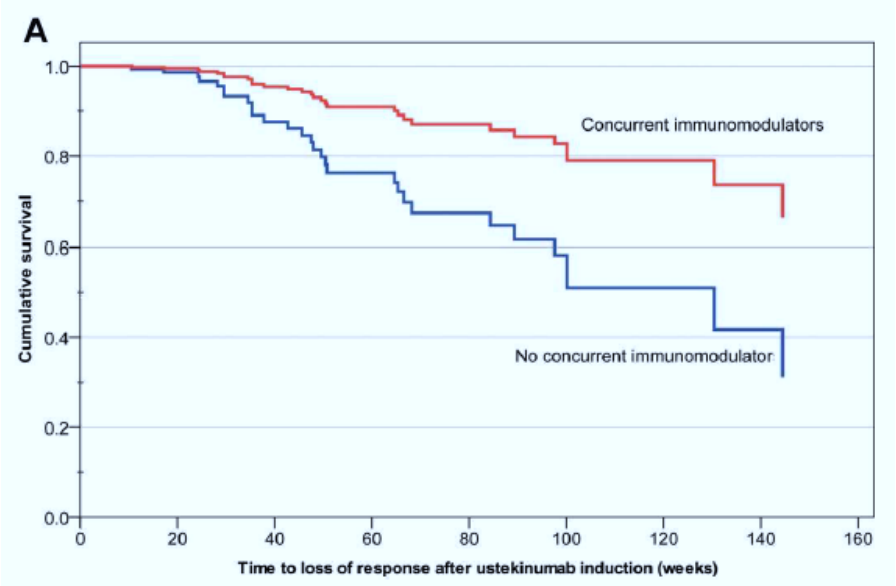
Ma C, et al. Aliment Pharmacol Ther 2017

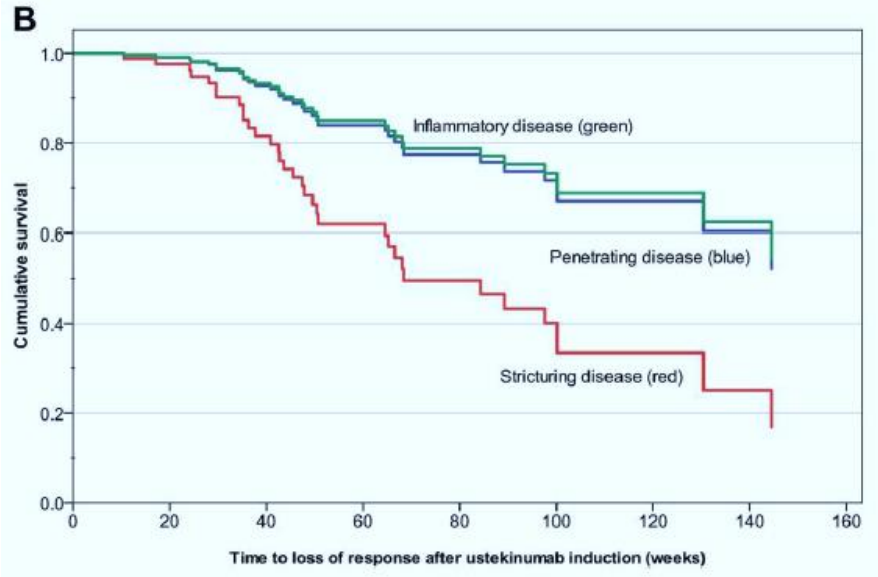
Long-term maintenance of clinical and objective outcomes with Ustekinumab in medically-refractory Crohn's disease

Characteristics	Patients (n=104)
Gender (female) - %	56.7
Age (years) – median	44.6
Disease Duration (years) – median	13.8
Previous intestinal resection - %	63.5
Perianal disease - %	24
Median CRP (mg/L)	9.1
Median HBI	8
Concomitant corticosteroids - %	38.5
Concomitant immunosuppressants - %	42.3
Previous failed anti-TNFs - % Infliximab Adalimumab	92.3 85.6 75.0
Median follow-up (weeks)	57.2

35 (33.7%) lost response after a median time of 47.5 weeks

Ma C, et al. Inflamm Bowel Dis 2017





Real-world short-term effectiveness of Ustekinumab in 305 patients with Crohn's disease: results from the ENEIDA registry

Characteristics	Patients (n=305)
Gender (female) - %	51
Age (years) – median	43,7
Disease Duration (years) – median	11,7
Previous intestinal resection - %	56
Median CRP (mg/L)	7.8
Median HBI	8
Concomitant corticosteroid – %	36
Concomitant immunosuppressants - %	40
Perianal disease- n %	41
Previous anti-TNFα experience- % 1 TNF antagonist 2 TNF antagonists ≥3 TNF antagonists	96 32 49 15
Previous Vedolizumab	29

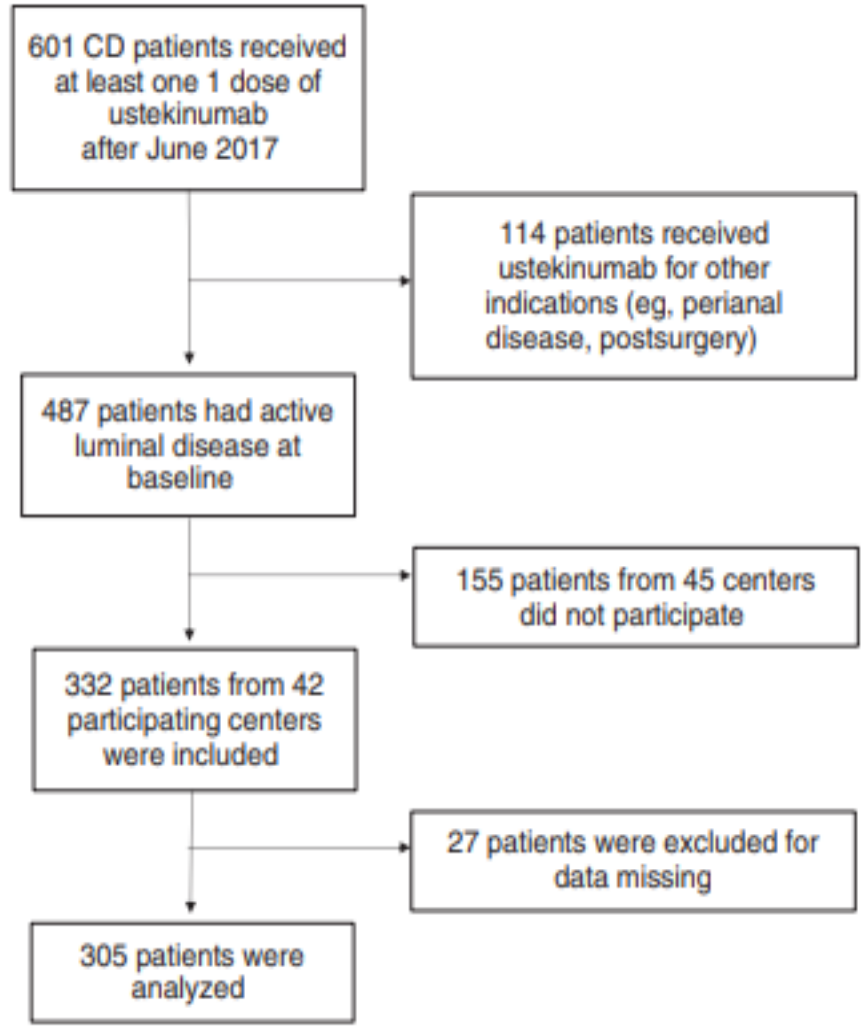
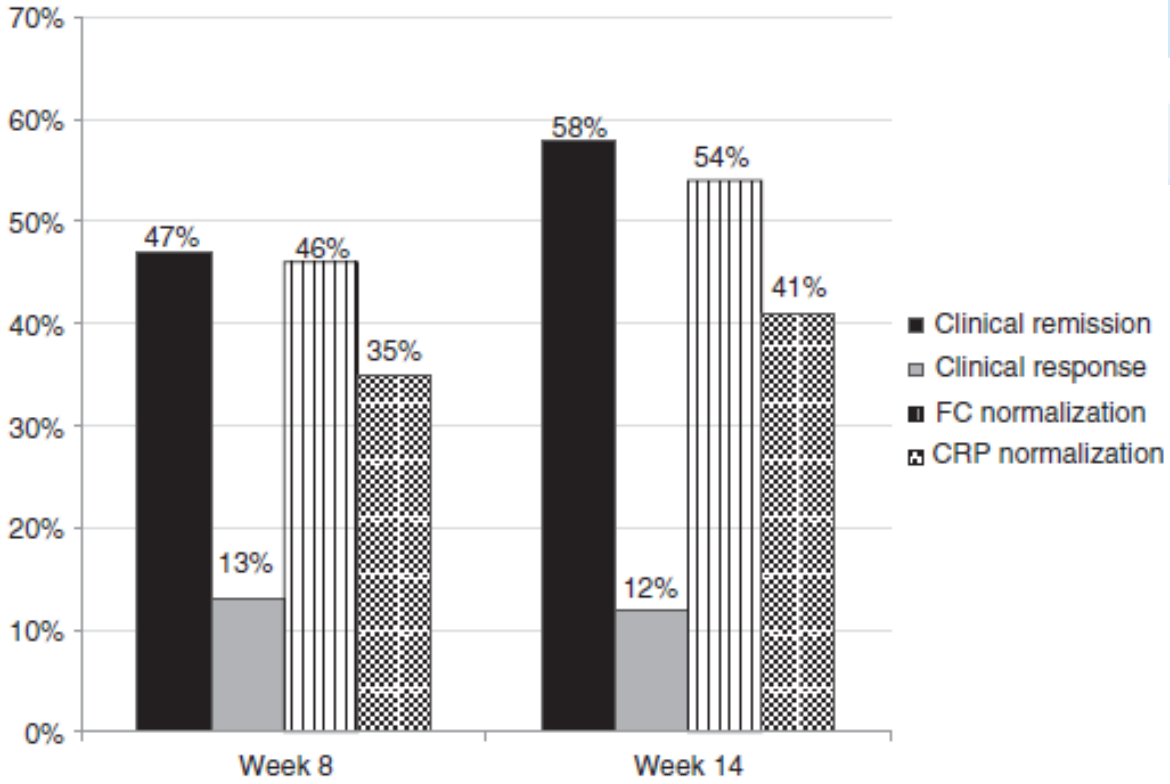


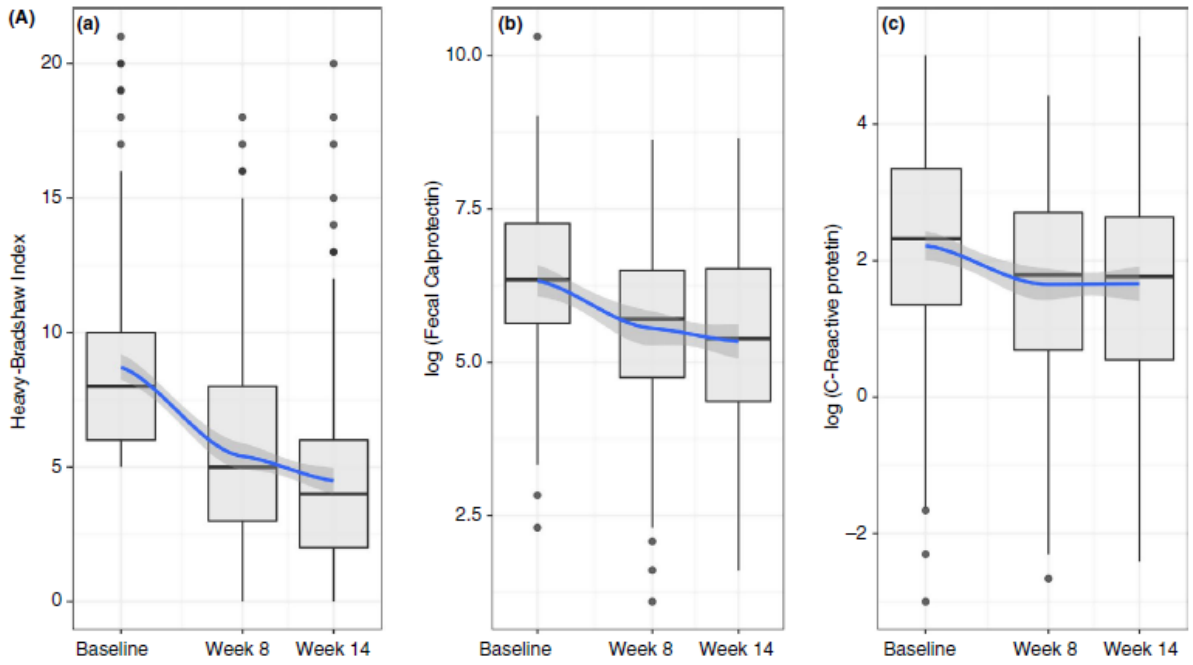
FIGURE 1 Flowchart of the study

Iborra M., Aliment Pharmacol Ther. 2019

Real-world short-term effectiveness of Ustekinumab in 305 patients with Crohn's disease: results from the ENEIDA registry



Number of previous anti-TNFα agents	0	1	2	3	4
All patients (n = 305)	9/11 (91)	76/98 (78)	98/151 (65)	19/35 (54)	4/10 (40)
Patients with previous vedolizumab (n = 87)	2/2 (100)	13/15 (87)	21/41 (51)	12/23 (52)	1/6 (17)



Iborra M., Aliment Pharmacol Ther. 2019

Real-world short-term effectiveness of Ustekinumab in 305 patients with Crohn's disease: results from the ENEIDA registry

TABLE 3 Preiated with ustekinumab-induced clinical remission at week 14. Multivariate analysis

Variable	OR	95% CI		*P*-value
Number of previous anti-TNFα drugs	0.65	0.441	0.95	0.027*
Naïve to anti-TNFα drugs	2.35	0.337	47.94	0.459
Previous anti-TNFα experience				
Primary failure	1.00	0.63	1.78	0.891
Secondary failure	1.01	0.55	1.83	0.981
Adverse events	2.59	1.13	6.30	0.029*
Previous vedolizumab	0.66	0.37	1.20	0.173
Disease behaviour				
Inflammatory	1.48	0.54	4.29	0.457
Stricturing	1.58	0.65	4.09	0.329
Penetrating	0.84	0.34	2.14	0.7
Disease location				
Colonic	0.72	0.32	1.62	0.425
Ileocolonic	1.05	0.59	1.87	0.858
Immunomodulators at baseline	1.37	0.80	2.34	0.25
Activity at baseline				
Faecal calprotectin levels	1	1	1.01	0.385
C-reactive protein levels	0.99	0.98	1.01	0.618
Severe endoscopic activity	0.08	0.01	0.37	0.004[a]

*statistically significant.

TABLE 4 Number of adverse events observed during the 14-week follow-up period

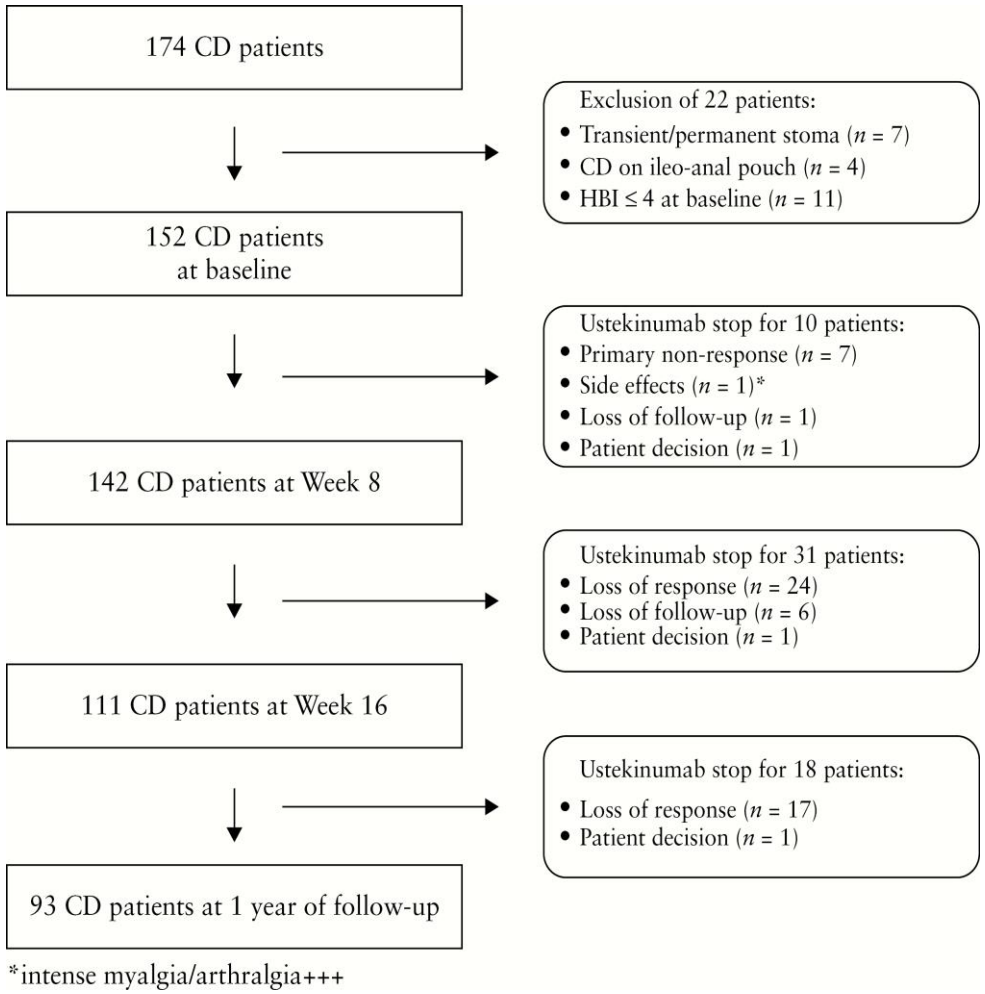
Adverse events	*n* = 38 (12%)
Dermatological events	10
Headache	1
Abdominal pain	1
Nausea	1
Fatigue	1
Infections	11
Respiratory (pneumonia, nasopharyngitis, pharyngotonsillitis[a], influenza)	6
Gastrointestinal (*Clostridium*[a] and *Campylobacter jejuni*)	2
Urinary (prostatitis, *Escherichia coli*, *Klebsiella*)	3
Flu-like syndrome	2
Arthralgia	3
Intestinal obstruction[a]	3
Abdominal septic shock[a]	1
Abscess	4
Perianal	2
Abdominal (psoas)[a]	1
Tonsil	1

[a]Adverse events leading to hospitalisation.

Iborra M., Aliment Pharmacol Ther. 2019

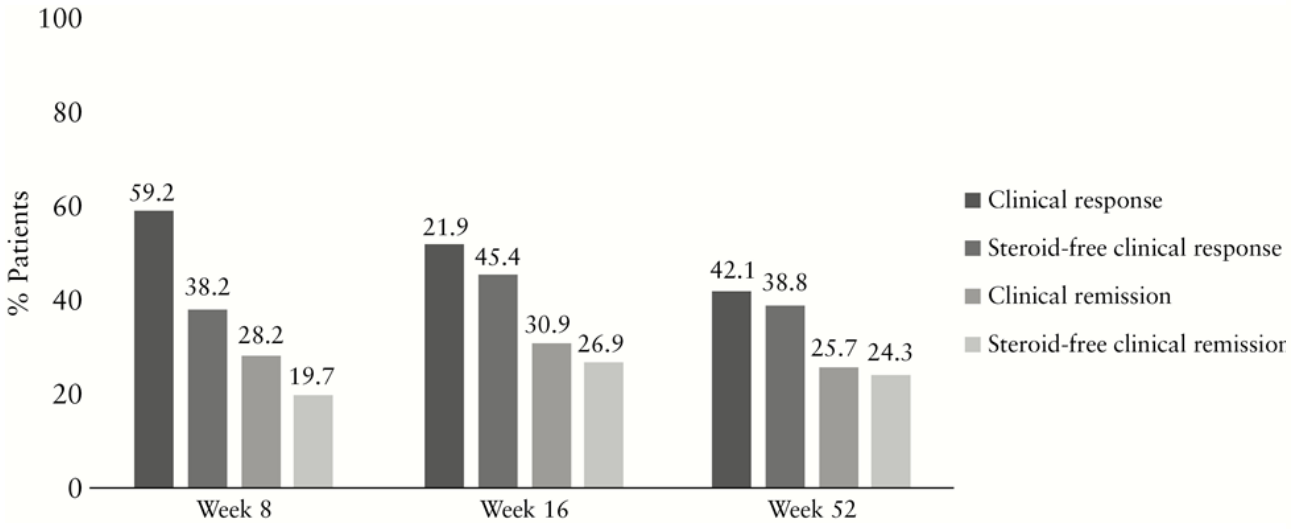
Long-term clinical effectiveness of Ustekinumab in patients with Crohn's disease who failed biological therapies: a national cohort study

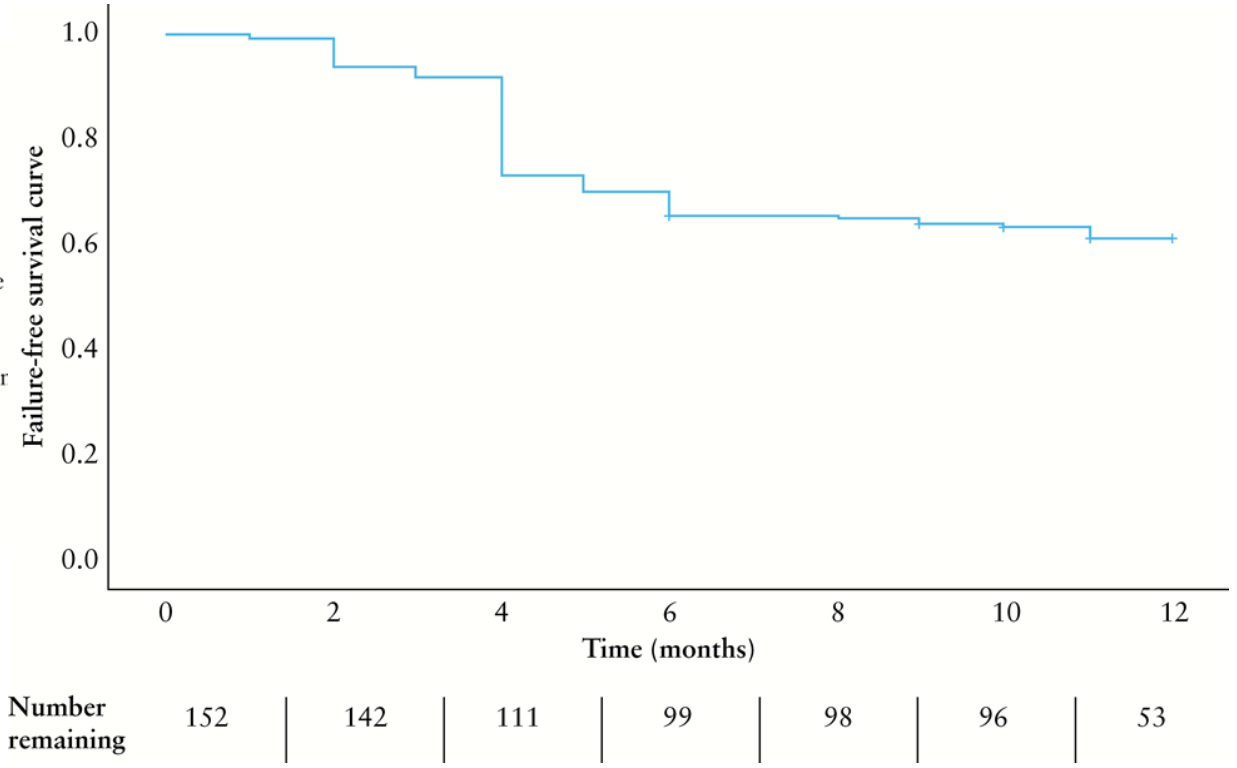
Characteristics	Patients (n=152)
Gender (female) - %	69,1
Age (years) – median	41
Previous intestinal resection - %	59.2
Perianal disease - %	40.8
Concomitant EIMs- %	26,9
Median CRP (mg/L)	16,2
Median HBI	10
Concomitant corticosteroids - %	44.7
Concomitant immunosuppressants - %	15.9
Previous exposure to anti-TNFα - % **1** **2** **2 Anti TNFα + Vedolizumab**	 99.4 82.2 69.7



Liefferinckx et al., J Crohns Colitis. 2019

Long-term clinical effectiveness of Ustekinumab in patients with Crohn's disease who failed biological therapies: a national cohort study





Uste was stopped in 38.8% of patients over the 12 months of fup

Liefferinckx et al., J Crohns Colitis. 2019

Variables associated with Ustekinumab response at 1 year of fup

Table 2. A Variables associated with ustekinumab response at 1 year of follow-up

	Univariate analysis			Multivariate analysis		
	p-value	OR	95% CI	*p*-value	OR	95% CI
Age	0.3	0.9	0.96–1.01			
Sex	0.52	0.8	0.39–1.61			
Age at diagnosis	0.9	0.99	0.97–1.03			
Perianal disease	0.6	1.2	0.62–2.3			
Ileal disease [L1]	0.9	1.05	0.43–2.58			
Colonic disease [L2]	0.03	2.5	1.08–5.80	0.01	3.55	1.34–9.41
Ileo-colonic disease [L3]	0.06	0.5	0.26–1.03			
Inflammatory behaviour [B1]	0.7	0.88	0.46–1.7			
Stricturing behaviour [B2]	0.43	0.75	0.37–1.53			
Penetrating behaviour [B3]	0.21	1.6	0.77- 3.34			
No history of CD surgery	0.84	0.94	0.48–1.8			
Smoking status	0.8	0.9	0.45–1.85			
BMI < 18	0.08	0.37	0.12–1.15			
Steroids at baseline	0.06	0.54	0.27–1.04			
IMM at baseline	0.8	0.9	0.38–2.2			
CRP > 10 mg/L at baseline	0.06	1.03	1.007–1.05			
Albumin < 40 g/L at baseline	0.02	0.4	0.18–0.87			
USK trough level at Week 8	0.34	0.9	0.86–1.05			

Liefferinckx et al., J Crohns Colitis. 2019

Variables associated with Ustekinumab remission at 1 year of fup

Table 3. Variables associated with ustekinumab remission at 1 year of follow-up

	Univariate analysis			Multivariate analysis		
	p-value	OR	95% CI	*p*-value	OR	95% CI
Age	0.3	0.9	0.96–1.01			
Sex	0.41	0.71	0.31–1.61			
Age at diagnosis	0.52	0.99	0.95–1.02			
Perianal disease	0.4	1.4	0.66–2.88			
Ileal disease [L1]	0.6	0.77	0.26–2.23			
Colonic disease [L2]	0.19	1.8	0.74–4.33			
Ileo-colonic disease [L3]	0.47	0.76	0.35–1.62			
Inflammatory behaviour [B1]	0.24	0.64	0.3–1.35			
Stricturing behaviour [B2]	0.78	0.89	0.39–1.99			
Penetrating behaviour [B3]	0.1	1.93	0.87- 4.25			
History of CD surgery	0.4	0.74	0.35–1.54			
Smoking status	0.4	1.4	0.65–3.05			
BMI < 18	0.03	0.28	0.09–0.87	0.008	0.18	0.05–0.64
Steroids at baseline	0.06	0.54	0.27–1.04			
IMM at baseline	0.8	0.9	0.38–2.2			
CRP > 10 mg/L at baseline	0.04	2.4	1.03–5.4			
Albumin < 40 g/L at baseline	0.01	0.29	0.11–0.78			
USK trough level at Week 8	0.57	0.96	0.85–1.09			

Liefferinckx et al., J Crohns Colitis. 2019

Adverse events and surgery

Table 4. Adverse events and surgery

Total numbers of adverse events, *n*	11
Allergic reaction IV ustekinumab infusion	1
Intense arthralgia	2
Deep venous thrombosis	1
Spontaneous abortion	1
Infections	5
Gastroenteritis	3
Pyelonephritis	1
Pneunomia	1
Abdominal abscess	1
Total numbers of CD surgery, *n*	17
Fistula surgery	4
Colostomia	1
Definitive ileostomia	2
Resection	6
Not described	3

Liefferinckx et al., J Crohns Colitis. 2019

Ustekinumab for Crohn's Disease: Results of the *ICC Registry*, a Nationwide Prospective Observational Cohort Study

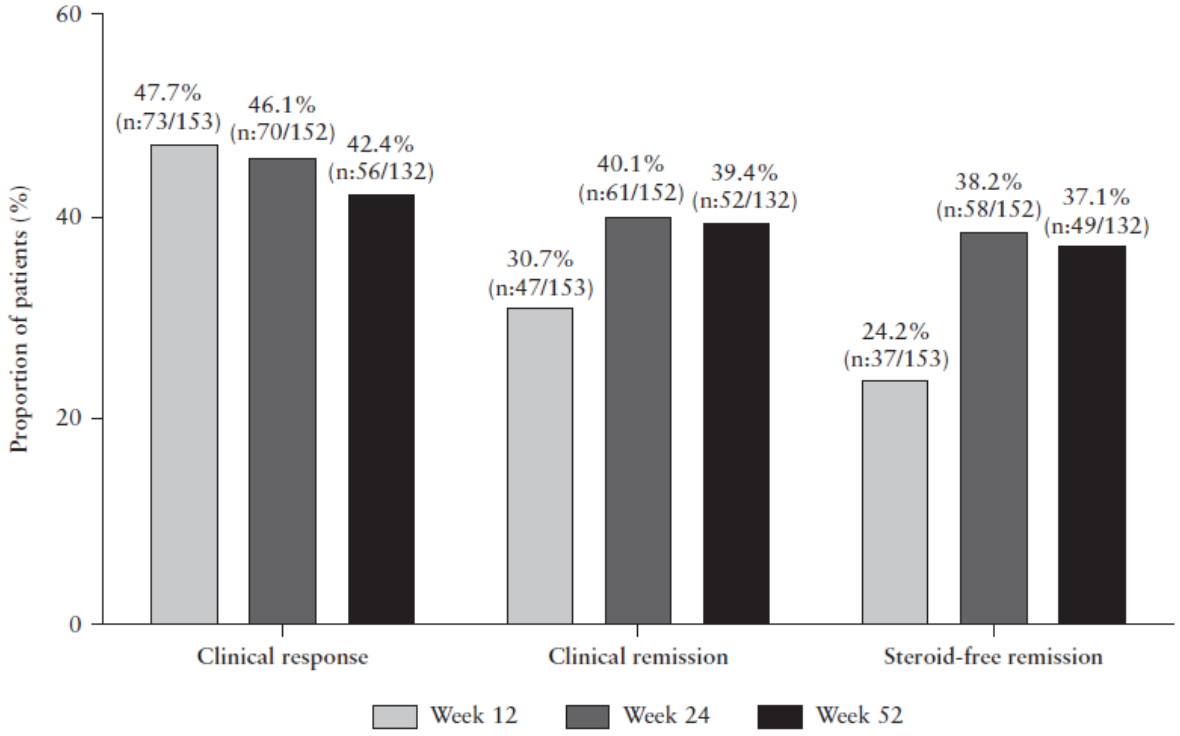
Characteristics	Patients (n=221)
Gender (male) - %	39.8
Age (years) – median	38.2
Disease Duration (years) – median	12.3
Previous intestinal resection - %	62
Median CRP (mg/L)	9
Median HBI	7
Perianal disease	16.7
Concomitant corticosteroid – %	15.8
Concomitant immunosuppressants - %	19.9
Previous anti-TNFα experience- % **≥1 TNF antagonist** **≥2 TNF antagonists** **3 TNF antagonists**	 98.6 73.3 5
Previous Vedolizumab	46.6
Previous anti-TNFα + Vedolizumab	46.2

Median of 52.0 weeks [IQR 49.3–58.4].

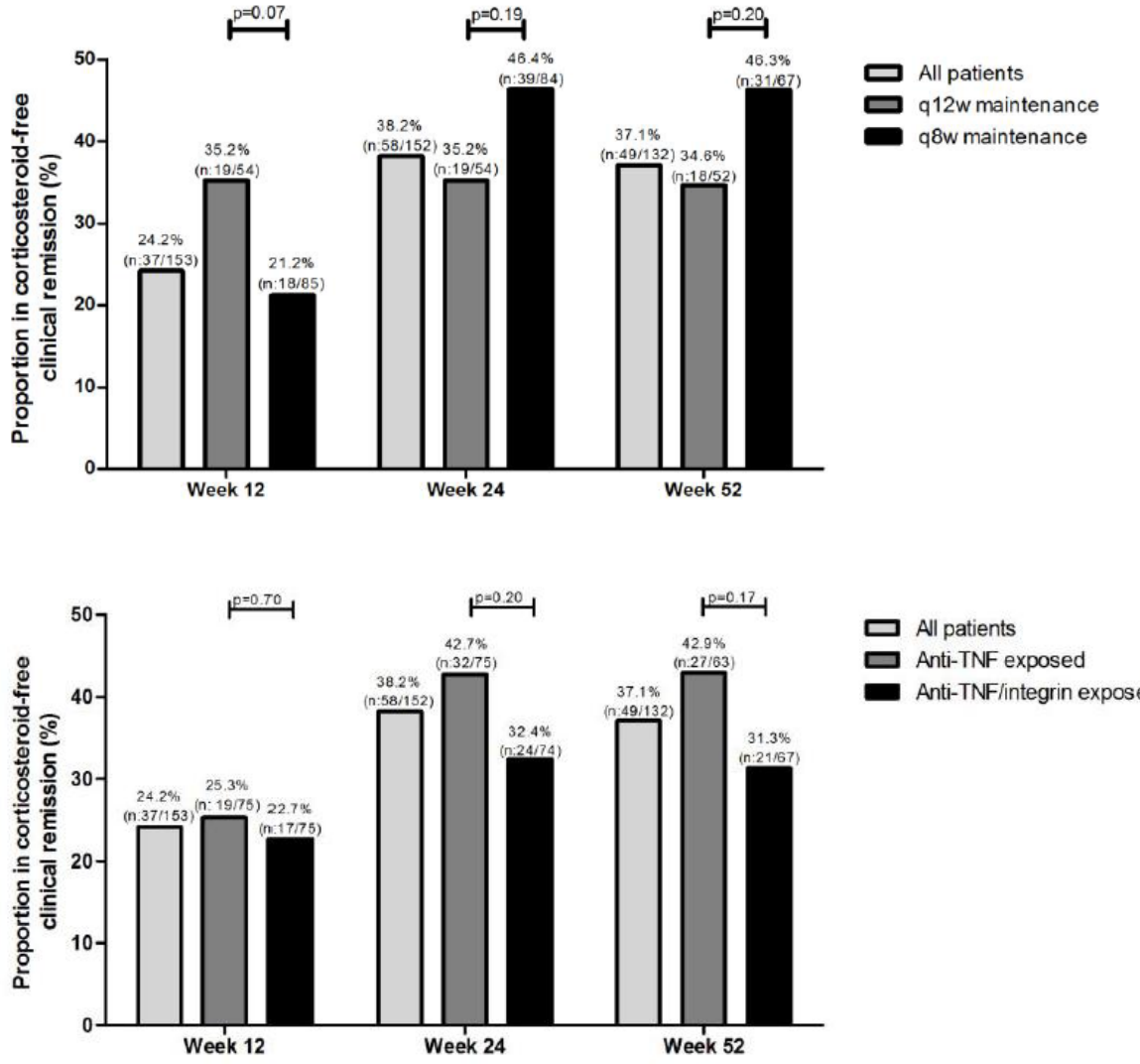
Maintenance interval:
85 pts q8w
54 pts q12w

Biemans V., J Crohns Colitis. 2019

Ustekinumab for Crohn's Disease: Results of the *ICC Registry*, a Nationwide Prospective Observational Cohort Study

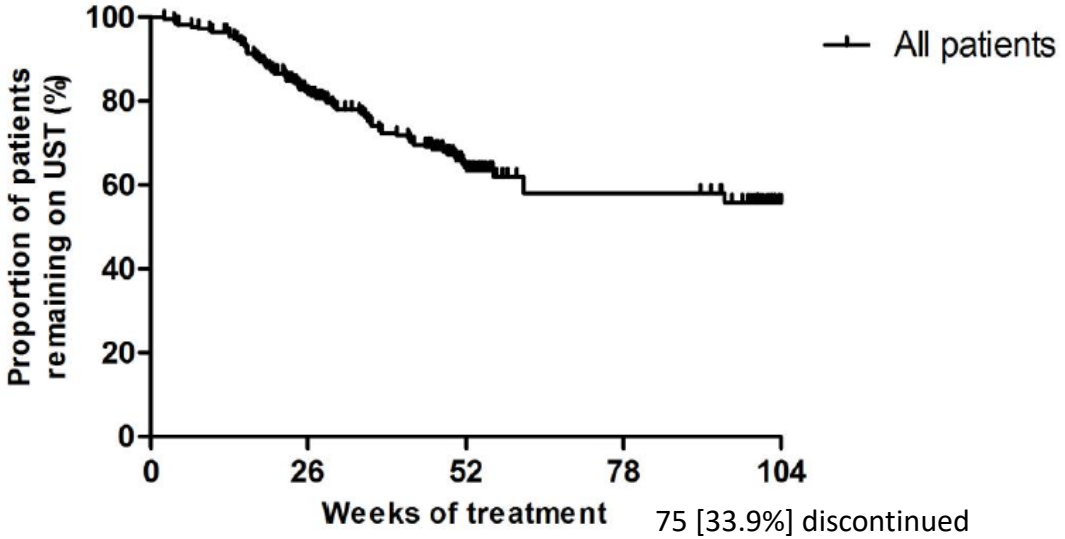


I. Proportion of patients with clinical response, clinical remission and corticosteroid-free clinical remission.



Biemans V., J Crohns Colitis. 2019

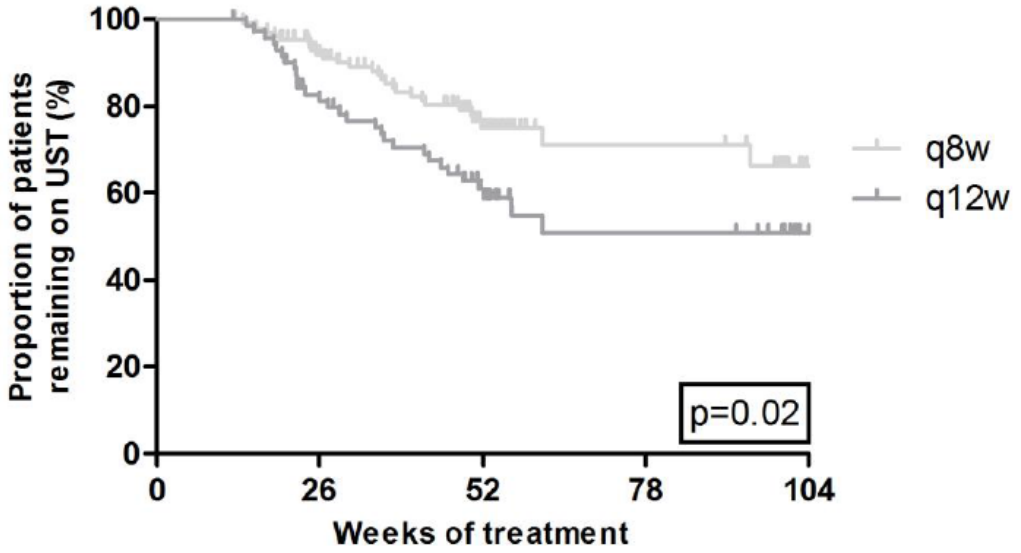
Ustekinumab for Crohn's Disease: Results of the *ICC Registry*, a Nationwide Prospective Observational Cohort Study

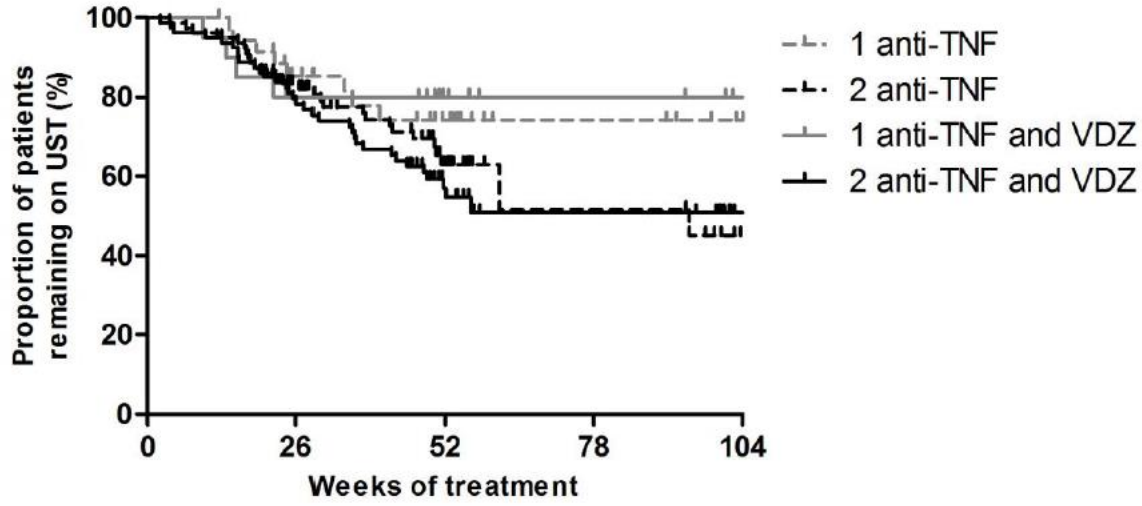


75 [33.9%] discontinued after a median 24.6 weeks [IQR 15.9–37.8]

Table 4. Discontinuation visit

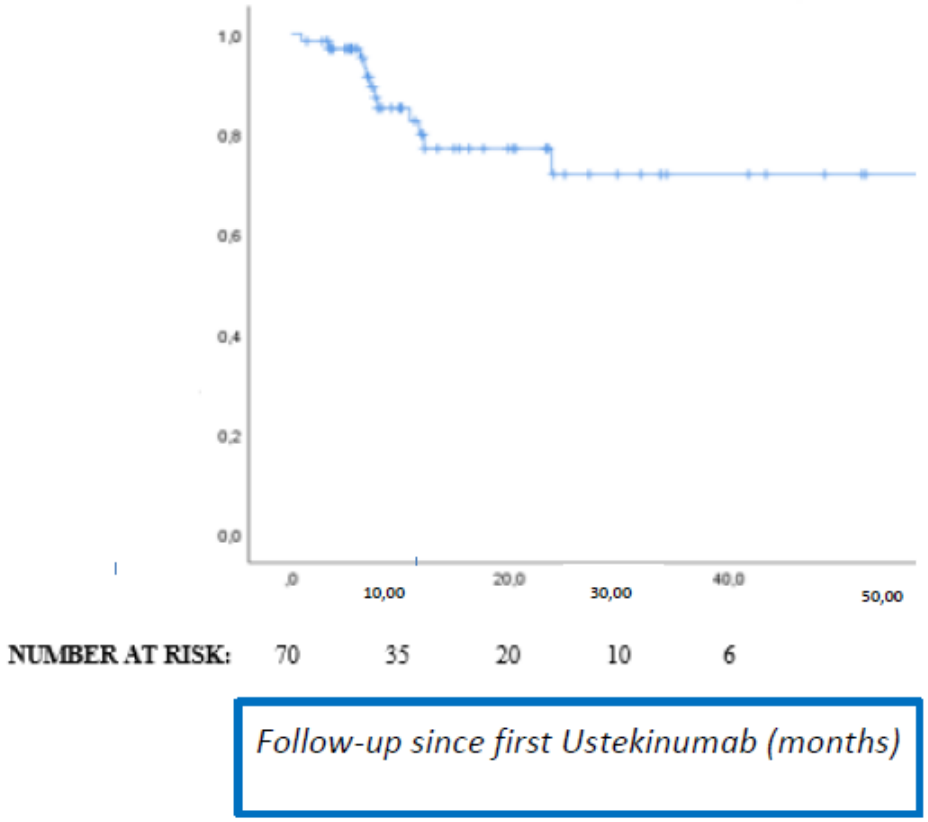
Discontinuation visit		*N* = 75
Treatment duration, weeks	Median [IQR]	24.6 [15.9–37.8]
Reason for discontinuation		
Lack of response	*N* [%]	53 [70.7]
Loss of response	*N* [%]	6 [8.0]
Adverse events	*N* [%]	8 [10.7]
Pregnancy	*N* [%]	1 [1.3]
Request of patient	*N* [%]	6 [8.0]
Other	*N* [%]	1 [1.3]



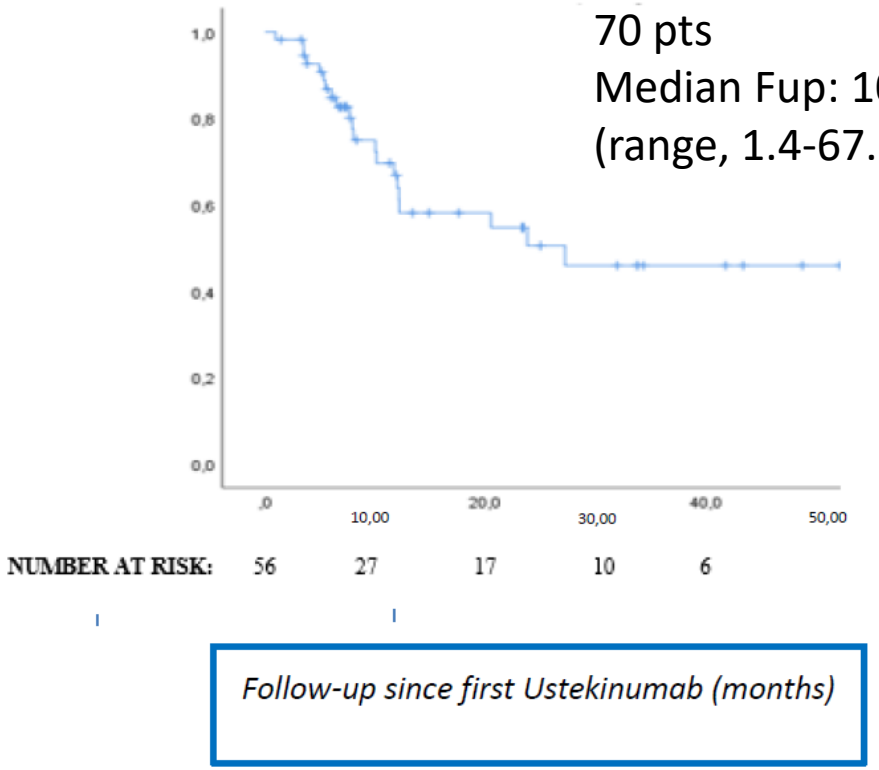


Biemans V., J Crohns Colitis. 2019

Real-life effectiveness of ustekinumab in inflammatory bowel disease patients with concomitant psoriasis or psoriatic arthritis: an IG-IBD study



a Ustekinumab persistence



70 pts
Median Fup: 10.7 months
(range, 1.4-67.3)

b Clinical IBD remission

Pugliese, DLD 2019

Dati Presidio Columbus

Baseline characteristics	69
Previous anti-TNF therapy, n (%)	67 (97.1%)
Previous Vedolizumab, n(%)	16 (23.1)
Paradoxical psoriasis/arthitis, n (%)	11 (15.9%)
Previous surgery, n (%)	39 (56.5%)
Perianal disease	12 (17.3)
Psoriasis, n (%)	22 (31.9%)
Arthritis, n (%)	25 (36.2%)
Concomitant immunosuppressants	2 (2)

Median follow-up on therapy: 7 months

2 pts discontinued for lack of response

Q8W 60 pts
Q12W 9 pts

Conclusions

- Real-world data are useful to understand and move outcomes from clinical trials into clinical practice
- The effectiveness of ustekinumab has been shown in different CD patient types (e.g. tough-to-treat patients)
- In a clinical practice setting, ustekinumab is demonstrating sustained effectiveness across measures that are relevant to physicians and patients