Meeting del 45° parallelo: the IBD and liver hemisphere

Anti-JAKs
Real-Life Studies

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Disclosures

Pr. Edoardo Vincenzo Savarino has following relationships with industry

Personal payments/honoraria/fees:

Abbvie, Agave, AGPharma, Alfasigma, Aurora Pharma, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Fresenius Kabi, Galapagos, Janssen, JB Pharmaceuticals, Innovamedica/Adacyte, Malesci, Mayoly Biohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Tillots, Unifarco

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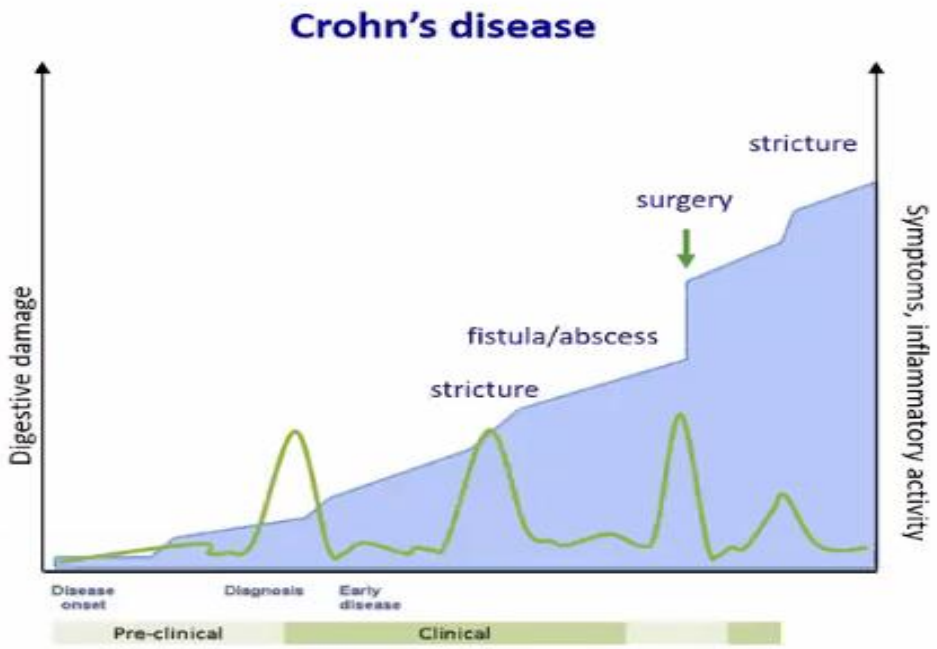
The content of this talk has not been influenced by any sponsors

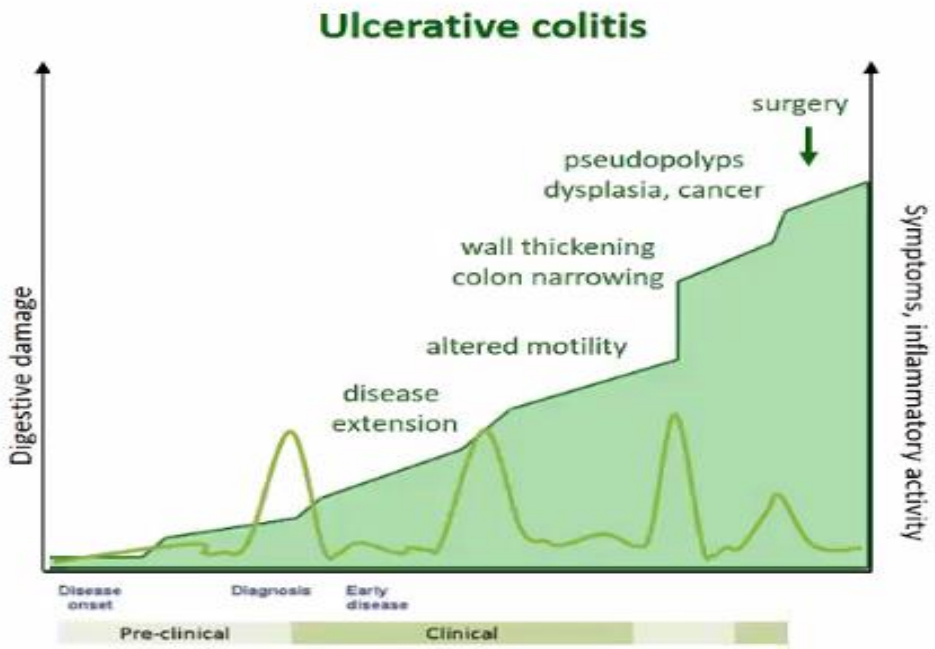
Rate of Progression to Structural Damage in IBD



Adapted from Pariente B, IBD 2011

Progression to stricturing or penetrating complications (population-based studies)	
9-22%	within 5 yrs
> 50%	within 30 yrs

Andersen, Am J Gastro 2014; Burish Gut 2018; Jeunng Am J Gasstro 2017; Soldberg Clin Gastro Hepatol 2007; Thia Gastroenterology 2010

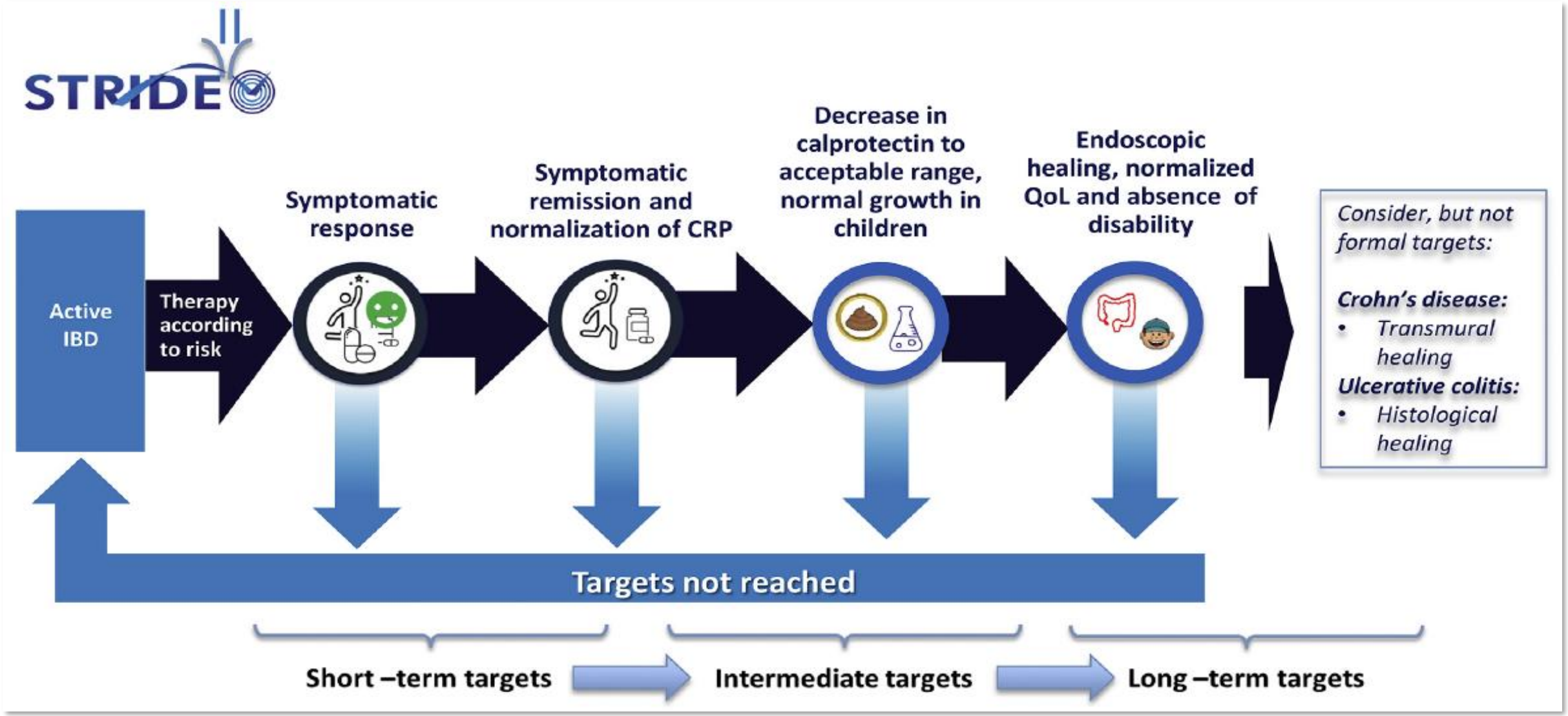


Adapted from Torres J, IBD 2012

Progression to pancolitis	
18%	within 5 yrs
31%	within 30 yrs

Roda G Aliment Pharmacol Ther. 2017

Treatment Targets in CD and UC

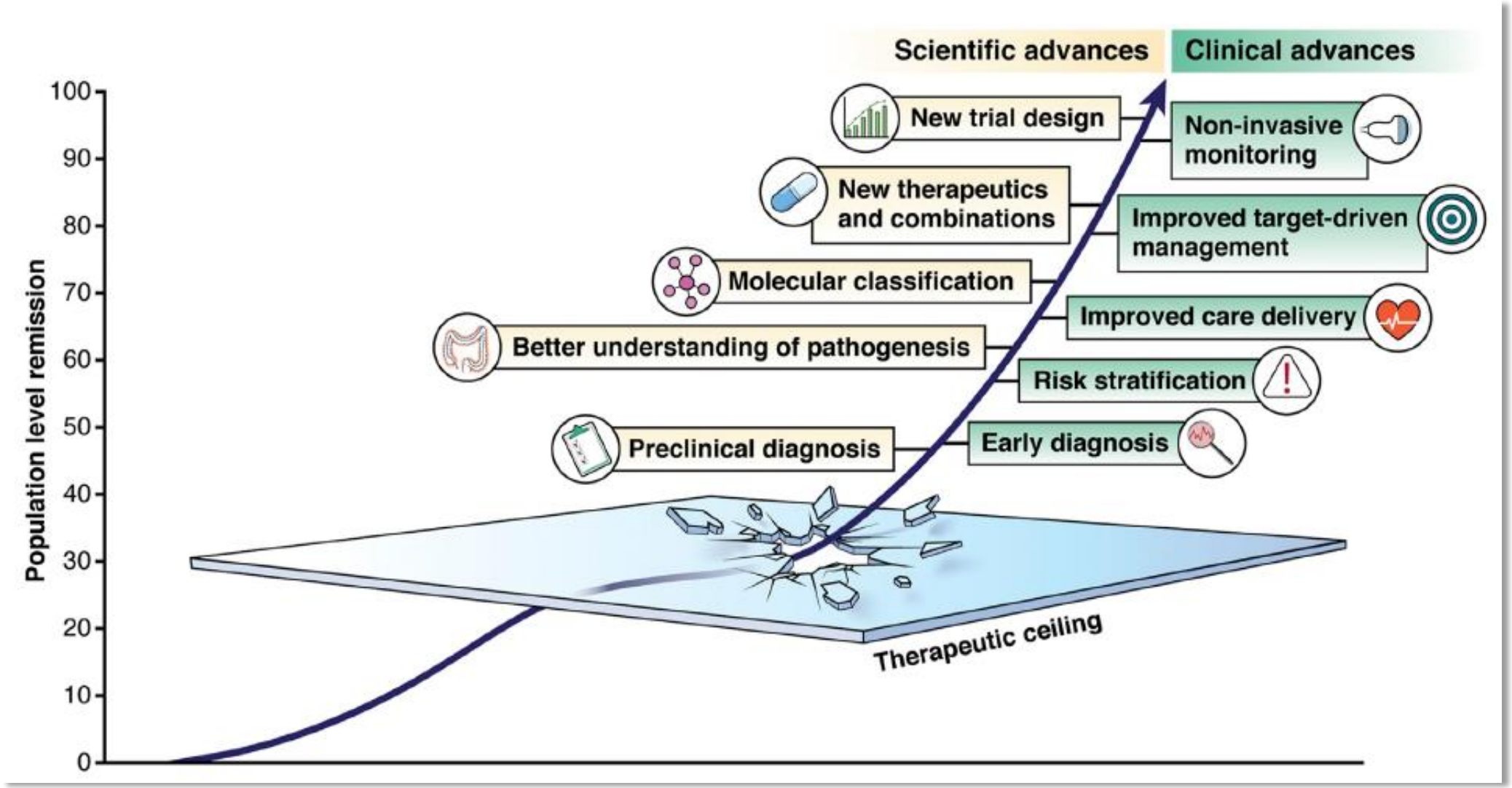


Tuner D, et al. Gastroenterology. 2021 Apr;160(5):1570-1583

To What Extent Do Current Therapies Meet These Treatment Goals?

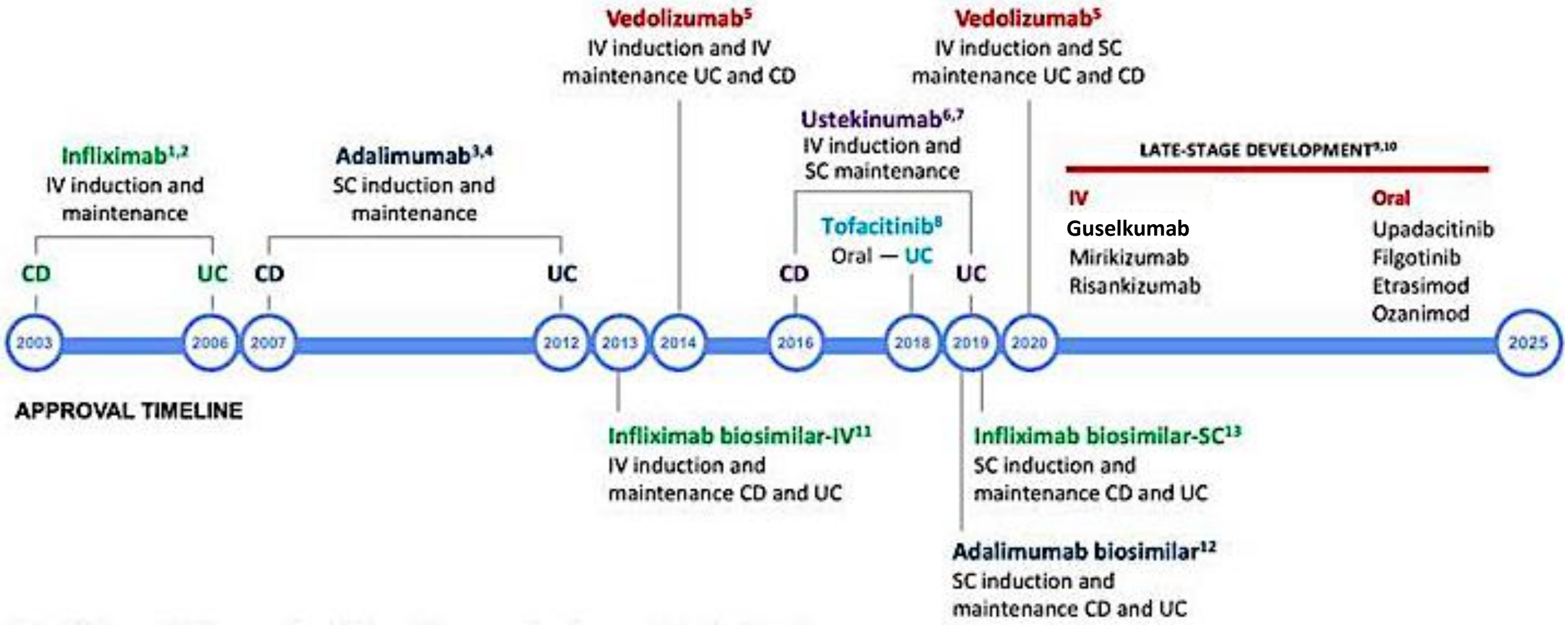
Goal	5-ASA	Steroids	AZA	MTX	Anti-TNFα	VDZ	USTE	TOFA
Short-term endpoints								
Clinical remission	UC[1]	CD+UC	CD+(UC)	CD[4]	CD+UC	CD+UC	CD+UC	UC
Steroid-free remission	?	No	(CD+UC)	CD[4]	CD+UC	CD+UC	CD+UC	UC
Clinical and mucosal remission (deep remission)	UC[1]	UC[3]	CD+UC	?	CD+UC	CD+UC	CD+UC	UC
Long-term disease modification								
Reduction of surgical risk	?	?	Conflicting	?	Conflicting	?	?	?
Reduction of disability	?	?	?	?	?	?	?	?
Reduction of 'damage'	?	?	?	?	?	?	?	?

Breaking Through the Therapeutic Ceiling: What Will It Take?



Raine T, et al. Gastroenterology. 2022 Apr;162(5):1507-1511

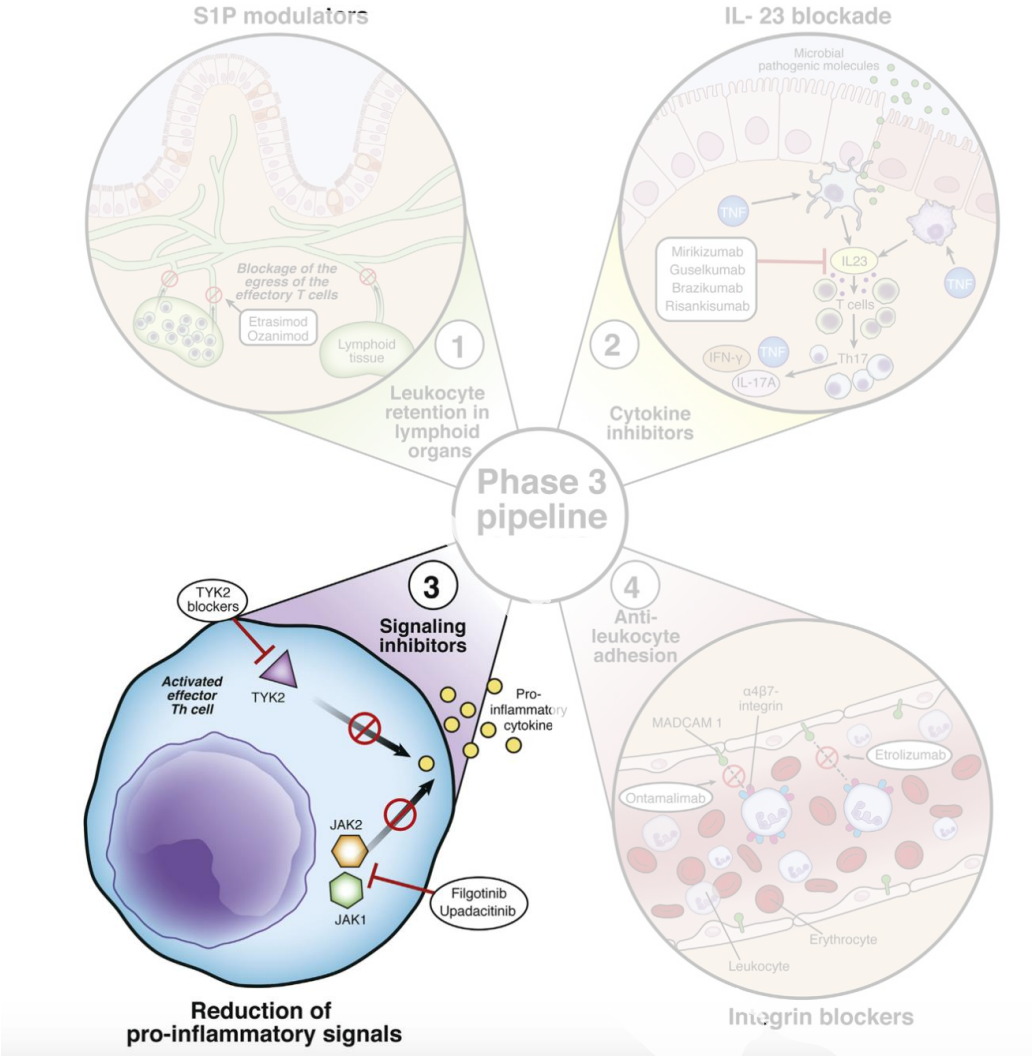
Drugs for IBD: 2024 and beyond



CD, Crohn's disease; IBD, inflammatory bowel disease; IV, intravenous; SC, subcutaneous; UC, ulcerative colitis.

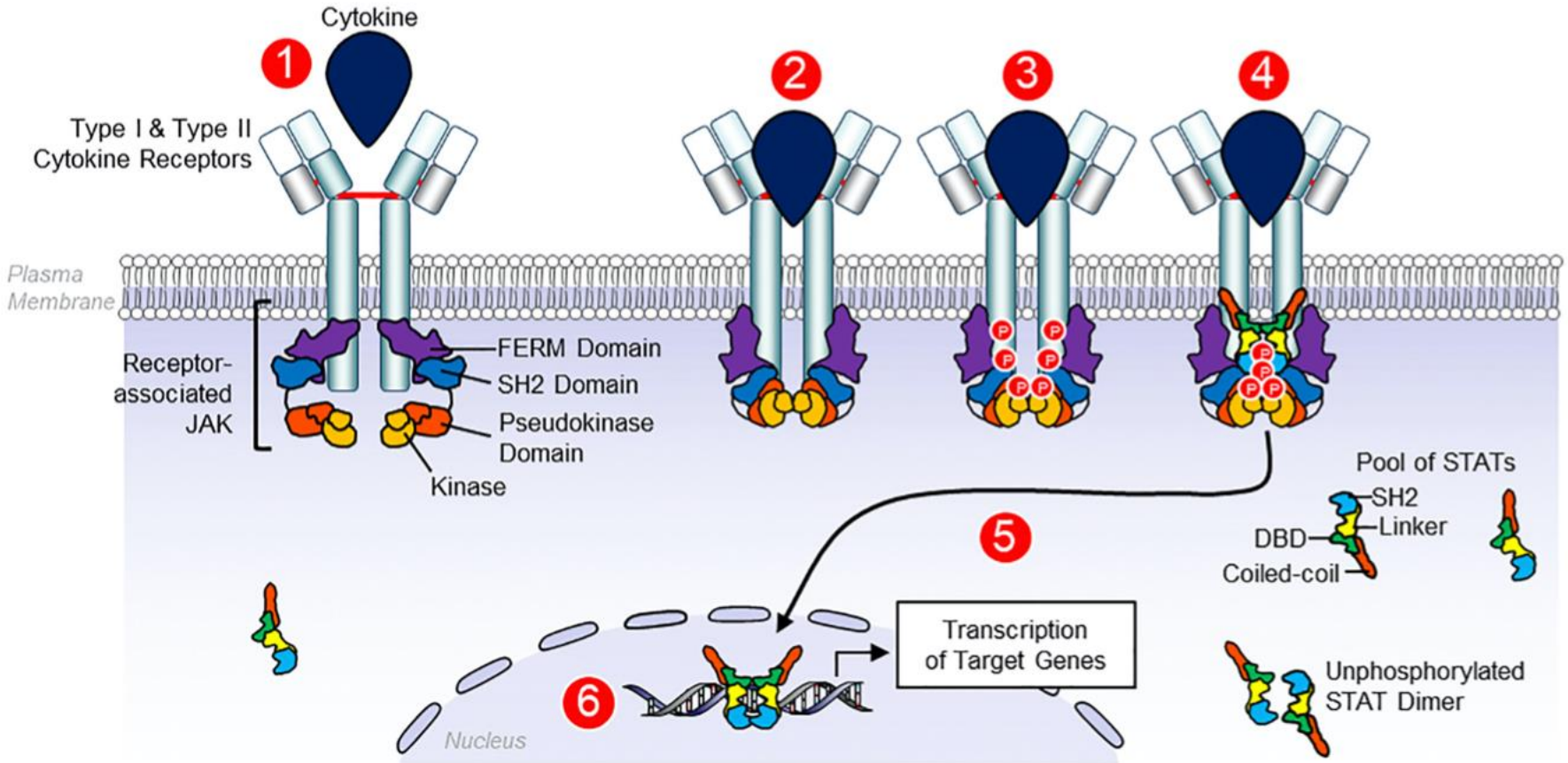
1. P&T Community. 21 May 2003. 2. P&T Community. 9 Mar 2006. 3. Abbott.11 Apr 2012. 4. Abbott. 30 Aug 2012. 5. Takeda. 28 May 2014. 6. Johnson & Johnson. 11 Nov 2016. 7. Johnson & Johnson. 21 Oct 2019
8. Pfizer. 1 Aug 2018. 9. Pérez-Jeldres T, et al. Front Pharmacol. 2019;10:212. 10. Rawla P, et al. J Inflamm Res. 2018;11:215-26. 11. Cision PR Newswire. 10 Sep 2013.
12. Sandoz. 27 Jul 2018. 13. Nadoara N, et al. Dig Dis Sci. 2020:10.1007/s10620-020-06471-4.

Current and Future Panorama of IBD Drugs



Janus Kinases (JAKs)

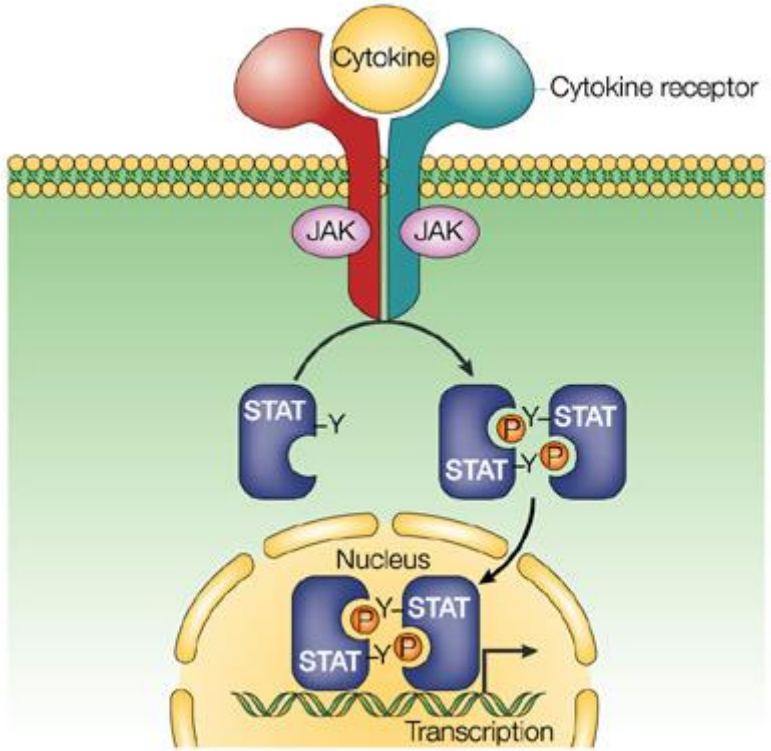
Janus kinases or JAKs are a family of intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals through several steps via the JAK-STAT pathway



Shuai K, Liu B. *Nat Rev Immunol* 2003;3:900–911

Janus kinases (JAKs) Transmit Signals from Cytokines and Growth Factors to Modulate Gene Transcription

1. Cytokine/growth factor binds receptor and activates JAKs
2. Activated JAKs phosphorylate STATs
3. STAT dimers translocate to nucleus and initiate gene transcription that leads to changes in cellular function



4 JAKs (JAK1, JAK2, JAK3, TYK2) **combine with 6 STATs** (STAT 1-6) **to transmit the cytokine / growth factor signal to the nucleus**

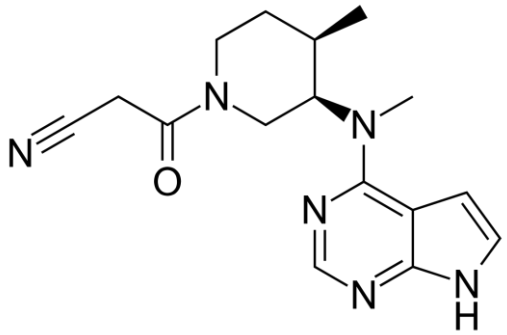
Cytokine / growth factor	JAKs	STATs
IFNα	JAK1/TYK2	STAT1/STAT2
IFNɣ	JAK1/JAK2	STAT1/STAT1
IL-2	JAK1/JAK3	STAT5/STAT5
IL-3	JAK2/JAK2	STAT5/STAT5
IL-4	JAK1/JAK3	STAT6/STAT6
IL-5	JAK1/JAK2	STAT1/3/5
IL-6	JAK1/JAK2/TYK2	STAT1/3/5
IL-7	JAK1/JAK3	STAT5/STAT5
IL-9	JAK1/JAK3	STAT1/3/5
IL-10	JAK1/TYK2	STAT3/STAT3
IL-12	JAK2/TYK2	STAT4/STAT4
IL-13	JAK1/JAK2/TYK2	STAT6/STAT6
IL-15	JAK1/JAK3	STAT5/STAT5
IL-21	JAK1/JAK3	STAT3/STAT3
IL-22	JAK1/TYK2	STAT3/STAT1/5
IL-23	JAK2/TYK2	STAT3/STAT4
EPO	JAK2/JAK2	STAT5/STAT5
TPO	JAK2/JAK2	STAT1/3/5
GM-CSF	JAK2/JAK2	STAT5/STAT5
GH	JAK2/JAK2	STAT1/3/5

STAT, signal transducer and activator of transcription.

Shuai K, Liu B. Nat Rev Immunol 2003;3:900–11; Yoshimura A et al. Arthr Res Ther 2005;7;100–10; Baker SJ et al. Oncogene 2007;26:6724–37; Rochman Y et al. Nat Rev Immunol 2009;9:480–90; Eyerich S et al. Trends Immunol 2010;31:354–61; Laurence A et al. Open Rheumatol J 2012;6:232–44; Vignali DAA, Kuchroo VK. Nature Immunol 2012:13:722–8; Tohyama M et al. J Invest Dermatol 2012;132:1933–5; Spolski R, Leonard WJ. Nat Rev Drug Discov 2014;13:379–95; Hunter, Jones. Nature Immunol 2015;16:448–57

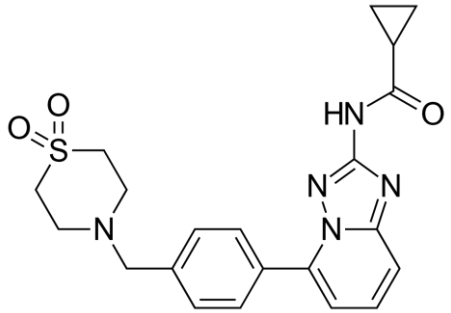
Available JAK Inhibitors for IBD

Tofacitinib



FDA/EMA approval for UC: 2018

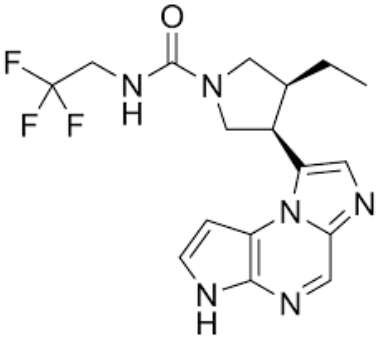
Filgotinib



FDA approval for UC: NA

EMA approval for UC: 2021

Upadacitinib



FDA/EMA approval for UC: 2022

FDA/EMA approval for CD: 2023

Real-world Effectiveness Studies

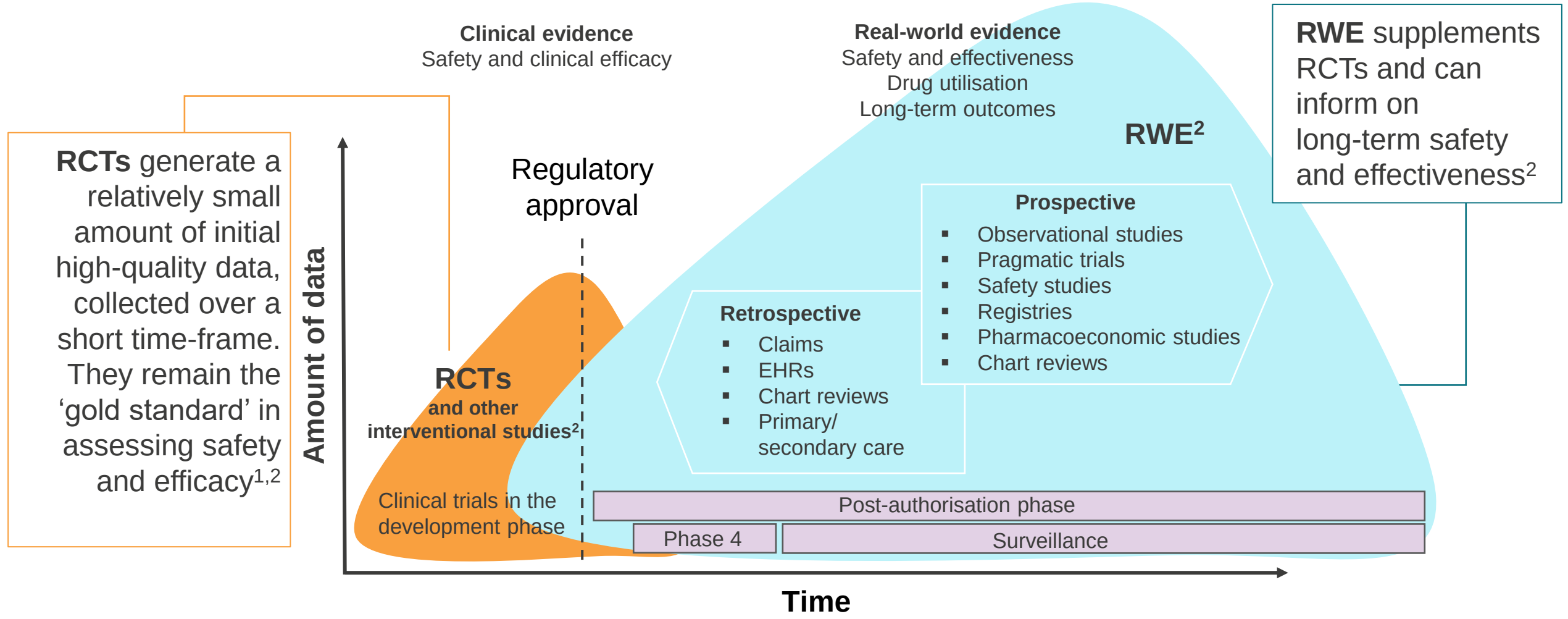


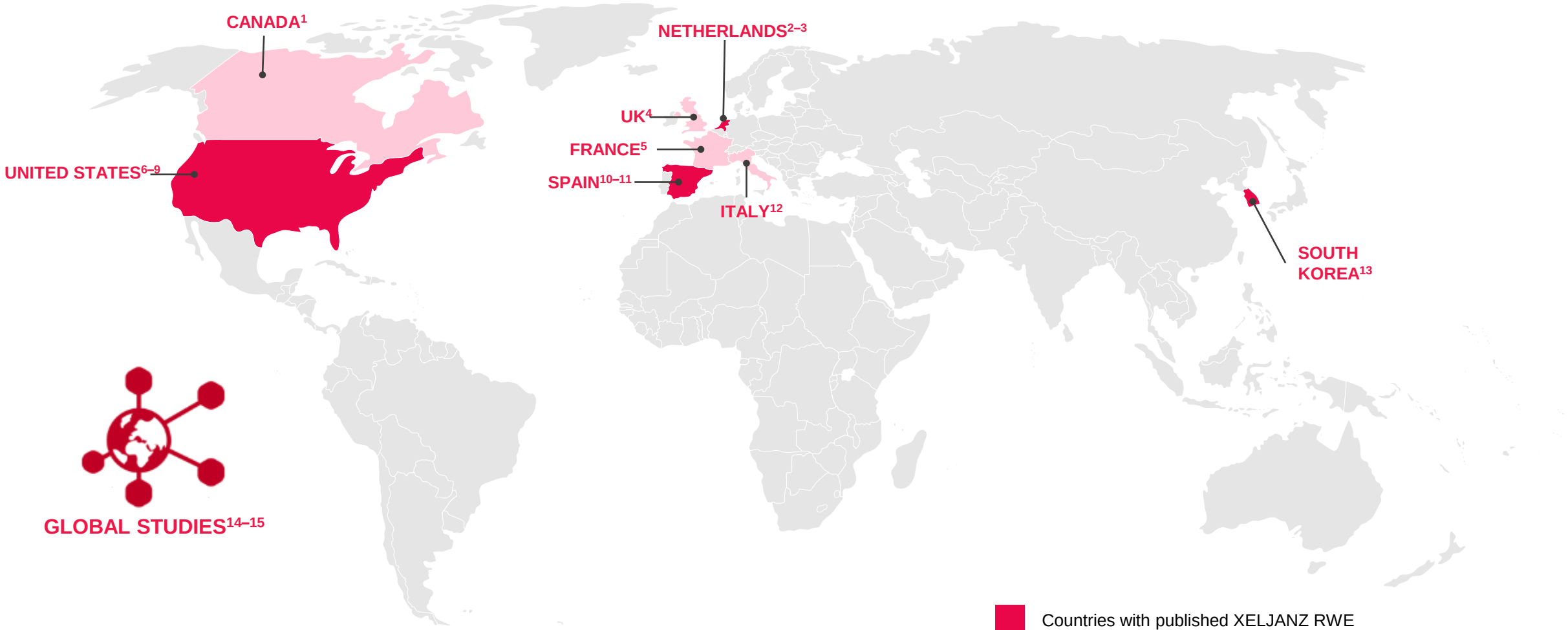
Figure adapted from Katkade VB, et al. J Multidiscip Healthc. 2018;11:295–304.
EHR, electronic health record; RCT, randomised controlled trial, RWE, real-world evidence.
1. Nallamothu BK, et al. Circulation. 2008;118(12):1294–1303; 2. Katkade VB, et al. J Multidiscip Healthc. 2018;11:295–304.

Tofacitinib: General Features

- Inhibition of all JAKs (mainly JAK1 and JAK3)
- Dose-dependent efficacy
- Oral formulation
- Recommended induction dose is 10 mg twice a day for 8 weeks (can be extended up to 16 weeks)
- Recommended maintenance dose: 5 mg twice a day
- Dose adjustment in case of renal impairment or liver disease
- Should be stopped if primary failure at week 16
- Can be restarted after a drug holiday

Flanagan ME et al. J Med Chem 2010;53:8468-84.11.
Danese S, et al. Am J Physiol Gastrointest Liver Physiol 2016; 310: G155-G162
https://www.ema.europa.eu/en/medicines/human/EPAR/xeljanz

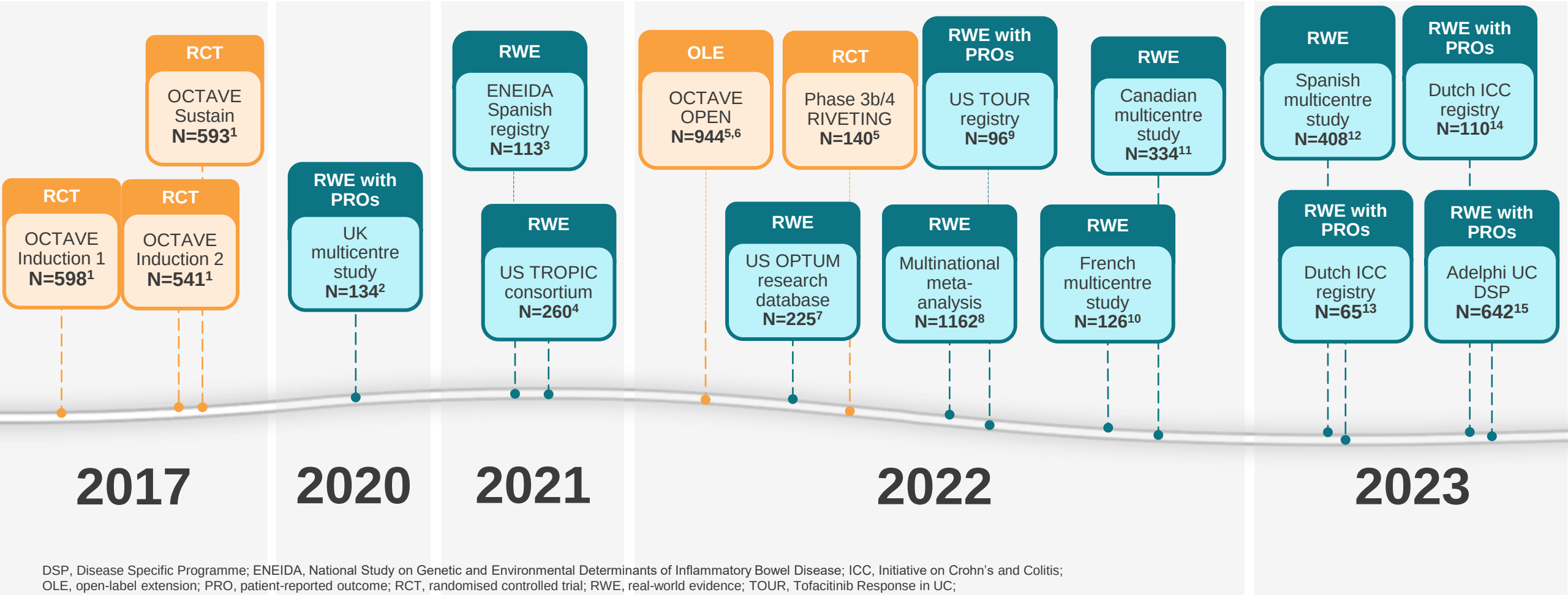
Tofacitinib: Real-World Effectiveness Studies



RWE, real-world evidence; UC, ulcerative colitis; UK, United Kingdom.

1. Ma C, et al. *Am J Gastroenterol.* 2023;118(5):861–871; 2. Straatmijer T, et al. *Clin Gastroenterol Hepatol.* 2023;21(1):182–191.e2;
3. Straatmijer T, et al. *Aliment Pharmacol Ther.* 2023;57(1):117–126; 4. Honap S, et al. *J Crohns Colitis.* 2020;14(10):1385–1393;
5. Buisson A, et al. *Aliment Pharmacol Ther*. 2023;57(6):676–688; 6. Deepak P, et al. *Clin Gastroenterol Hepatol.* 2021;19(8):1592–1601;
7. Chiorean MV, et al. *BMC Gastroenterol*. 2022;22:177; 8. Long MD, et al. *Inflamm Bowel Dis.* 2023;29(4):570–578;
9. Dalal RS, et al. *Inflamm Bowel Dis*. 2023. doi:10.1093/ibd/izad087; 10. Chaparro M, et al. *J Crohns Colitis.* 2021;15:35–42;
11. Chaparro M, et al. *J Gastroenterol.* 2023. doi:10.14309/ajg.0000000000002145; 12. Tursi A, et al. *Expert Opin Pharmacother.* 2023:1–8;
13. Shin SH, et al. *Therap Adv Gastroenterol.* 2023;16:1–15; 14. Taxonera C, et al. *Inflamm Bowel Dis.* 2021;28(1):32–40; 15. Armuzzi A, et al. *BMC Gastroenterol.* 2023;23(1):17.

Tofacitinib: Real-World Effectiveness Studies



DSP, Disease Specific Programme; ENEIDA, National Study on Genetic and Environmental Determinants of Inflammatory Bowel Disease; ICC, Initiative on Crohn's and Colitis; OLE, open-label extension; PRO, patient-reported outcome; RCT, randomised controlled trial; RWE, real-world evidence; TOUR, Tofacitinib Response in UC; TROPIC, Tofacitinib Real-world Outcomes in Patients with ulcerative colitis and Crohn's disease; UC, ulcerative colitis; UK, United Kingdom; US, United States.

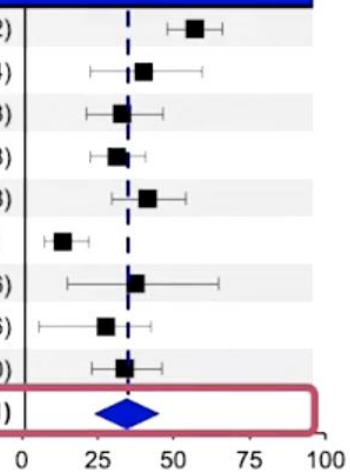
1. Sandborn WJ, et al. *N Engl J Med.* 2017;376:1723–1736; 2. Honap S, et al. *J Crohns Colitis.* 2020;14(10):1385–1393; 3. Chaparro M, et al. *J Crohns Colitis.* 2021;15(1):35–42; 4. Deepak P, et al. *Clin Gastroenterol Hepatol.* 2021;19(8):1592–1601. 5. Sandborn WJ, et al. *J Crohns Colitis*. 2022; doi: 10.1093/ecco-jcc/jjac141; 6. Sandborn WJ, et al. *J Crohns Colitis.* 2022; doi: 10.1093/ecco-jcc/jjac141. [Supplementary appendix]; 7. Chiorean MV, et al. *BMC Gastroenterol.* 2022;22(1):177; 8. Taxonera C, et al. *Inflamm Bowel Dis.* 2022;28(1):32–40; 9. Long MD, et al. *Inflamm Bowel Dis*. 2023;29(4):570-578; 10. Buisson A, et al. *Aliment Pharmacol Ther*. 2023;57(6):676–688; 11. Ma C, et al. *Am J Gastroenterol*. 2022; doi: 10.14309/ajg.0000000000002129; 12. Chaparro M, et al. *Am J Gastroenterol*. 2022; doi: 10.14309/ajg.0000000000002145; 13. Straatmijer T, et al. *Clin Gastroenterol Hepatol*. 2023;21(1):182–191; 14. Straatmijer T, et al. *Aliment Pharmacol Ther*. 2023;57(1):117–126; 15. Armuzzi A, et al. *BMC Gastroenterol*. 2023;23:17. doi: 10.1186/s12876-023-02640-7.

Effectiveness at Weeks 8, 12-16 and at Month 6

Meta-analysis of Tofacitinib Real-world Trials

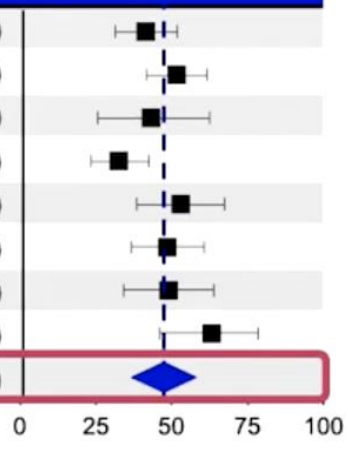
Week 8 remission rate (%)†

	Patients, N	Patients in remission, N	Weight, %	Effect size (95% CI)
Honap et al.	119	68	12.17	57.1 (47.7-66.2)
Shimizu et al.	30	12	9.66	40.0 (22.7-59.4)
Weisshoff et al.	58	19	11.31	32.8 (21.0-46.3)
Chaparro et al.	109	34	12.21	31.2 (22.7-40.8)
Cremer et al.	70	29	11.46	41.4 (29.8-53.8)
Patel et al.	96	13	12.63	13.5 (7.4-22.0)
Rutka et al.	16	6	7.85	37.5 (15.2-64.6)
Watanabe et al.	47	13	11.10	27.7 (15.6-42.6)
Yoshimura et al.	71	24	11.61	33.8 (23.0-46.0)
Overall			**100.00**	**34.7 (24.4-45.1)**



Week 12-16 remission rate (%)‡

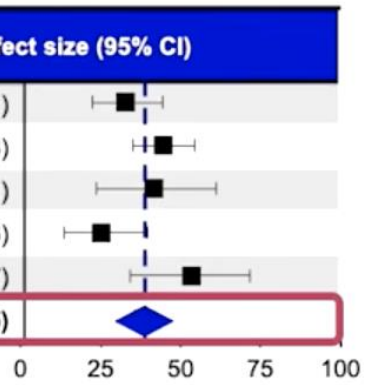
	Patients, N	Patients in remission, N	Weight, %	Effect size (95% CI)
Biemans et al.	99	41	15.02	41.4 (31.6-51.8)
Honap et al.	103	53	15.07	51.5 (41.4-61.4)
Shimizu et al.	30	13	8.59	43.3 (25.5-62.6)
Chaparro et al.	102	33	15.65	32.4 (23.4-42.3)
Cremer et al.	49	26	11.18	53.1 (38.3-67.5)
Patel et al.	74	36	13.40	48.6 (36.9-60.6)
Watanabe et al.	47	23	10.93	48.9 (34.1-63.9)
Xiao et al.	38	24	10.15	63.2 (46.0-78.2)
Overall			**100.00**	**47.0 (40.3-53.6)**



- **Clinical response** was achieved in:
  - **62.1%** of patients at Week **8** (95% CI: 55.0-69.1%)
  - **64.2%** of patients at Weeks **12 to 16** (95% CI: 56.3-73.2%)
  - **50.8%** of patients at Month **6** (95% CI: 42.1-59.5%)
  - **41.8%** of patients at Month **12** (95% CI: 31.8-51.8%)
- Patients who were biologic-naïve had a significantly higher rate of **clinical response** at Week 8:
  - RR, 1.38; 95% CI: 1.03-1.84; *P*=0.032

Month 6 remission rate (%)§

	Patients, N	Patients in remission, N	Weight, %	Effect size (95% CI)
Biemans et al.	77	25	23.71	32.5 (22.2-44.1)
Honap et al.	108	48	25.24	44.4 (34.9-54.3)
Shimizu et al.	29	12	14.85	41.4 (23.5-61.1)
Weisshoff et al.	48	12	21.28	25.0 (13.6-39.6)
Xiao et al.	30	16	14.92	53.3 (34.3-71.7)
Overall			**100.00**	**38.3 (29.2-47.5)**



†Study heterogeneity, I^2=87%; Tau^2=2.1%; Cochrane *Q* test, *P*<0.001; Egger weighted regression, *P*=0.37. ‡Study heterogeneity, I^2=59%; Tau^2=0.5%; Cochrane *Q* test, *P*=0.02; Egger weighted regression, *P*=0.15. §Study heterogeneity, I^2=61%; Tau^2=0.6%; Cochrane *Q* test, *P*=0.04.
CI=confidence interval; RR=risk ratio.
Taxonera C, et al. *Inflamm Bowel Dis.* 2021;izab011. doi:10.1093/ibd/izab011 [Epub ahead of print].

Tofacitinib Safety

Meta-analysis of Tofacitinib Real-world Trials

Adverse events

- 211 AEs (**26%**) in 811 patients (95% CI: 22.9-29.1%; 11 studies)
- The IR for any AE was 52.4 patients per 100 patient-years (95% CI: 45.3-59.4)

Serious adverse events

- 35 SAEs (**4.4%**) in 794 patients (95% CI: 2.9%-5.9%; 13 studies)
- The IR for SAEs was 8.9 patients per 100 patient-years (95% CI: 5.9-11.8)

Herpes zoster

- 32 events of herpes zoster (**3.4%**) in 952 patients (95% CI: 2.2%-4.5%; 13 studies)
- The IR for herpes zoster was 6.9 patients per 100 patient-years (95% CI: 4.5-9.3)

MACE/ VTE

- **None** of the studies reported major adverse cardiovascular events or thromboembolic events

AE=adverse event; CI=confidence interval; IR=incidence rate; MACE=major adverse cardiovascular event; SAE=serious adverse event; VTE=venous thromboembolism.

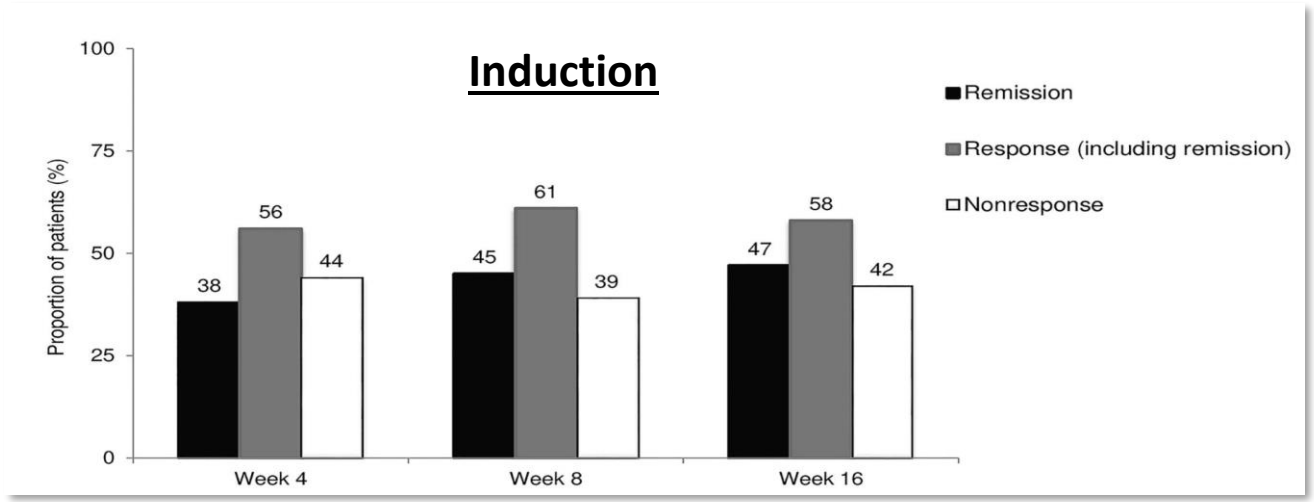
Taxonera C, et al. *Inflamm Bowel Dis*. 2021;izab011. doi:10.1093/ibd/izab011 [Epub ahead of print].

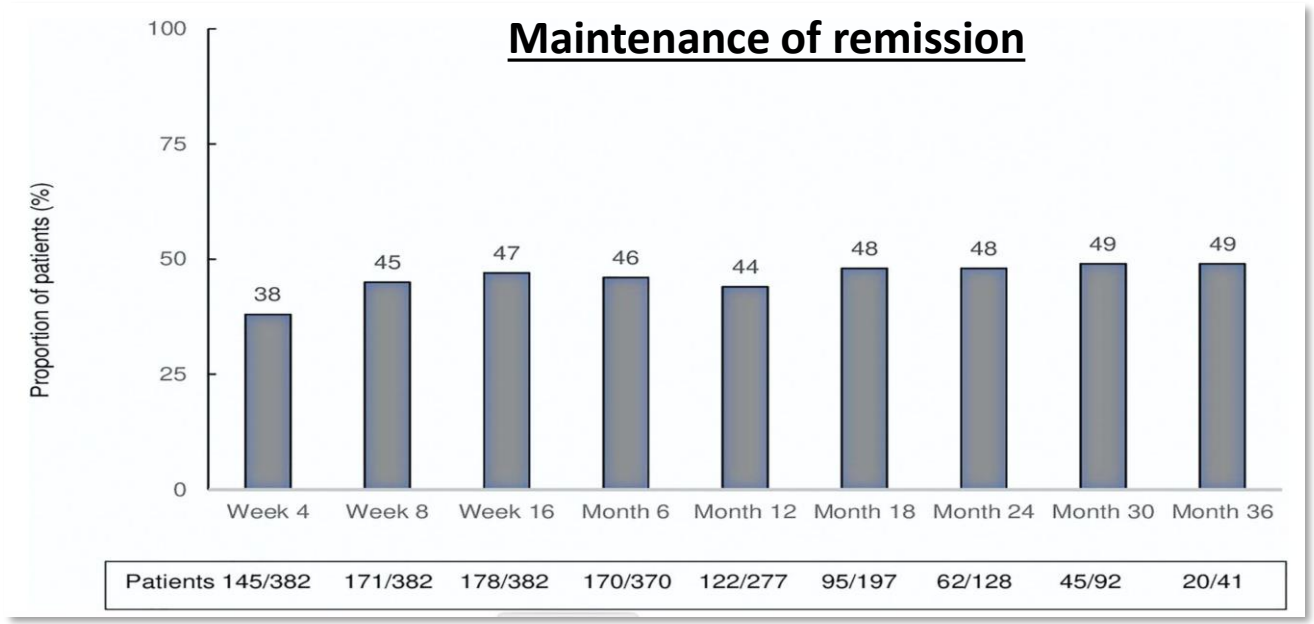
Real-World Evidence of Tofacinitib in Ulcerative Colitis: Short-Term and Long-Term Effectiveness and Safety

Table 1. Characteristics of the study population

Variables	N = 408
Age (yr), mean (SD)	44 (15)
Median time of follow-up (mo) (IQR)	18 (10–29)
Median time from UC diagnosis (yr) (IQR)	7.5 (4–13)
Male sex, n (%)	232 (57)
Comorbidities, n (%)	182 (45)
Cardiovascular and thrombotic risk factors, n (%)	124 (30)
Family history of IBD, n (%)	61 (15)
Ulcerative colitis extension	
Extensive colitis, n (%)	234 (57)
Left-sided colitis, n (%)	151 (37)
Proctitis, n (%)	23 (6)
Extraintestinal manifestations, n (%)	115 (28)
Previous biologic agents, n (%)	397 (97)
Anti-TNF, n (%)	377 (92)
Vedolizumab, n (%)	298 (73)
Ustekinumab, n (%)	24 (5.9)
Mean no. of previous biologic agents (SD)	2 (0.9)
Median partial mayo score at baseline (IQR)	6 (5–7)
Severe endoscopic activity, n (%)	140 (55)
Anemia at baseline, n (%)	132 (32)
Concomitant mesalazine, n (%)	163 (40)

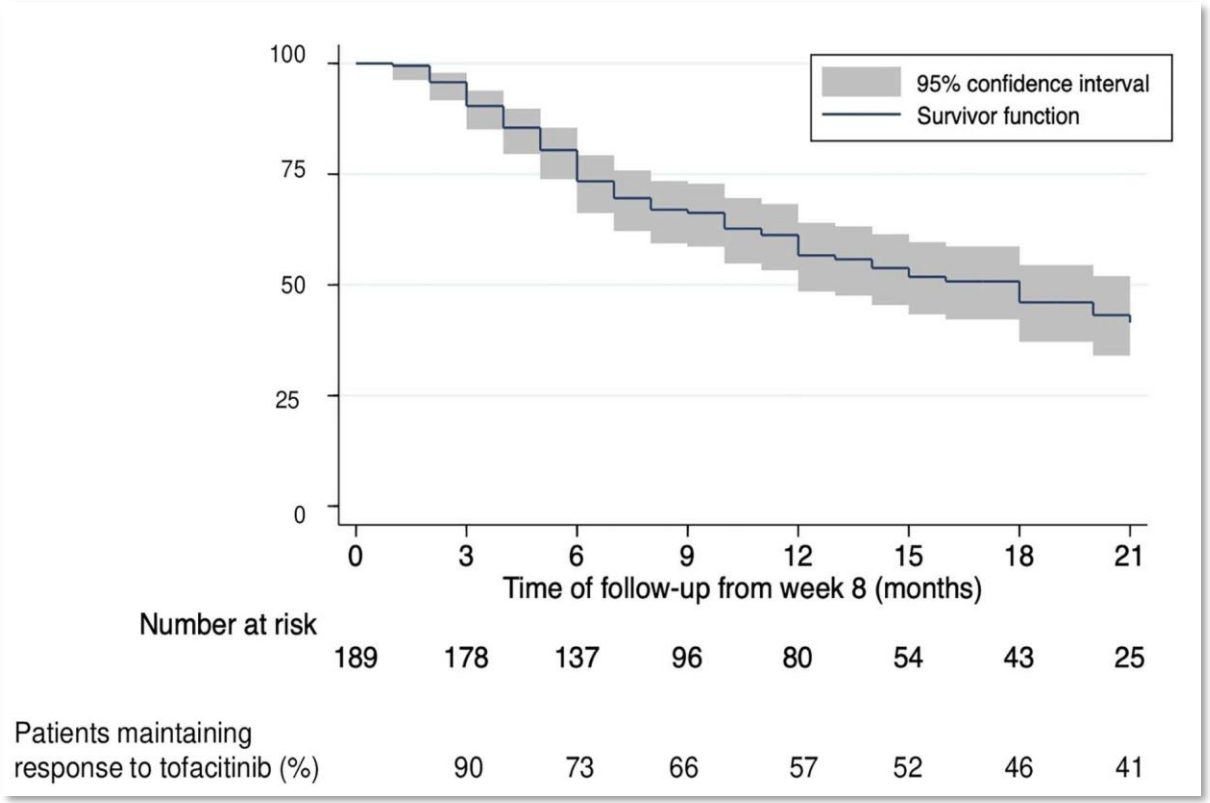
IBD, inflammatory bowel disease; IQR, interquartile range; TNF, tumor necrosis factor.





Chaparro M et al. Am J Gastroenterol . 2023 Jul 1;118(7):1237-1247

Real-World Evidence of Tofacinitib in Ulcerative Colitis: Short-Term and Long-Term Effectiveness and Safety



Tofacitinib dose was escalated in 55 (66%) of those patients who relapsed

- 33 (60%) reached remission
- 12 (22%) had response
- 10 (18%) did not respond.

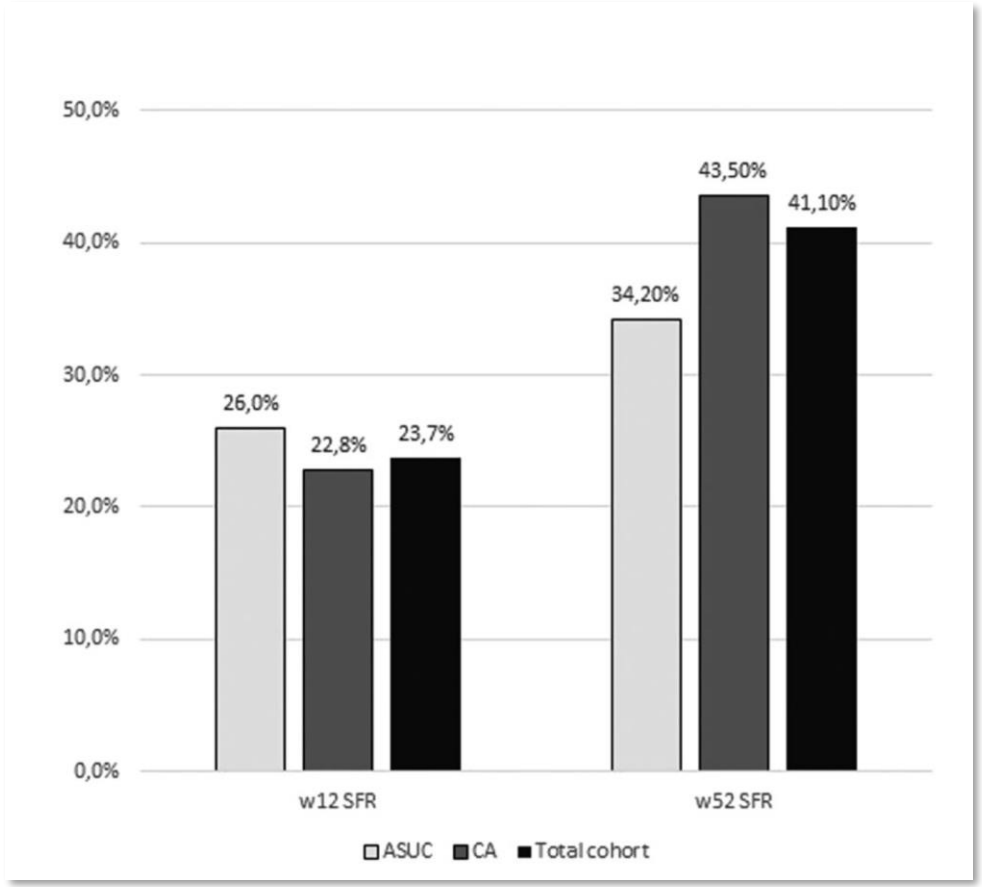
Previous active at tofacitinib start	n (%)	Outcome attributable to tofacitinib treatment
Juvenile idiopathic arthritis	1 (0.2)	No change
Peripheral arthropathy	32 (7.8)	8 (25%) remission, 13 (40.6%) improvement, 11 (34.4) no change
Rheumatoid arthritis	4 (1)	1 (25%) remission, 1 (25%) improvement, 1 (25%) no change, 1 (25%) worsening
Primary sclerosing cholangitis	1 (0.2)	No change
Autoimmune thyroid disease	1 (0.2)	No change
Erythema nodosum	2 (0.5)	2 (100%) remission
Axial spondiloarthropathy	15 (3)	3 (23%) remission, 7 (54%) improvement, 5 (33%) no change, 1 (7%) worsen
Systemic lupus erythematosus	1 (0.2)	No change
Pyoderma gangrenosum	1 (0.2)	1 (100%) improvement
Psoriasis	1 (0.2)	No change
Uveitis	1 (0.2)	No change
Others	2 (0.5)	No change

Chaparro M et al. Am J Gastroenterol . 2023 Jul 1;118(7):1237-1247

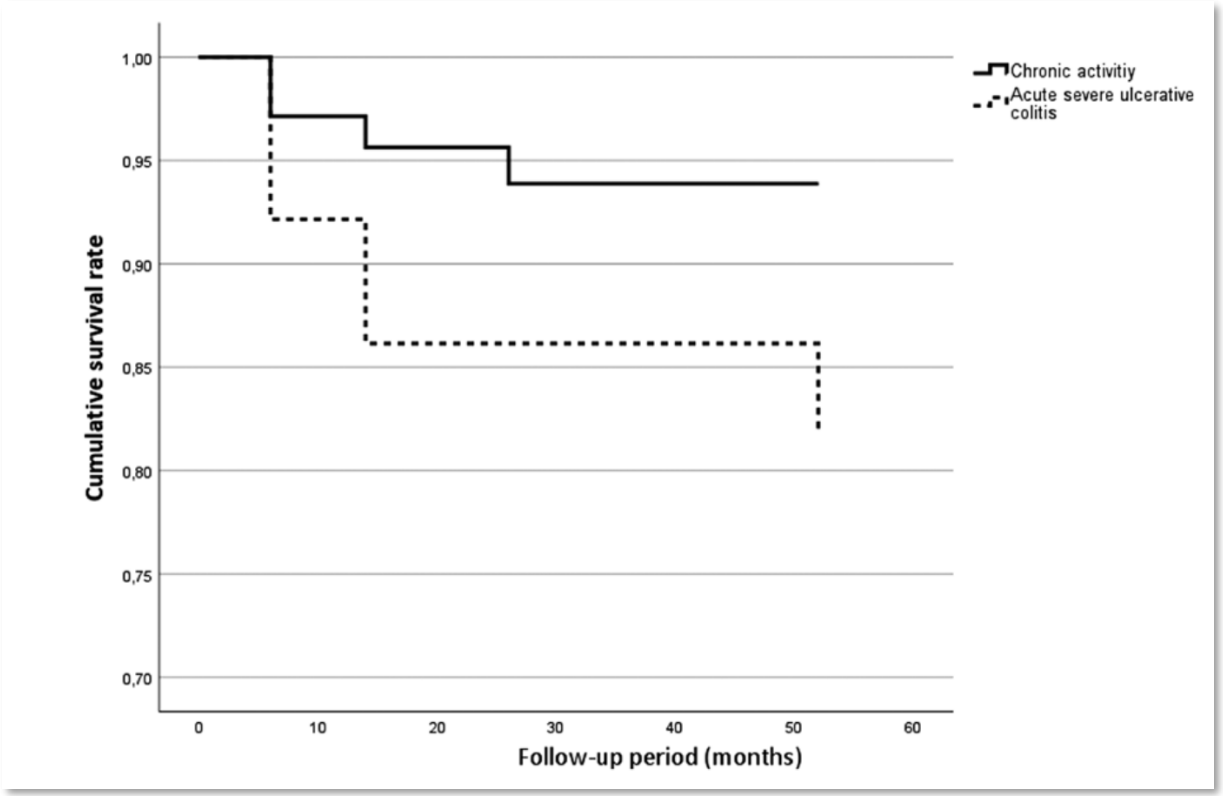
Real-Life Efficacy of Tofacitinib in Various Situations in UC: A Retrospective Worldwide Multicenter Collaborative Study

Retrospective multicenter cohort study

N= 391 UC patients receiving TOFA for ASUC (Truelove and Witts' criteria) or Chronic Activity (CA)



Colectomy-free survival



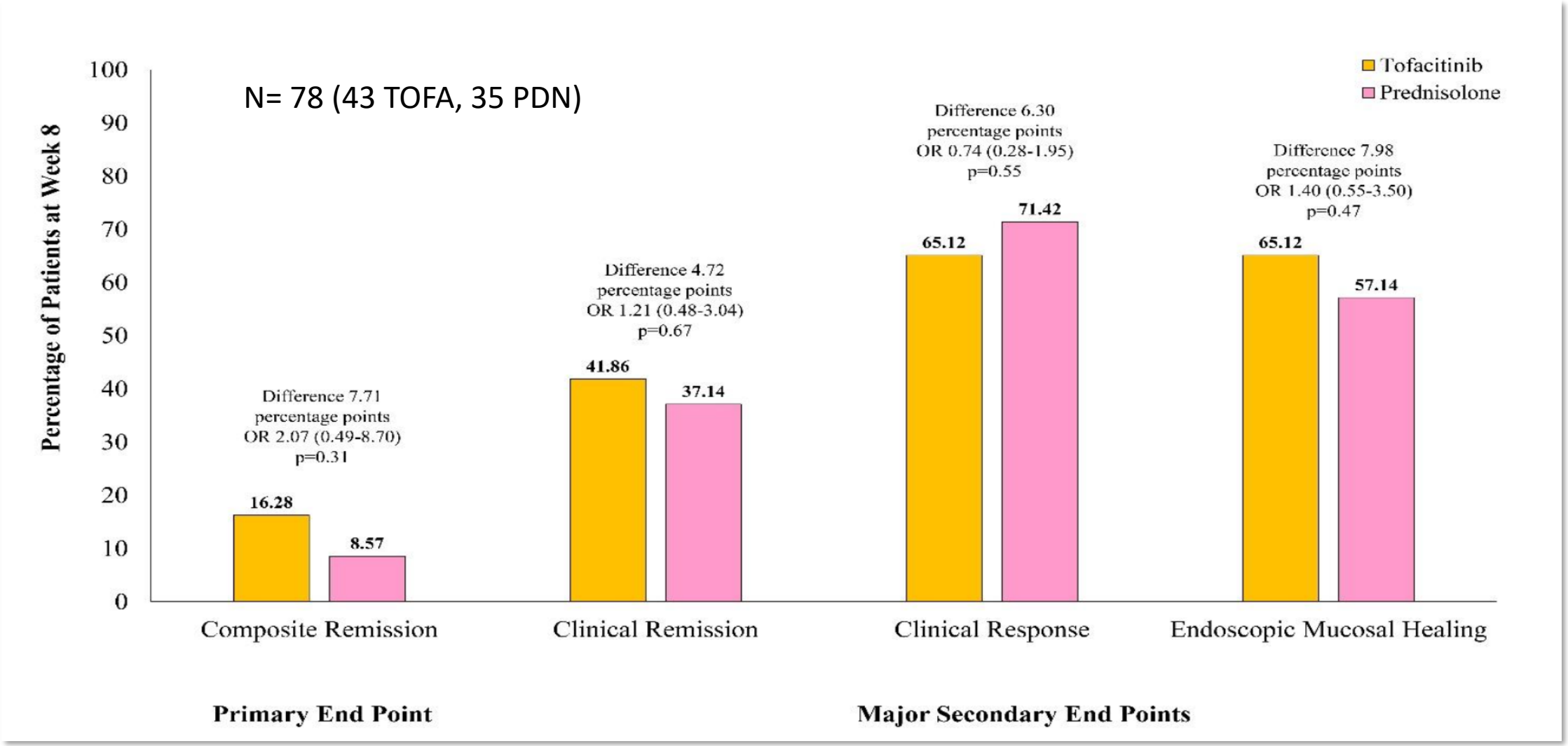
Resal T et al. Inflamm Bowel Dis . 2024 May 2;30(5):768-779

Real-Life Efficacy of Tofacitinib in Various Situations in UC: A Retrospective Worldwide Multicenter Collaborative Study

			OR	SE	*z*	*P* value	95% CI
SFR predictive factors							
Week 12	ASUC	Constant	1.658	0.682	0.741	.459	0.426-6.394
		Baseline pMayo	0.765	0.107	-2.502	.012[b]	0.616-0.940
	CA	Constant	0.589	0.300	-1.763	.078	0.324-1.058
		Male	0.503	0.334	-2.058	.040[b]	0.260-0.967
		Baseline CRP	0.962	0.018	-2.163	.031[b]	0.926-0.992
	Total cohort	Constant	0.785	0.367	-0.658	.510	0.377-1.602
		Baseline pMayo	0.850	0.059	-2.764	.006[b]	0.756-0.954
Week 52	ASUC	Constant	0.341	0.299	-3.599	<.001[b]	0.190-0.613
		Biologic naive	5.378	0.589	2.856	.004[b]	1.695-17.061
	CA	Constant	0.290	0.434	-2.855	.004[b]	0.124-0.678
		Age	1.026	0.011	2.415	.016[b]	1.005-1.047
	Total cohort	Constant	0.632	0.130	-3.525	<.001[b]	0.489-0.815
		Biologic naive	2.078	0.357	2.052	.040[b]	1.033-4.180
Colectomy rate predictive factors							
Week 52	Total cohort	Constant	0.374	0.763	-1.288	.198	0.084-1.670
		ASUC	4.829	0.501	3.144	.002[b]	1.810-12.886
		Age	0.946	0.022	-2.482	.013[b]	0.906-0.988

Resal T et al. Inflamm Bowel Dis . 2024 May 2;30(5):768-779

Tofacitinib Versus Oral Prednisolone for Induction of Remission in Moderately Active Ulcerative Colitis [ORCHID]: A Prospective, Open-Label, Randomized, Pilot Study



<u>Composite remission:</u> total Mayo clinic score ≤2, with endoscopic sub-score of 0 and fcal. <100 mcg/g) at 8 weeks

Singh A et al. J Crohns Colitis . 2024 Feb 26;18(2):300-307

Tofacitinib Versus Oral Prednisolone for Induction of Remission in Moderately Active Ulcerative Colitis [ORCHID]: A Prospective, Open-Label, Randomized, Pilot Study

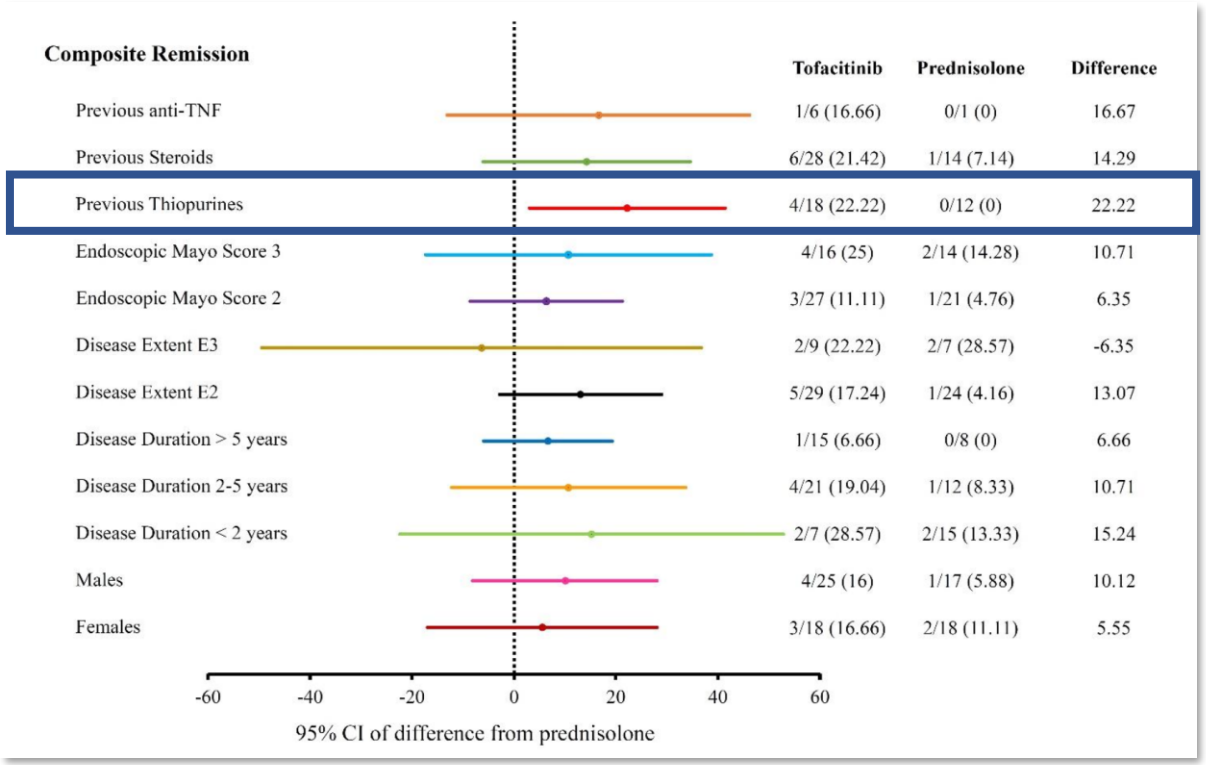


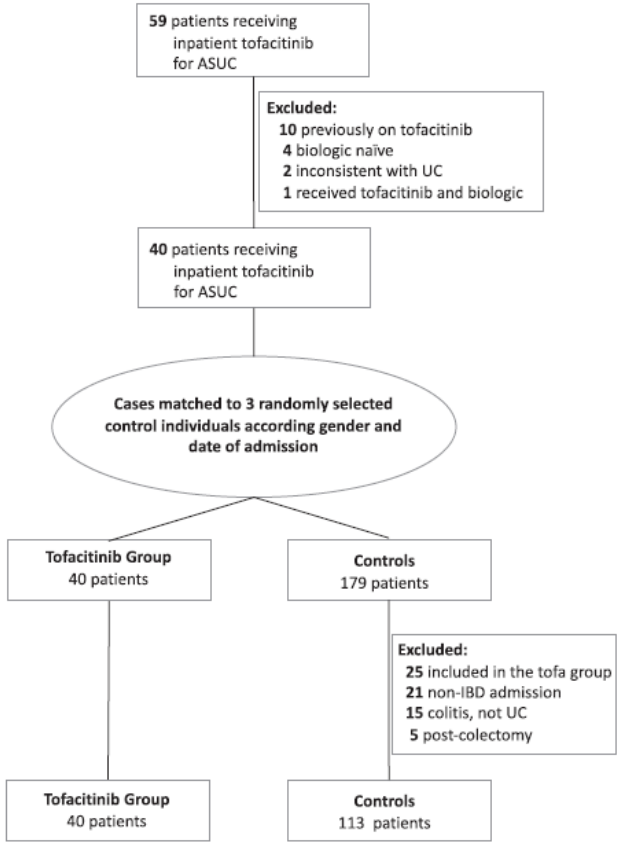
Table 2. Safety outcomes at week 8

Adverse event	Tofacitinib (n=43)	Prednisolone (n=35)	Significance (p value)
Total adverse events	20 (46.51)	20 (57.14)	0.35
Hair loss	6 (13.95)	2 (5.71)	0.23
Cushingoid features	-	12 (34.28)	<0.0001
Increase in disease activity of ulcerative colitis	5 (11.62)	2 (5.71)	0.37
Acne	4 (9.30)	7 (20)	0.18
Nasopharyngitis	1 (2.32)	-	0.37
Arthralgia	2 (4.65)	-	0.20
Headache	1 (2.32)	-	0.37
Mood changes	-	1 (2.85)	0.27
Infections			
Serious infection	-	-	-
Herpes zoster	1 (2.32)	-	0.37
Tuberculosis	1 (2.32)	-	0.37
Hyperglycaemia (drug induced)	-	2 (5.71)	0.11
Dyslipidaemia (requiring addition of lipid lowering drugs)	2 (4.65)	1 (2.85)	0.68
Cardiovascular adverse events	-	-	-
Lymphopenia	-	-	-
Abnormal liver enzymes	-	-	-
Elevated creatinine kinase	-	-	-

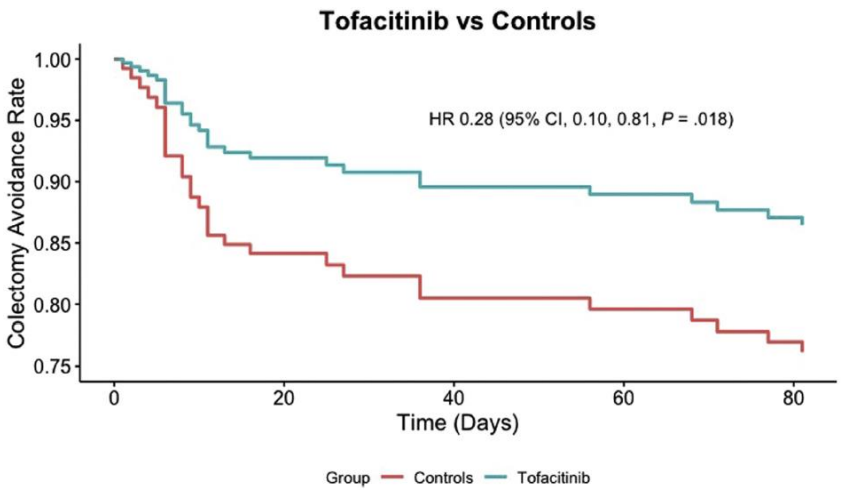
Singh A et al. J Crohns Colitis . 2024 Feb 26;18(2):300-307

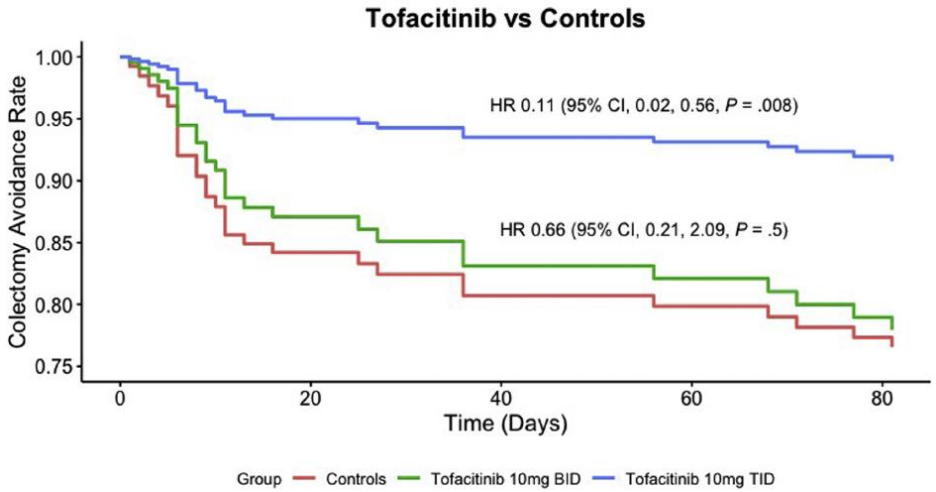
Tofacitinib for Biologic-Experienced Hospitalized Patients With Acute Severe Ulcerative Colitis

- A Retrospective Case-Control Study was performed evaluating the efficacy of tofacitinib induction in biologic-experienced patients admitted with ASUC requiring intravenous corticosteroids



Risk of colectomy at 90 days





	HR	95% CI	*P* value
Tofacitinib	0.28	0.10–0.81	**.018**
Albumin (*g/dL*)	0.27	0.12–0.59	**.001**
No. of failed targeted therapies	1.61	1.13–2.29	**.009**
Colonic dilation	4.13	1.39–12.3	**.011**
Endoscopic Mayo Score	6.28	1.85–21.4	**.003**

When stratifying according to treatment dose:

- 10 mg three times daily (HR, 0.11; 95% CI, 0.02–0.56) was protective
- 10 mg twice daily was not significantly protective (HR, 0.66; 95% CI, 0.21–2.09).

Berinstein J. et al. Clin Gastroenterol Hepatol . 2021 Oct;19(10):2112-2120.e1

Tofacitinib in Acute Severe Ulcerative Colitis (TACOS): A Randomized Controlled Trial

- Single-center, double-blind, placebo-controlled trial randomized adult patients with ASUC (defined by the Truelove Witts severity criteria) to receive either tofacitinib (10 mg thrice daily) or a matching placebo for 7 days while continuing intravenous corticosteroids (hydrocortisone 100 mg every 6 hours).
- A total of 104 patients were randomly assigned to a treatment group (53 to tofacitinib and 51 to placebo).
- At day 7, response to treatment was achieved in 44/53 (83.01%) patients receiving tofacitinib vs 30/51 (58.82%) patients receiving placebo (odds ratio 3.42, 95% confidence interval 1.37–8.48, *P* = 0.007).
- The need for rescue therapy by day 7 was lower in the tofacitinib arm (odds ratio 0.27, 95% confidence interval 0.09–0.78, *P* = 0.01).
- The cumulative probability of need for rescue therapy at day 90 was 0.13 in patients who received tofacitinib vs 0.38 in patients receiving placebo (log-rank *P* = 0.003).
- Most of the treatment-related adverse effects were mild. One patient, receiving tofacitinib, developed dural venous sinus thrombosis

Singh A et al. Am J Gastroenterol . 2024 Jan 22

Combined Targeted Treatment Using Biologic-Tofacitinib Co-Therapy in Chronic Active Ulcerative Colitis

AIM: to report the experience of **combination biologic** tofacitinib therapy in an Australian tertiary IBD center.

TABLE 1. Baseline Patient, Treatment, Clinical, Biochemical, and Endoscopic Characteristics Before Commencing Tofacitinib Followed by Treatment Response at Day 180 of Combination Therapy

Baseline Characteristics								Treatment Response			
Patient	Age	Sex	Biologic	FCP (μg/mL)	CRP (mg/L)	MES	Partial Mayo Score	FCP (μg/mL)	CRP (mg/L)	MES	Partial Mayo Score
1	43	M	IFX	2810	57	3	10	10	2	1	2
2	19	M	UST	2260	41	2	8	1120	0	2	2
3	17	F	IFX	682	31	3	9	631	3	3	8
4	50	M	VDZ	300	12	2	7	369	10	2	5
5	27	M	IFX	3440	62	3	10	42	4	1	4
6	34	F	IFX	485	9	2	6	980	2	1	2
7	19	M	IFX	2230	6	3	11	179	8	2	3

Safety:

- One patient was diagnosed with **hypercholesterolemia**
- One developed an uncomplicated **varicella zoster infection** (successfully treated with oral valaciclovir and discontinuation of tofacitinib for 2 weeks)

At 6 months of follow-up:

- All patients remained on combination therapy
- 71% (5/7) achieved a **clinical response** (decrease in partial Mayo score of ≥3).
- 71% (5/7) showed **biochemical improvement**
- 43% (3/7) achieved **endoscopic remission**

Hilley P. et al. Inflamm Bowel Dis . 2021 Aug 19;27(9):e105-e106

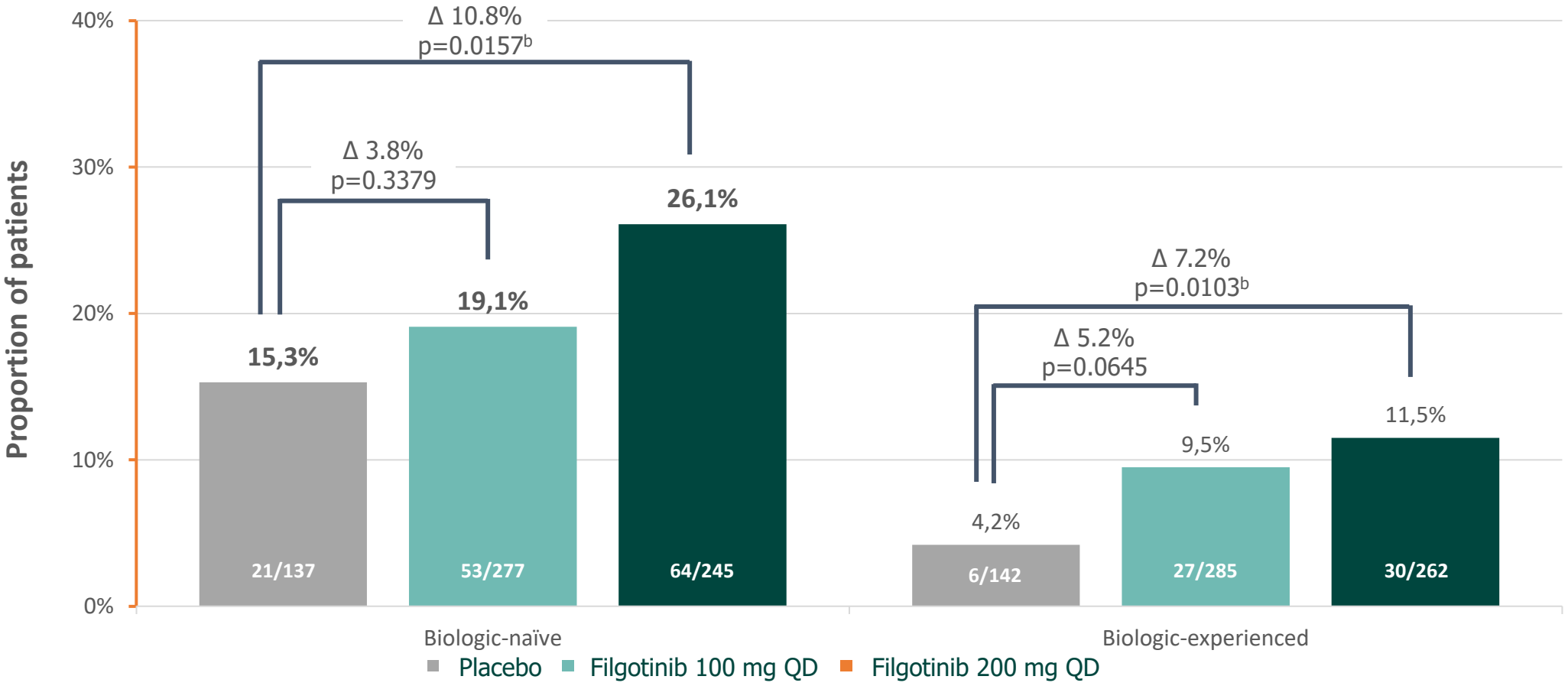
Filgotinib: General Features

- Selective inhibition of JAK1
- Non-dose dependent efficacy
- Non-liver dependent activation and metabolism
- Oral formulation
- Recommended dose is 200 mg once a day
- Dose adjustment to 100 mg per day if renal impairment (CrCl < 60 mL / min)
- Should be stopped if primary failure at week 16
- Can be restarted after a drug holiday

https://www.ema.europa.eu/en/medicines/human/EPAR/jyseleca

Filgotinib Efficacy in Ulcerative Colitis

Clinical Remission at Week 10

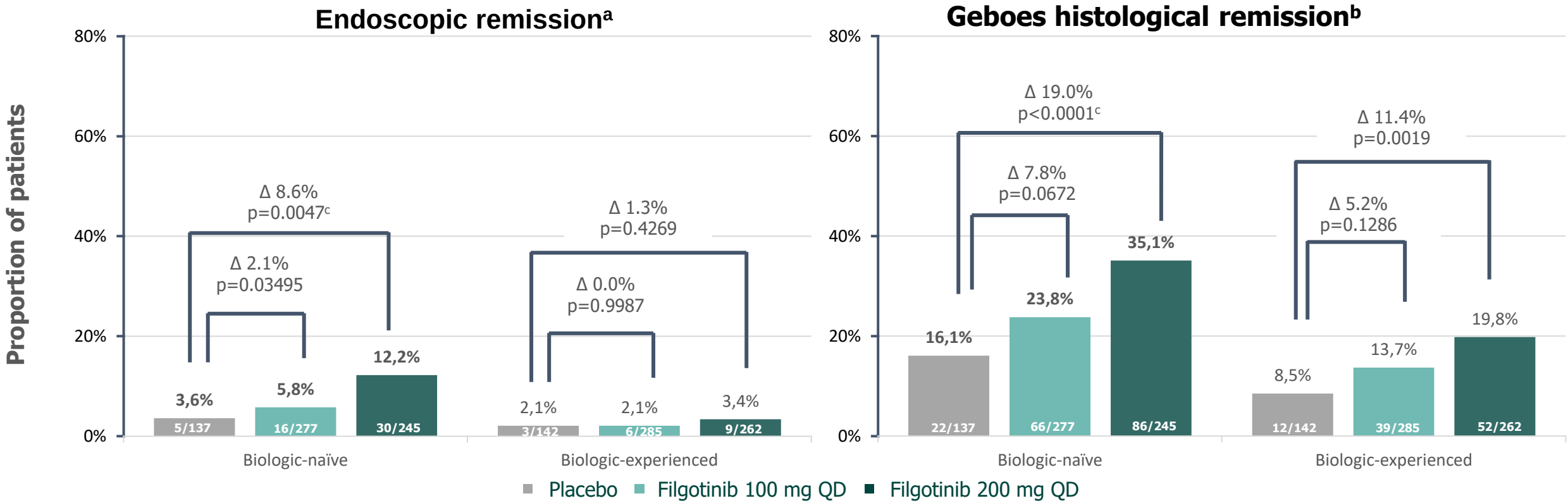


Filgotinib 200 mg demonstrated a significant difference in achieving the primary endpoint of clinical remission at Week 10 in both the biologic-naïve and biologic-experienced studies

Feagan et al. Lancet . 2021 Jun 19;397(10292):2372-2384

Filgotinib Efficacy in Ulcerative Colitis

Endoscopic and Geboes histological remission at Week 10

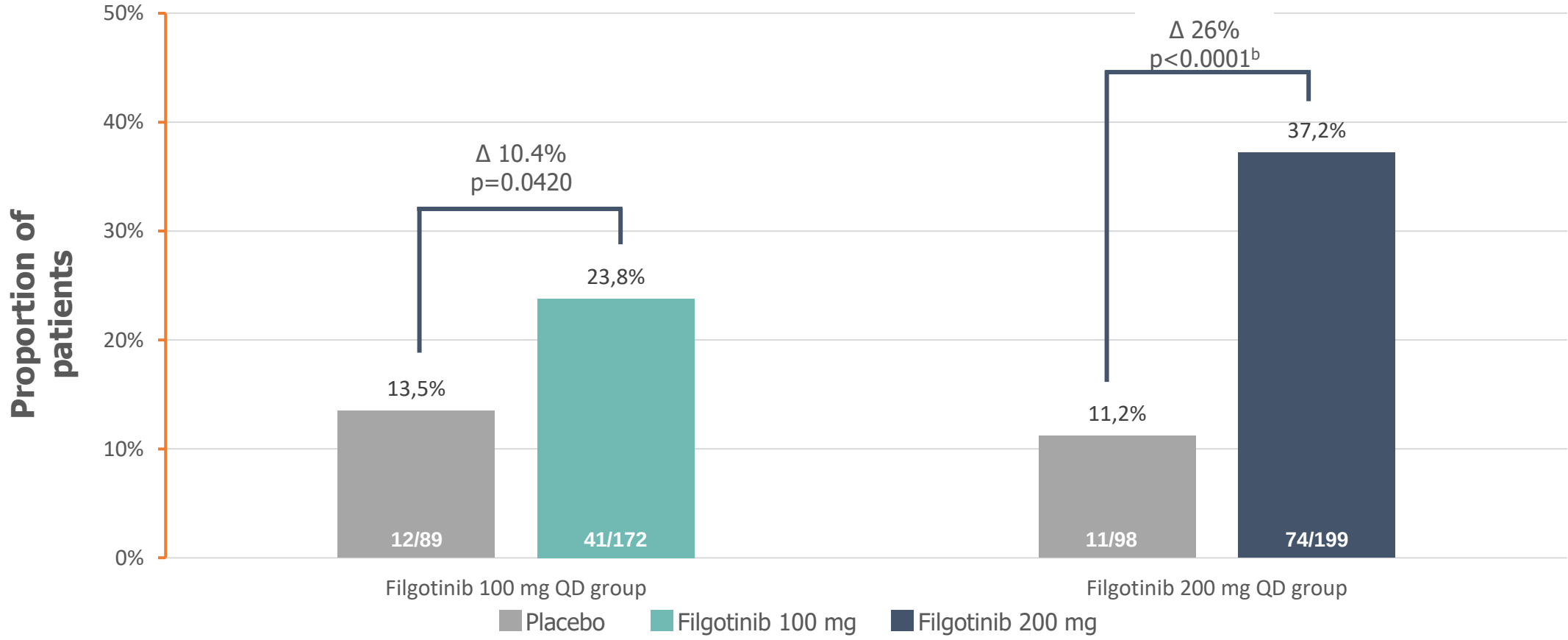


Filgotinib 200 mg demonstrated a significant difference in achieving endoscopic remission and histologic remission measured with the Geboes Index at Week 10 compared with placebo in the biologic-naïve study

Feagan et al. Lancet . 2021 Jun 19;397(10292):2372-2384

Filgotinib Efficacy in Ulcerative Colitis

Clinical Remission at Week 58



Filgotinib 200 mg and 100 mg demonstrated a significant difference in achieving clinical remission at Week 58 when compared with their matched placebos

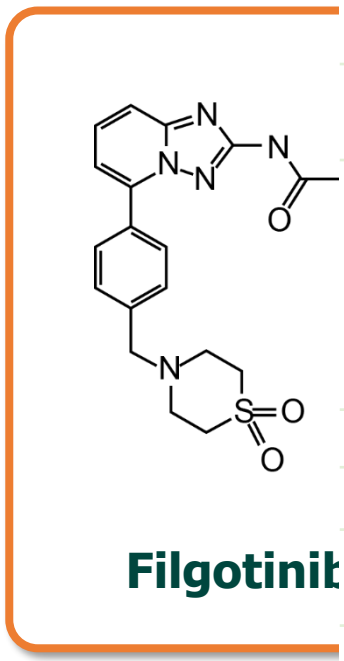
Feagan et al. Lancet . 2021 Jun 19;397(10292):2372-2384

Filgotinib Safety Profile

	Placebo* (n=93)	Placebo‡ (n=99)	Filgotinib 200 mg (n=202)
Total duration of study drug exposure, weeks	38·1 (15·2)	28·8 (17·7)	39·4 (14·3)
Treatment-emergent adverse events			
Adverse events	57 (61·3%)	59 (59·6%)	135 (66·8%)
Serious adverse events	4 (4·3%)	0	9 (4·5%)
Adverse events leading to study drug discontinuation	3 (3·2%)	2 (2·0%)	7 (3·5%)
Deaths	0	0	2 (1·0%)
Adverse events of interest			
Infections	21 (22·6%)	25 (25·3%)	71 (35·1%)
Serious infections	1 (1·1%)	0	2 (1·0%)
Herpes zoster	0	0	1 (0·5%)
Opportunistic infections	0	0	0
Malignancies§	0	0	1 (0·5%)
Non-melanoma skin cancer	0	0	0
Gastrointestinal perforation	0	0	0
Venous thrombosis excluding pulmonary embolism	2 (2·2%)	0	0
Pulmonary embolism	0	0	0
Arterial thrombosis¶	0	0	0
Cerebrovascular events¶	0	0	0

Modified from Feagan et al. Lancet . 2021 Jun 19;397(10292):2372-2384

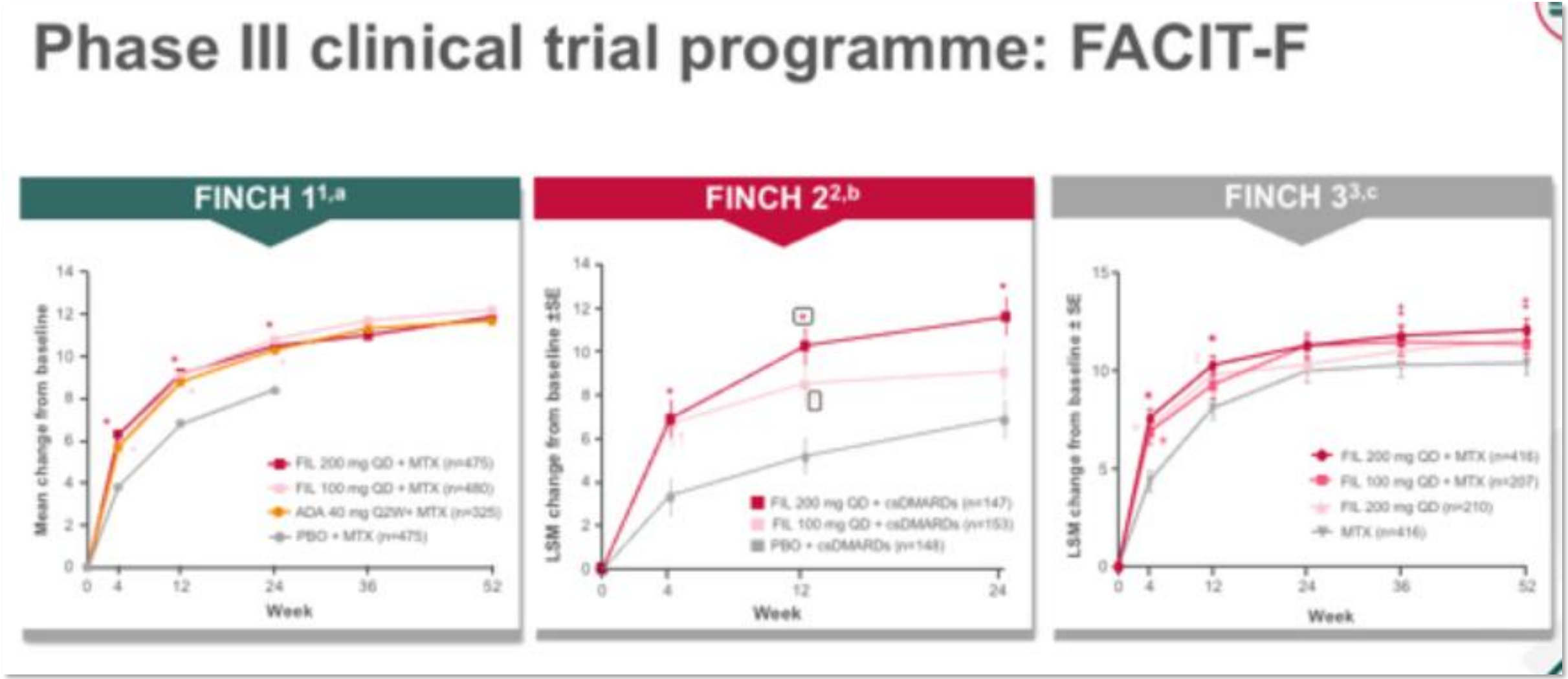
Filgotinib: Intestinal Metabolism



EFFECT OF OTHER MEDICINAL PRODUCTS ON FIL	
	• FIL is primarily metabolised by CES2, which can be inhibited *in vitro* by medicinal products such as fenofibrate, carvedilol, diltiazem or simvastatin. The clinical relevance of this interaction is unknown
EFFECT OF FIL ON OTHER MEDICINAL PRODUCTS	
CYP450 enzymes and UGT	• FIL is **not a clinically relevant inhibitor or inducer** of most enzymes or transporters such as CYP450 and UGT* • *In vivo* data demonstrated no inhibition or induction of CYP3A4 mediated metabolism
CYP2B6	• *In vitro* studies are inconclusive regarding the potential of FIL to induce CYP2B6. *In vivo* induction cannot be excluded
CYP1A2	• *In vitro* studies are inconclusive regarding the potential of FIL to induce or inhibit CYP1A2. No clinical studies have been performed to investigate interactions with CYP1A2 substrates and therefore the potential *in vivo* effect of concomitant induction and inhibition of CYP1A2 by filgotinib is unknown. • **Caution** is recommended when FIL is co-administered with CYP1A2 substrates with a narrow therapeutic index
P-gp and BCRP	• *In vitro* studies indicate that FIL and GS-829845 are not inhibitors of P-gp or BCRP.
Oral contraceptives	• No effect in pharmacological study with ethinyl estradiol/levonorgestrel; **no dose adjustment**
HMG-CoA reductase inhibitors	• No effect in pharmacological study with single dose atorvastatin, pravastatin or rosuvastatin; **no dose adjustment**
Antimycobacterials, antifungals, gastric acid reducing agents, oral anti-diabetics, sedatives/ hypnotics	• **No dose adjustment** is required upon co-administration *(See SmPC Table 7 for more details)*

Namour F, et al. Drug Metab Lett . 2016;10(1):38-48

Filgotinib: Efficacy on Fatigue



Upadacitinib: General Features

- Selective inhibition of JAK1
- Dose-dependent efficacy
- Oral formulation
- UC: Recommended induction dose is 45 mg once a day for 8 weeks (can be extended up to 16 weeks)
- UC: Recommended maintenance dose: 30 or 15 mg mg once a day
- Dose adjustment in case of renal impairment or liver disease
- Flexible dosage: three different dosages
- Both UC and CD
- Can be restarted after a drug holiday

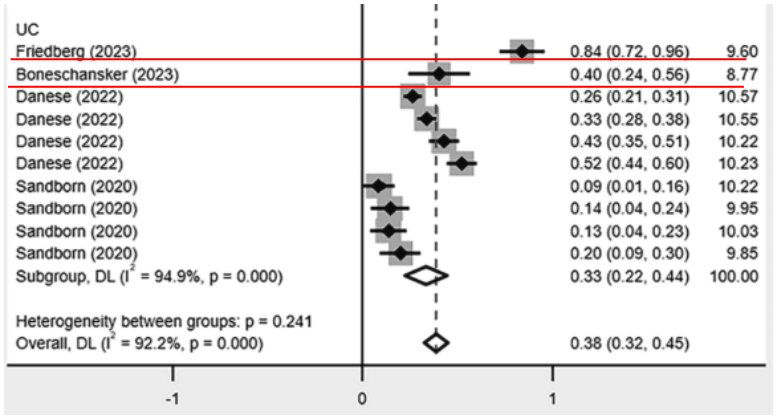
https://www.ema.europa.eu/en/medicines/human/EPAR/rinvoq

Effectiveness and safety of upadacitinib for inflammatory bowel disease: A systematic review and meta-analysis of RCT and real-world observational studies

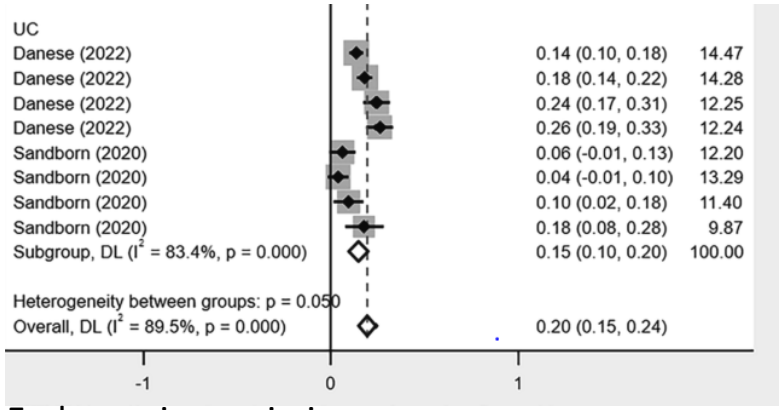
International Immunopharmacology 126 (2024) 111229

Dian-yu Zheng, Yi-nuo Wang, Yu-Hong Huang, Min Jiang, Cong Dai *

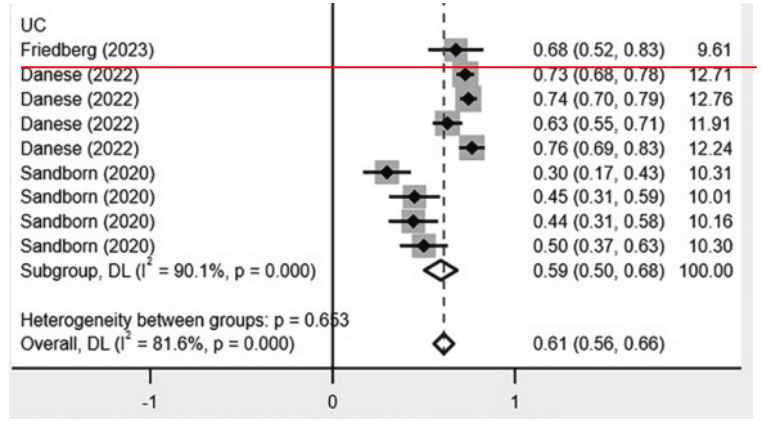
Department of Gastroenterology, First Hospital of China Medical University, Shenyang City, Liaoning Province, China



Clinical response



Endoscopic remission



Clinical remission

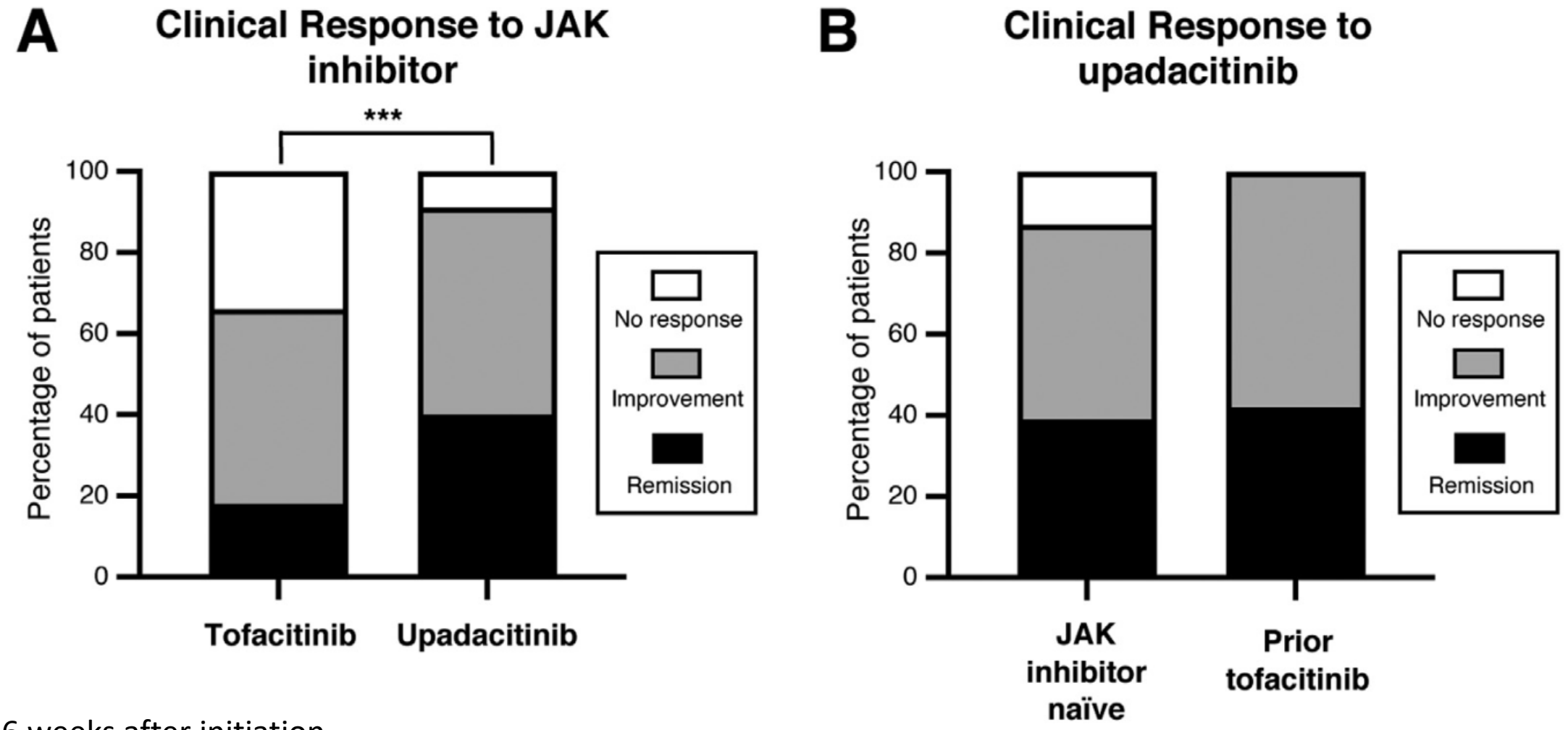
Comparative Effectiveness of Upadacitinib and Tofacitinib in Inducing Remission in UC: Real-World Data

	Tofacitinib (n = 119)	Upadacitinib (n = 35)	*P* value
Age at start of JAK inhibitor, *y*, means ± SD	42 ± 16	39 ± 13	.28
Disease duration, *y*, means ± SD	9.1 ± 7.9	9.6 ± 7.5	.73
Female gender, %	46	55	.31
Disease location, %			.79
Proctosigmoiditis	12	11	
Left sided	21	29	
Pancolitis	67	60	
Prior medications, %			
Mesalamine	95	91	.43
Steroids	99	100	.59
Thiopurines	43	43	.99
Methotrexate	13	17	.49
Cyclosporine	3	3	
Anti–tumor necrosis factor	97	97	.91
Vedolizumab	66	74	.38
Ustekinumab	12	40	<.001
Concomitant medication use during induction, %			
Steroids	48	40	.41
Vedolizumab	5	0	.18
Ustekinumab	1	3	.35

In UPA group, 12 had been treated previously with TOFA but stopped treatment due to a lack of sustained efficacy

Boneschansker L et al. Clin Gastroenterol Hepatol 2023 Aug;21(9):2427-2429.e1

Comparative Effectiveness of Upadacitinib and Tofacitinib in Inducing Remission in UC: Real-World Data



8 to 16 weeks after initiation

Boneschansker L et al. Clin Gastroenterol Hepatol 2023 Aug;21(9):2427-2429.e1

Comparative Effectiveness of Upadacitinib and Tofacitinib in Inducing Remission in UC: Real-World Data

- On multivariable analysis adjusting for demographics, disease duration, and extent, upadacitinib users had a 3 times higher odds of achieving clinical remission than tofacitinib users (OR 3.66; 95% CI, 1.52–8.78) and a 6 times higher odds of achieving either remission or improvement (OR 6.34; 95% CI, 1.76–22.87)
- There was no difference in the odds of achieving remission in those who had been treated previously with tofacitinib (n° 12) compared with those naïve to JAK inhibition (n° 23) (42% vs 39%; OR, 0.79; 95% CI, 0.08–7.96).
- No Safety issues were arised

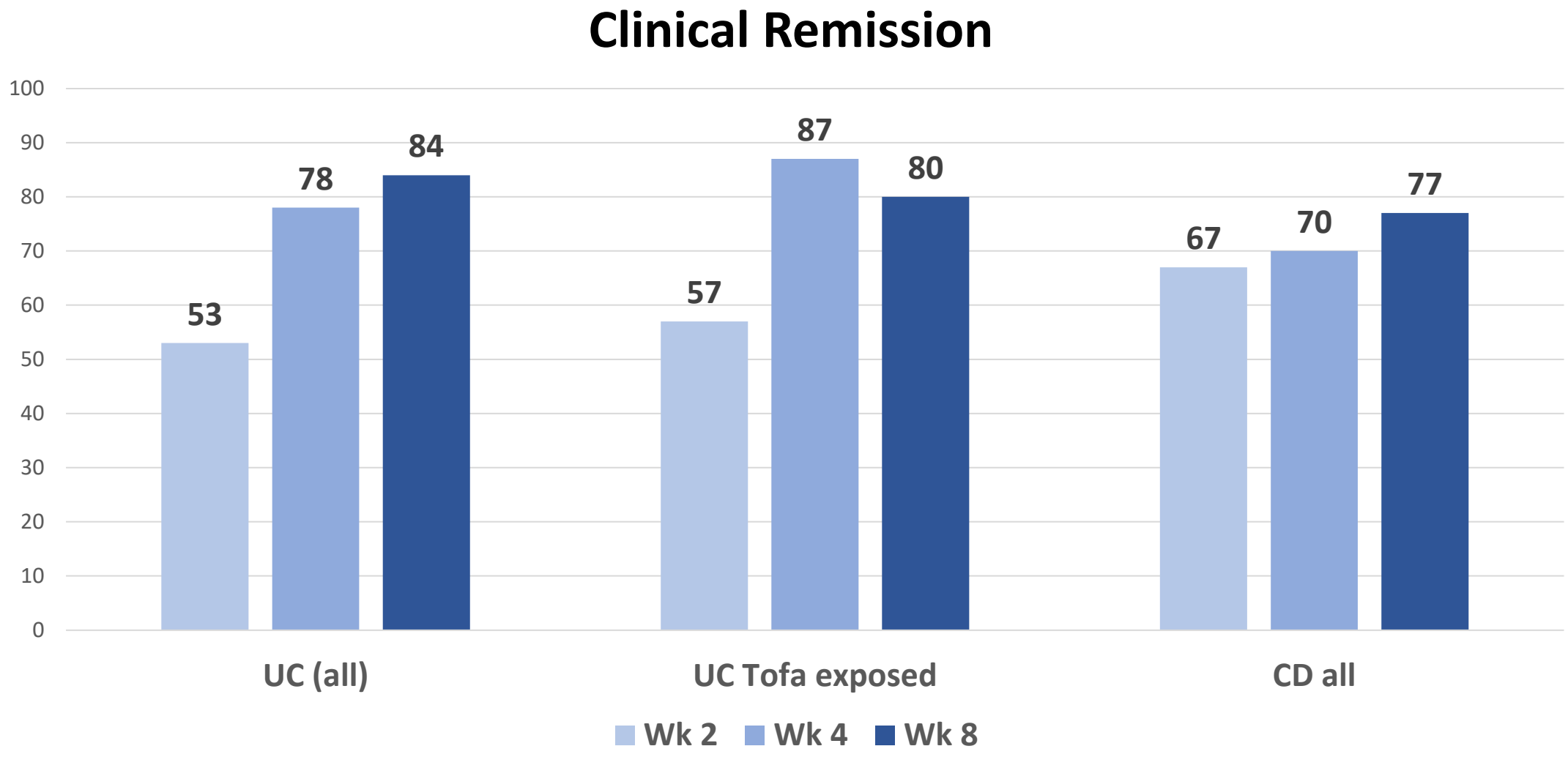
Boneschansker L et al. Clin Gastroenterol Hepatol 2023 Aug;21(9):2427-2429.e1

Upadacitinib Is Effective and Safe in Both Ulcerative Colitis and Crohn's Disease: Prospective Real-World Experience

	UC (n = 44)	CD (n = 40)
Age, *y*, means ± SD	38.9 (15.1)	36.9 (13.8)
Age of IBD diagnosis, *y*, means ± SD	26.5 (12.0)	19.3 (10.0)
Disease duration, *y*, means ± SD	12.4 (11.3)	16.7 (11.0)
Sex		
Female, n (%)	21 (47.73)	21 (52.50)
Male, n (%)	23 (52.27)	19 (47.50)
Medication history		
Biologic-exposed, n (%)	44 (100)	40 (100)
Infliximab, n (%)	29 (65.91)	38 (95.00)
Adalimumab, n (%)	23 (52.27)	33 (82.50)
Ustekinumab, n (%)	16 (36.36)	34 (85.00)
Vedolizumab, n (%)	27 (61.36)	20 (50.00)
Tofacitinib, n (%)	17 (38.64)	7 (17.50)
More than 1 prior advanced therapy, n (%)	36 (81.82)	39 (97.50)
Number of prior advanced therapies		
1, n (%)	8 (18.18)	1 (2.50)
2, n (%)	16 (36.36)	10 (25.00)
3, n (%)	8 (18.18)	8 (20.00)
4, n (%)	6 (13.64)	11 (27.50)
5, n (%)	5 (11.36)	9 (22.50)
6, n (%)	1 (2.27)	1 (2.50)

Friedberg S et al. Clin Gastroenterol Hepatol . 2023 Jul;21(7):1913-1923.e2

Upadacitinib Is Effective and Safe in Both Ulcerative Colitis and Crohn's Disease: Prospective Real-World Experience



Friedberg S et al. Clin Gastroenterol Hepatol . 2023 Jul;21(7):1913-1923.e2

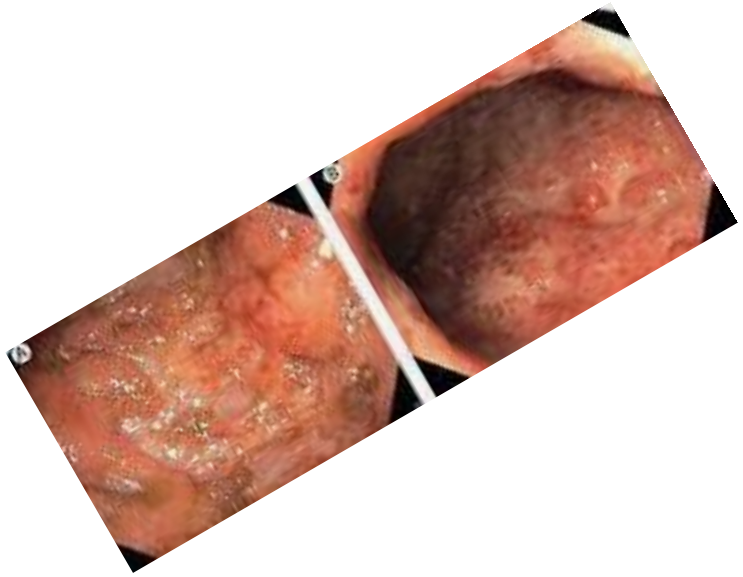
Upadacitinib Is Effective and Safe in Both Ulcerative Colitis and Crohn's Disease: Prospective Real-World Experience

	UC		
	Week 0	Week 4	Week 8
FCP			
<50	0/24 (0)	2/12 (16.67)	6/20 (30.00)
<150	5/24 (20.83)	5/12 (41.67)	13/20 (65.00)
<250	5/24 (20.83)	6/12 (50.00)	14/20 (70.00)
FCP normalization, *μg/g*			
<50	0/13 (0)	1/8 (12.50)	2/9 (22.22)
<150	3/13 (23.08)	3/6 (50.00)	3/7 (42.86)
<250	3/13 (23.08)	3/6 (50.00)	3/7 (42.86)
CRP, *mg/L*			
<5	23/32 (69.44)	9/14 (64.29)	22/26 (84.62)
<8	26/32 (77.78)	9/14 (64.29)	23/26 (88.46)
CRP normalization, *mg/L*			
<5	14/21 (66.67)	2/5 (40.00)	3/6 (50.00)
<8	15/21 (71.43)	1/4 (25.00)	3/6 (50.00)

Table 4. Safety Data of Upadacitinib in Ulcerative Colitis and Crohn's Disease Patients

	N = 105
Adverse effects, n (%)	34 (32.4)
Acne, n (%)	24 (22.9)
Nausea, n (%)	3 (2.9)[a]
Headaches, n (%)	2 (1.9)[a]
Anemia, n (%)	2 (1.9)
Arthralgias, n (%)	1 (1)[a]
Abdominal pain, n (%)	1 (1)
Hypertension, n (%)	1 (1)
Increased liver enzyme levels, n (%)	1 (1)
Serious adverse effects, n (%)	1 (1)[b]
Adverse events leading to discontinuation, n (%)	6 (5.7)[c]

Friedberg S et al. Clin Gastroenterol Hepatol . 2023 Jul;21(7):1913-1923.e2



Dig Dis Sci. 2024 Feb 28. doi: 10.1007/s10620-024-08302-2. Online ahead of print.

Upadacitinib as Rescue Therapy for the Treatment of Acute Severe Colitis in an Acute Care Setting

Joseph Clinton [1], Kiran K Motwani [2], Stephen Schwartz [3], Patrick McCarthy [2], Jordan E Axelrad [4], Raymond K Cross [2], Lauren George [2]

Inflamm Bowel Dis. 2024 Feb 26:izae038. doi: 10.1093/ibd/izae038. Online ahead of print.

Clinical Outcomes at 8–16 Weeks After Upadacitinib Initiation for Acute Severe Ulcerative Colitis: A Case Series in the United States

Rahul S Dalal [1], Rachel W Winter [1], Sanchit Gupta [1], Gila F Sasson [1], Matthew J Hamilton [1], Jessica R Allegretti [1]

Effectiveness of **Upadacitinib** for Patients with Acute Severe Ulcerative **Colitis**: A Multi-Center Experience.

Berinstein JA, Karl T, Patel A, Dolinger M, Barrett TA, Ahmed W, Click B, Steiner CA, Dulaney D, Levine J, Hassan SA, Perry C, Flomenhoft D, Ungaro RC, Berinstein EM, Sheehan J, Cohen-Mekelburg S, Regal RE, Stidham RW, Bishu S, Colombel JF, Higgins PDR.

Am J Gastroenterol. 2024 Jan 26. doi: 10.14309/ajg.0000000000002674. Online ahead of print.

Journal of Crohn's and Colitis, 2023, **17**, 2033–2036
https://doi.org/10.1093/ecco-jcc/jjad115
Advance access publication 9 July 2023
Short Report

Upadacitinib Salvage Therapy for Infliximab-Experienced Patients with Acute Severe Ulcerative Colitis

Robert Gilmore[a,b,c], Wei Lian Tan[a], Richard Fernandes[a,b,c], Yoon-Kyo An[a,b,c,d], Jakob Begun[a,b,c,d]

Effectiveness of **Upadacitinib** for Patients with Acute Severe Ulcerative **Colitis**: A Multi-Center Experience.

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Am J Gastroenterol. 2024 Jan 26. doi: 10.14309/ajg.0000000000002674. Online ahead of print.

Six patients who received upadacitinib for steroid-refractory ASUC

Case	Baseline characteristics									
	Age [years]	Sex	Duration of disease [years]	Extent of disease	Prior therapies	FCP [µg/mL]	CRP [mg/L]	IUS [Limberg]	MES [UCEIS]	Partial Mayo score
1	22	F	3	E3	Infliximab, vedolizumab	936	47	3	2 [6]	9
2	25	F	2	E3	Infliximab, vedolizumab	6000	19	2	3 [6]	7
3	26	M	2	E3	Infliximab	3338	39	2	2 [5]	7
4	24	M	1	E3	Infliximab	2989	122	2	3 [5]	8
5	58	M	38	E3	Infliximab, vedolizumab	1355	5	3	2 [5]	7
6	41	M	5	E2	Infliximab, vedolizumab, golimumab	7000	28	3	3 [6]	8

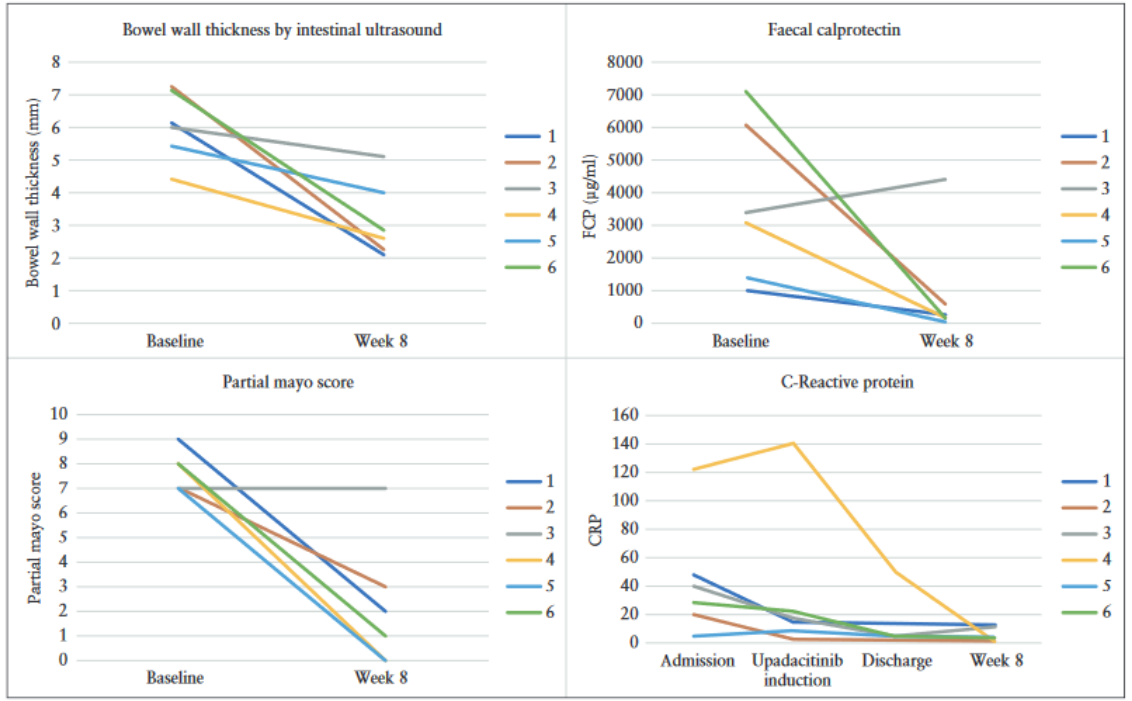


Figure 1. Faecal calprotectin, bowel wall thickness by intestinal ultrasound, partial Mayo score and CRP at baseline and after 8 weeks of upadacitinib 45 mg daily. FCP: faecal calprotectin; CRP: C-reactive protein.

JAK inhibitor safety

EMA recommendations to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

EMA's safety committee (PRAC) conclusions

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
News 28/10/2022

The review confirmed Tofacitinib increases the risk of major CV problems, cancer, VTE, serious infections and death due to any cause when compared with TNF-alpha inhibitors

These safety findings apply to **all approved uses of JAK inhibitors** in chronic inflammatory disorders (RA, PsA, JIA, axSpA, UC, AD and alopecia areata)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
News 11/11/2022

EMA recommendations to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

https://www.ema.europa.eu/en/news/ema-recommends-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic

In patients with:

- **> 65 years or above**
- **increased risk of major CV problems** (such as heart attack, stroke)
- **history of current or past smoking**
- **increased risk of cancer**

JAK-is should be used **only if no suitable treatment alternatives are available**

In patients with:

- **risk factors for blood clots in the lungs and in deep veins (VTE)**

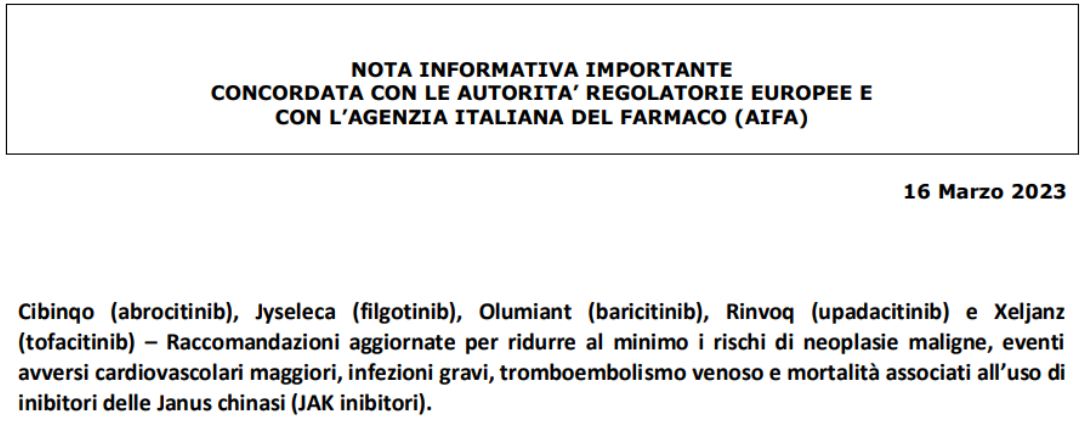
The doses should be reduced in some patient groups who may be at risk of VTE, cancer or major CV problems

Use JAK inhibitors with caution

JAK Inhibitors Safety: EMA (PRAC) Restrictions

Doctors need caution to prescribe JAKs in patients without therapeutic alternatives in the following seetings:

- with heart failure
- with inherited coagulation disorders
- who have had venous thromboembolism, either deep venous thrombosis or pulmonary embolism
- who use combined hormonal contraceptives or hormone replacement therapy
- with malignancy
- who are undergoing major surgery
- Age >65 years
- Obesity (BMI>30)
- smoking
- immobilisation.



NOTA INFORMATIVA IMPORTANTE
CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE E
CON L'AGENZIA ITALIANA DEL FARMACO (AIFA)

16 Marzo 2023

Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) e Xeljanz (tofacitinib) – Raccomandazioni aggiornate per ridurre al minimo i rischi di neoplasie maligne, eventi avversi cardiovascolari maggiori, infezioni gravi, tromboembolismo venoso e mortalità associati all'uso di inibitori delle Janus chinasi (JAK inibitori).

Journal of Crohn's and Colitis, 2022, **XX**, 1–27
https://doi.org/10.1093/ecco-jcc/jjac115
Advance access publication 25 August 2022
ECCO Guideline/Consensus Paper

AQ1-AQ4

European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation

Joana Torres,[a,b,c] María Chaparro,[d] Mette Julsgaard,[e,f] Konstantinos Katsanos,[g] Zuzana Zelinkova,[h,i] Manasi Agrawal,[j,f] Sandro Ardizzone,[k] Marjo Campmans-Kuijpers,[l] Gabriele Dragoni,[m,n] Marc Ferrante,[o,p] Gionata Fiorino,[q] Emma Flanagan,[r] Catarina Frias Gomes,[a] Ailsa Hart,[s] Charlotte Rose Hedin,[t,u] Pascal Juillerat,[v,w] Annemarie Mulders,[x] Pär Myrelid,[y,z] Aoibhlinn O'Toole,[aa] Pauline Rivière,[bb] Michael Scharl,[cc] Christian Philipp Selinger,[dd,ee] Elena Sonnenberg,[ff] Murat Toruner,[gg] Jantien Wieringa,[hh,ii] C. Janneke Van der Woude[jj]

Drug	During pregnancy	During lactation
Mesalazine	Low risk	Low risk
Sulphasalazine	Low risk	Low risk
Corticosteroids	Low risk	Low risk
Metronidazole	Low risk*	Avoid
Ciprofloxacin	Avoid in T1*	Low risk[a]
Thiopurines	Low risk	Low risk
Thiopurines + allopurinol	Limited data	Limited data
Ciclosporin Tacrolimus	Low risk, limited data	Limited data
Anti-TNF	Low risk	Low risk
Vedolizumab	Low risk, limited data	Low risk, limited data
Ustekinumab	Low risk, limited data	Low risk, limited data
Methotrexate	Contraindicated	Contraindicated
Thalidomide	Contraindicated	Contraindicated
Tofacitinib	Contraindicated	No data; avoid
Filgotinib	Contraindicated	No data; avoid
Ozanimod	Contraindicated	No data; avoid

Efficacy and Safety of Biologics and Small Molecule Drugs for Patients with Moderate-to-Severe UC: A Systematic Review and Network Meta-analysis

Upadacitinib	**2·70 (1·18–6·20)**	**4·49 (2·18–9·24)**	**6·15 (2·98–12·72)**	**2·84 (1·28–6·31)**	**4·91 (2·59–9·31)**	**2·92 (1·31–6·51)**	**3·56 (1·84–6·91)**	**3·00 (1·32–6·82)**	**4·64 (2·47–8·71)**	**2·70 (1·18–6·20)**	**9·54 (5·45–16·69)**
3·01 (1·59–5·67)	Ozanimod	1·65 (0·77–3·55)	**2·27 (1·05–4·89)**	1·05 (0·45–2·41)	1·81 (0·91–3·60)	1·07 (0·46–2·49)	1·31 (0·65–2·67)	1·10 (0·47–2·61)	1·71 (0·87–3·37)	0·93 (0·47–1·85)	**3·52 (1·91–6·49)**
2·91 (1·19–7·10)	0·97 (0·39–2·39)	Filgotinib 200 mg	1·37 (0·71–2·62)	0·63 (0·30–1·31)	1·09 (0·63–1·89)	0·65 (0·31–1·35)	0·79 (0·44–1·41)	0·66 (0·31–1·42)	1·03 (0·60–1·77)	**0·56 (0·32–0·97)**	**2·12 (1·34–3·35)**
5·96 (2·35–15·14)	1·98 (0·77–5·09)	2·04 (0·66–6·33)	Filgotinib 100 mg	**0·46 (0·22–0·95)**	0·79 (0·45–1·39)	**0·47 (0·22–0·99)**	0·57 (0·32–1·03)	0·48 (0·22–1·03)	0·75 (0·43–1·30)	**0·41 (0·23–0·71)**	1·54 (0·97–2·45)
3·05 (1·68–5·51)	1·01 (0·55–1·86)	1·04 (0·43–2·50)	0·51 (0·20–1·27)	Tofacitinib	1·72 (0·90–3·29)	1·02 (0·45–2·30)	1·25 (0·64–2·45)	1·05 (0·46–2·41)	1·63 (0·86–3·08)	0·89 (0·46–1·69)	**3·35 (1·90–5·91)**
4·71 (2·83–7·83)	1·56 (0·92–2·66)	1·61 (0·71–3·65)	0·78 (0·33–1·86)	1·54 (0·96–2·48)	Etrolizumab	0·59 (0·31–1·14)	0·72 (0·48–1·08)	0·61 (0·31–1·21)	0·94 (0·69–1·29)	**0·51 (0·36–0·72)**	**1·94 (1·42–2·64)**
3·45 (1·90–6·24)	1·14 (0·62–2·11)	1·18 (0·49–2·83)	0·57 (0·23–1·44)	1·13 (0·64–1·99)	0·73 (0·45–1·18)	Ustekinumab	1·22 (0·62–2·39)	1·02 (0·44–2·35)	1·59 (0·83–3·02)	0·86 (0·45–1·66)	**3·26 (1·83–5·79)**
4·71 (2·68–8·28)	1·56 (0·87–2·81)	1·61 (0·68–3·79)	0·79 (0·32–1·93)	1·54 (0·90–2·63)	1·00 (0·64–1·55)	1·36 (0·79–2·33)	Vedolizumab	0·84 (0·41–1·68)	1·30 (0·96–1·74)	0·71 (0·45–1·10)	**2·67 (1·87–3·80)**
4·52 (2·55–8·01)	1·50 (0·83–2·72)	1·54 (0·65–3·65)	0·75 (0·30–1·86)	1·48 (0·86–2·55)	0·95 (0·61–1·51)	1·31 (0·76–2·26)	0·95 (0·57–1·60)	Golimumab	1·54 (0·79–3·01)	0·84 (0·43–1·65)	**3·17 (1·74–5·79)**
5·41 (3·30–8·86)	**1·79 (1·07–3·01)**	1·85 (0·82–4·15)	0·90 (0·38–2·12)	**1·77 (1·11–2·81)**	1·14 (0·88–1·49)	1·56 (0·98–2·48)	1·15 (0·75–1·75)	1·19 (0·77–1·84)	Adalimumab	**0·54 (0·37–0·79)**	**2·05 (1·54–2·73)**
2·75 (1·66–4·55)	0·91 (0·54–1·54)	0·94 (0·41–2·14)	0·46 (0·19–1·09)	0·90 (0·56–1·44)	**0·58 (0·43–0·78)**	0·79 (0·49–1·27)	**0·58 (0·37–0·91)**	**0·60 (0·39–0·95)**	**0·51 (0·37–0·69)**	Infliximab	**3·76 (2·77–5·12)**
8·23 (5·32–12·75)	**2·74 (1·72–4·34)**	**2·82 (1·30–6·12)**	1·38 (0·60–3·14)	**2·71 (1·81–4·02)**	**1·74 (1·34–2·26)**	**1·74 (1·34–2·26)**	**1·74 (1·22–2·49)**	**1·82 (1·25–2·63)**	**1·52 (1·21–1·92)**	**3·00 (2·33–3·82)**	Placebo

Endoscopic improvement

Clinical remission

N=29 trials (4 head-to-head) were eligible for inclusion

Lasa JS et al. Lancet Gastroenterol Hepatol. 2021 Nov 29;S2468-1253(21)00377-0

Efficacy and Safety of Biologics and Small Molecule Drugs for Patients with Moderate-to-Severe UC: A Systematic Review and Network Meta-analysis

Ozanimod	0·89 (0·58–1·37)	1·30 (0·84–1·99)	1·14 (0·73–1·78)	0·98 (0·62–1·55)	1·41 (0·82–2·42)	1·12 (0·71–1·78)	1·16 (0·68–1·98)	1·06 (0·67–1·69)	1·16 (0·53–2·56)	1·09 (0·78–1·53)
2·02 (0·65–6·18)	Upadacitinib	1·46 (0·99–2·11)	1·27 (0·86–1·89)	1·10 (0·73–1·65)	1·58 (0·94–2·60)	1·26 (0·83–1·90)	1·31 (0·80–2·13)	1·19 (0·79–1·80)	1·30 (0·61–2·79)	1·22 (0·93–1·59)
1·22 (0·41–3·65)	0·61 (0·24–1·52)	Filgotinib	0·87 (0·59–1·29)	0·75 (0·50–1·13)	1·08 (0·66–1·78)	0·86 (0·57–1·30)	0·89 (0·55–1·46)	0·82 (0·54–1·23)	0·89 (0·41–1·91)	0·84 (0·64–1·09)
2·00 (0·66–6·03)	1·00 (0·39–2·51)	1·63 (0·66–4·01)	Tofacitinib	0·86 (0·56–1·31)	1·23 (0·74–2·06)	0·98 (0·64–1·51)	1·02 (0·62–1·69)	0·93 (0·61–1·43)	1·02 (0·47–2·20)	0·95 (0·71–1·28)
2·56 (0·80–8·19)	1·26 (0·46–3·44)	2·08 (0·79–5·51)	1·27 (0·47–3·40)	Ustekinumab	1·43 (0·85–2·42)	1·14 (0·73–1·78)	1·18 (0·71–1·98)	1·08 (0·70–1·68)	1·19 (0·54–2·58)	1·11 (0·81–1·51)
3·89 (0·94–16·04)	1·93 (0·53–6·96)	3·18 (0·90–11·21)	1·94 (0·54–6·90)	1·52 (0·40–5·70)	Vedolizumab	0·79 (0·47–1·34)	0·82 (0·46–1·48)	0·75 (0·44–1·27)	0·82 (0·36–1·88)	0·77 (0·50–1·17)
2·84 (0·85–9·46)	1·40 (0·49–4·00)	2·31 (0·83–6·40)	1·41 (0·50–3·95)	1·11 (0·37–3·30)	0·73 (0·18–2·83)	Golimumab	1·03 (0·61–1·73)	0·94 (0·61–1·47)	1·03 (0·47–2·25)	0·96 (0·71–1·32)
1·14 (0·31–4·12)	0·56 (0·18–1·76)	0·93 (0·30–2·82)	0·56 (0·18–1·74)	0·44 (0·13–1·45)	0·29 (0·07–1·22)	0·40 (0·12–1·35)	Etrolizumab	0·91 (0·54–1·53)	1·00 (0·43–2·27)	0·93 (0·62–1·41)
2·31 (0·74–7·17)	1·14 (0·43–3·00)	1·88 (0·74–4·79)	1·15 (0·45–2·96)	0·90 (0·32–2·49)	0·59 (0·16–2·16)	0·81 (0·28–2·34)	2·02 (0·64–6·41)	Adalimumab	1·09 (0·50–2·37)	1·02 (0·74–1·39)
1·85 (0·52–6·61)	0·92 (0·30–2·82)	1·51 (0·51–4·51)	0·92 (0·31–2·78)	0·72 (0·22–2·32)	0·47 (0·11–1·96)	0·65 (0·19–2·17)	1·62 (0·45–5·88)	0·80 (0·25–2·49)	Infliximab	0·93 (0·46–1·90)
1·23 (0·51–3·01)	0·61 (0·31–1·19)	1·00 (0·53–1·87)	0·61 (0·32–1·16)	0·48 (0·23–1·01)	**0·25 (0·10–0·94)**	**0·43 (0·19–0·96)**	1·07 (0·43–2·71)	0·53 (0·26–1·06)	0·66 (0·27–1·62)	Placebo

Serious adverse events

Adverse events

N=29 trials (4 head-to-head) were eligible for inclusion

Lasa JS et al. Lancet Gastroenterol Hepatol. 2021 Nov 29;S2468-1253(21)00377-0

JAKs vs Biologics: When?

- Tofa in second line vs Ustekinumab

Statement 7: For adults with moderate to severe UC refractory to at least one biologic, IG-IBD recommends using tofacitinib or ustekinumab for the induction of remission. *(Strong recommendation; moderate-quality evidence for tofacitinib; low-quality evidence for ustekinumab – Agreement rate: 91%)*

Digestive and Liver Disease 54 (2022) 440–451

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Guidelines

Use of biologics and small molecule drugs for the management of moderate to severe ulcerative colitis: IG-IBD clinical guidelines based on the GRADE methodology ☆

Fabio Salvatore Macaluso[a,*], Ambrogio Orlando[a], Claudio Papi[b], Stefano Festa[b], Daniela Pugliese[c], Stefanos Bonovas[d,e], Claudia Pansieri[d,e], Daniele Piovani[d,e], Gionata Fiorino[f], Massimo Claudio Fantini[g,h], Flavio Caprioli[i,j], Marco Daperno[k], Alessandro Armuzzi[d,l], Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

And the other JAKis?

Take Home Messages

- Anti-JAKs are effective and relatively safe in ulcerative colitis and CD
- Efficient patient's selection, screening and regular monitoring can reduce risks for safety at minimum
- Data are lacking on paediatric population, elderly patients (> 65), and pregnancy
- Several anti-JAK inhibitors are now available and head-to-head trials are needed to compare their efficacy and safety.
- More data on combination therapy between anti-JAK and biologics or between anti-JAK and other small molecules are needed

Thank You for Your Attention