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Landscape of new drugs and targets in inflammatory bowel disease

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Abstract

Although the therapeutic armamentarium of Inflammatory bowel diseases (IBD) physicians has expanded rapidly in recent years, a proportion of patients remain with a suboptimal response to medical treatment due to primary no response, loss of response or intolerance to currently available drugs. Our growing knowledges of IBD pathophysiology has led to the development of a multitude of new therapies over time, which may, 1 day, be able to address this unmet medical need. This review aims to provide physicians an update of emerging therapies in IBD by focusing on drugs currently in phase 3 clinical trials. Among the most promising molecules are anti-IL-23, JAK-inhibitors, anti-integrins and S1P modulators. While the results in terms of efficacy and safety are fairly clear for some classes, the question of safety remains more uncertain for other classes. Molecules at a more preliminary stage of development (phase 1 and 2), one of which may 1 day offer an optimal benefit-risk ratio, will also be presented as well as their respective mechanisms of action.

KEYWORDS
clinical trials, inflammatory bowel disease, new drugs, phase 1, phase 2, phase 3

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract, which encompass two main entities, namely ulcerative colitis (UC) and Crohn's disease (CD). Evolving by relapses interspersed with periods of remission, these conditions generally require long-term treatments to not only induce remission but also maintain it, in order to avoid the occurrence of complications over the years. To date, a series of biologics and small molecules are available for the treatment of IBD, including anti-tumour necrosis factor-α or tumour necrosis factor alpha (TNF-α) (such as infliximab (IFX),[1,2] adalimumab,[3] certolizumab pegol[4] and golimumab(GOL)[5]), anti-integrin $\alpha_4\beta_7$ (vedolizumab),[6,7] anti-interleukin (interleukin)-12/23 (ustekinumab ,UST),[8] Janus kinase

(JAK) inhibitors in UC (such as tofacitinib and filgotinib),[9,10] as well as sphingosine-1 phosphate (S1P) receptor modulator, for the treatment of moderately to severely active UC, which is approved by the United States (US) Food and Drug Administration since May 2021 and available in US.[11]

Despite these plentiful therapeutic options, a suboptimal response to medical therapy (due to primary non response, secondary loss of response or intolerance to currently available treatments), remains a significant issue for a proportion of patients.[12] Our expanding knowledges of the IBD pathophysiology has led to the development of a multitude of new therapies over time, which could, 1 day, be able to tackle this unmet medical need. The mechanisms targeted by these new therapeutic options include anti-IL, new JAK inhibitors, therapies interfering with T-cell trafficking such as anti-integrins (preventing the migration of lymphocytes from the blood vessels to the gut) or sphingosine-1-phosphate (S1P) modulators (blocking lymphocytes in the lymph nodes) and toll like receptor (TLR) agonist, among many others.

This review aims to present promising molecules for the treatment of IBD, their mechanism of action as well as results in terms of effectiveness and safety when available. We will mainly focus on molecules currently being evaluated in phase 3 clinical trials (CTs) and will then describe, more briefly, drugs (and their respective targets) currently being evaluated in phase 1 and 2 CTs.

METHODS

An exhaustive search was conducted using ClinicalTrials.gov up to 30 June 2022, to identify IBD drugs whose development is still in progress (in a phase 1, 2 or 3 CT). A comprehensive literature search was then performed using Medline, Embase and ClinicalTrials.gov, to identify relevant studies for these drugs (reporting results of assessment of their efficacy and safety), published in English. This was performed using the following terms (alone or matched with the Boolean operators AND or OR) "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "clinical trial" in combination with each drug identified through ClinicalTrials.gov, separately. In addition, we manually reviewed the abstracts from major gastroenterology conferences (Digestive Disease Week, United European Gastroenterology, European Crohn's and Colitis Organisation) to include pertinent information. For molecules currently in development in a phase 3 CT, studies or abstracts reporting the results of phase 2, 3 and real-world studies were included. For molecules currently in development in a phase 1 or 2 CT, only studies reporting the results of the most advanced published phase have been included and reported. Studies related to cell and faecal therapies, treatments for perianal disease alone, treatment for analgesic purposes, those evaluating colonoscopy preparations, those evaluating assessment tools, dietary supplements, but also studies in withdrawal or terminated status (whatever the reason), leading to a cessation of the molecule development (after verification on the sponsor's website) were excluded.

RESULTS

Many therapies are currently being evaluated in IBD, either in phase 1, 2 or 3 CTs in UC and CD (Figure 1a and b, respectively). Table 1 (for UC) and 2 (for CD) resume the results (in terms of efficacy and safety) of phase 2,3 and real-world studies of the molecules currently under assessment in an IBD phase 3 study. Table 3 shows data for molecules currently being evaluated in a phase 1 or 2 study in IBD.

DRUG BEING EVALUATED IN A PHASE 3 CLINICAL TRIAL

Anti-IL-23

IL-23 is a pro-inflammatory cytokine, composed of 2 subunits (p19, specific to IL-23 and p40, common to IL-12), playing a key role in IBD.[13,14] Although UST (an inhibitor of p40 subunit) has been shown to be effective in IBD,[8] the p19 antagonists (selective IL-23 inhibitors) have proven to be more effective than UST in other immune-mediated conditions, leading us to evaluate them in IBD.[15,16] Four IL-23 p19 inhibitors are currently being evaluated in IBD: risankizumab, guselkumab, brazikumab and mirikizumab.

Risankizumab (BI655066/ABBV066) is an IgG1 monoclonal antibody.[17] In moderately to severely active CD, the two phase 3 induction studies (ADVANCE and MOTIVATE) demonstrated that risankizumab (600 or 1200 mg, administered intravenously or IV at weeks 0,4 and 8) was superior to placebo ,PBO to induce all coprimary endpoints (clinical remission and endoscopic response) at week 12 (p-values $\leq$0.0001).[18] In ADVANCE (included biologic-naïve or experienced patients), clinical remission and endoscopic response rates were, respectively, 45% and 40% with risankizumab 600 mg, 42% and 32% with risankizumab 1200 mg versus 25% and 18% with PBO.[18] In MOTIVATE (included biologic-experienced patients), clinical remission and response rates were, respectively, 42% and 29% with risankizumab 600 mg, 40% and 34% with risankizumab 1200 mg and 20% and 11% with PBO.[18] All secondary endpoints (stool frequency and abdominal pain score clinical remission, clinical response, endoscopic remission and ulcer free endoscopy) were also achieved at week 12, with a rapid improvement (as early as week 4).[17–20] Continued maintenance therapy with risankizumab (180 or 360 mg subcutaneously or SC every 8 weeks) led to significantly higher rates of clinical remission (55% with 180 mg (p = 0.0031), 52% with 360 mg (p = 0.0054) versus. 41% with PBO) and endoscopic response (47% with 180 and 360 mg (p < 0.0001 for both) versus. 22% with PBO) at week 52. Risankizumab was also able to achieve higher rate of patients with clinical response, endoscopic remission,[21] corticosteroids ,CS-free remission,[22] higher improvement of biomarkers (hs-CRP and fecal calprotectin),[23] and reductions in hospitalizations and surgeries at week 52 compared to withdrawal/PBO.[21,24] Patients without prior bio-failure (53.8% of patients with endoscopic response at week 52 compared to 43.7% of patients with a biologic experience), with any colonic involvement (p < 0.001) and with short CD

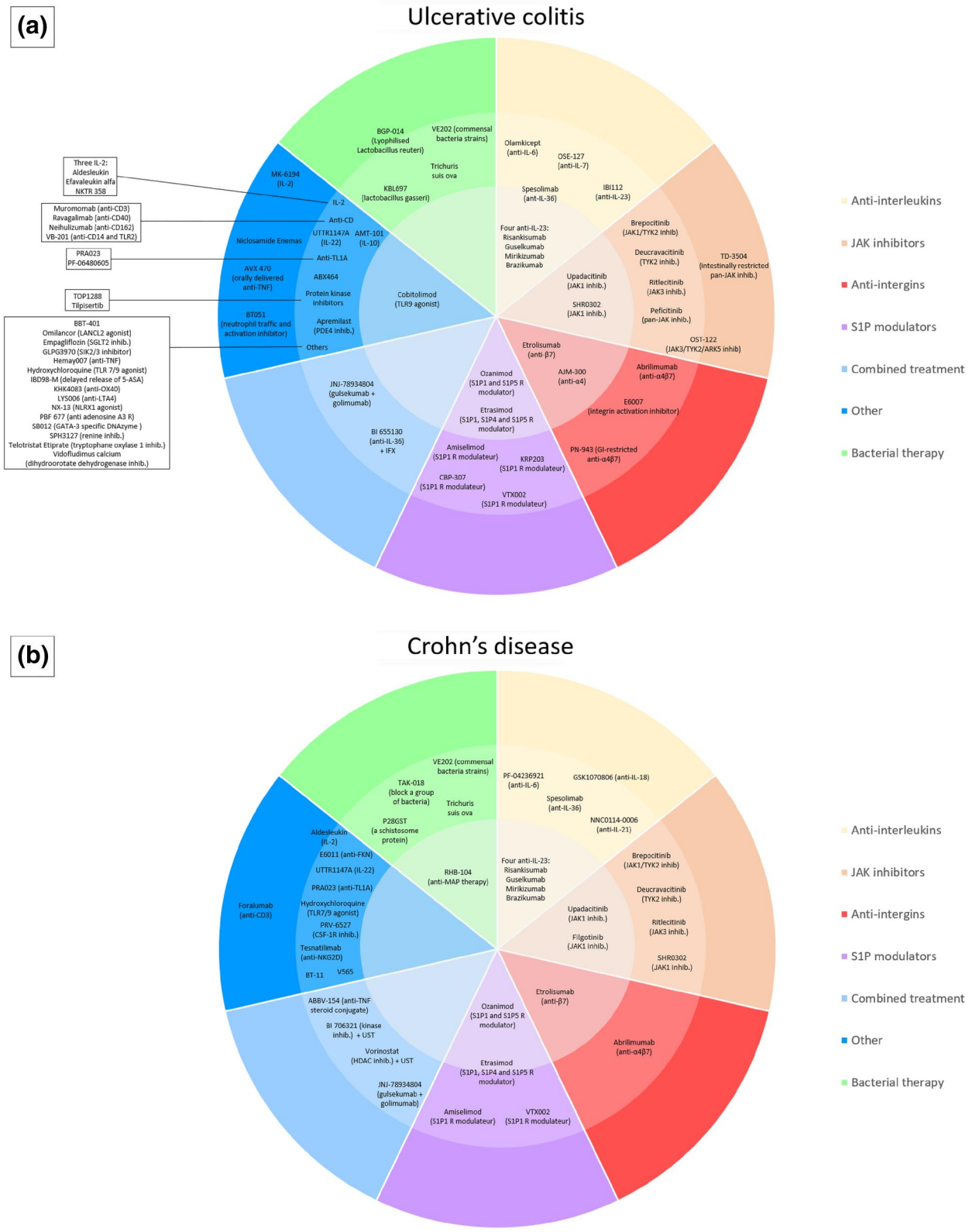

FIGURE 1 UC (a) and Crohn's disease (CD) (b) drugs pipeline. Outer ring: Phase 1, Middle ring: Phase 2, Inner circle: Phase 3. 5-ASA, 5-aminosalicylic acid; CSF-1R, Colony Stimulating Factor-1 Receptor; DNA, deoxyribonucleic acid; FKN, fractalkine; HDAC, Histone deacetylase inhibitor; IFX, infliximab; IL, interleukin; Inhib., inhibitor; LANCL2, Lanthionine synthetase C-like 2; MAP, *mycobacterium avium* subspecies paratuberculosis; NLRX1, nucleotide-binding oligomerization domain, leucine rich repeat containing X1; R, receptor; SGLT2, sodium/glucose cotransporter 2; S1P, sphingosine-1-phosphate; SGLT2, sodium/glucose cotransporter 2; SIK, salt-inducible kinase; TLR, toll like receptor; UST, ustekinumab

TABLE 1 Results of phase 2 and 3 studies for drugs currently being evaluated in phase 3 clinical trials (CTs), in ulcerative colitis (UC)

	Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Author
Anti-IL-23											
Guselkumab	2bNCT04033445	QUASAR	Guselkumab IV (200 or 400 mg) versus PBO at wks 0,4 and 8	I	$n = 313$	Anti-TNF-naive and anti-TNF-experienced	12 weeks	Clinical response at week 12 Guselkumab 200 mg: 61.4%; $p < 0.001$ Guselkumab 400 mg: 60.7%; $p < 0.001$ PBO: 27.6%	Clinical remission, symptomatic remission, endoscopic improvement, histo-endoscopic mucosal improvement, and endoscopic normalization at week 12: Significant for both dose (except endoscopic normalization with the dose of 400 mg)	The proportions of patients reporting AEs, SAEs, and AEs leading to discontinuation in the guselkumab groups were not greater compared with PBO. No serious infections were reported.	Dignass A, et al. (2022)[35]
	2aNCT03662542	VEGA	Guselkumab (200 mg IV at wks 0,4,8) versus golimumab (200 mg SC at wk 0 then 100 mg SC at wks 2,6,10) versus a combination with guselkumab and golimumab (GUS 200 mg IV + GOL 200 mg SC at wk 0, GOL 100 mg SC at wks2, 6, and 10, and GUS 200 mg IV at wks 4 and 8)	I	$n = 214$	Anti-TNF-naive	12 weeks	Clinical response at week 12 Golimumab: 44/72 (61.1%) Guselkumab: 53/71 (74.6%) Golimumab + Guselkumab: 59/71 (83.1%); $p = 0.003$ for golimumab and $p = 0.215$ for guselkumab	Clinical remission, symptomatic remission, endoscopic improvement, normalized fecal calprotectin at week 12: Significant compared to both Gol and Gus Endoscopic normalization at week 12: Significant compared to Gus Histologic remission at week 12: Significant compared to Gol	AEs, SAEs, and infection rates were comparable among treatment groups. One pt receiving combination therapy experienced a serious infection of influenza and sepsis. No deaths, malignancies, or tuberculosis cases were reported through wk 12	Sands BE, et al. (2022)[178]
Mirikizumab	2NCT02589665	I6T- MC-AMAC	Mirikizumab IV (50, 200 or 600 mg) versus PBO at wks 0,4 and 8	I	$n = 249$	Anti-TNF-naive and anti-TNF-experienced	12 weeks	Clinical remission at week 12 Mirikizumab 50 mg: 10/63 (15.9%); $p = 0.066$ Mirikizumab 200 mg: 14/62 (22.6%); $p = 0.004$ Mirikizumab 600 mg: 7/61 (11.5%); ns Combined mirikizumab: 31/186 (17.4%); $p = 0.20$ PBO: 3/63 (4.8%)	Clinical response, endoscopic improvement, symptomatic remission and histologic remission at week 12: Significant in combined mirikizumab group compared to PBO	There were comparable frequencies of treatment-emergent AEs across treatment groups, with the exception of worsening of UC, which was numerically higher in the PBO group.	Sandborn WJ, et al. (2020)[47]
			Mirikizumab 200 mg SC every 4 or 12 weeks	M	$n = 106$		52 weeks	Clinical remission at week 52 Mirikizumab 200 mg/4 weeks: 22/47 (46.8%)	Clinical response, endoscopic remission, endoscopic improvement,		

TABLE 1 (Continued)

	Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Author
								Mirikizumab 200 mg/12 weeks: 17/46 (37.0%) PBO/4 weeks: 1/13 (7.7%)	symptomatic remission, histologic remission at week 52: Higher rate in mirikizumab group (200 mg/4 or 12 weeks) Fecal calprotectin was lower in mirikizumab groups		
	3NCT03518086	LUCENT-1	Mirikizumab IV 300 mg/4 weeks	I	$n = 1162$	Anti-TNF-naive and anti-TNF-experienced	12 weeks	Clinical remission at week 12 Mirikizumab 300 mg IV/4 weeks: (24.2%); $p = 0.00006$ PBO/4 weeks: (13.3%)	Clinical response, endoscopic remission, symptomatic remission, clinical response in biologic-failed patients, histologic-endoscopic mucosal improvement, and improvement in bowel urgency at week 12: Mirikizumab-treated patients achieved all key secondary endpoints	The frequencies of TEAEs in mirikizumab-treated patients were similar to PBO. There were numerically fewer serious AEs (2.8% on mirikizumab and 5.3% on PBO) and discontinuations due to AEs in miritreated patients compared to PBO (1.6% on mirikizumab and 7.2% on PBO). There were 2 colon malignancies in the mirikizulab arm (0.2%) and no deaths during the treatment period	D'Haens G, et al. (2022)[41]
	3NCT03524092	LUCENT-2	Mirikizumab SC 200 mg/4 weeks	M	$n = 544$		40 weeks	Clinical remission at week 40 Mirikizumab 200 mg/4 weeks: 182/365 (49.9%); $p < 0.001$ PBO/4 weeks: 45/179 (25.1%)	CS-free remission, endoscopic remission, HEMR, improvement in bowel urgency, bowel urgency remission, and maintenance of clinical remission at week 40: All achieved (each: $p < 0.001$)	The frequency of TEAEs in mirikizumab patients was similar to PBO. There were fewer serious adverse events and discontinuations due to AEs in mirikizumab patients compared to PBO. The most common TEAEs were nasopharyngitis and arthralgia with mirikizumab and UC with PBO	Dubinsky M, et al. (2022)[42]
JAK inhibitors											
Upadacitinib	2bNCT02819635		Upadacitinib PO (7.5, 15, 30 or 45 mg) versus PBO once daily	I	$n = 250$	Anti-TNF-naive and anti-TNF-experienced	8 weeks	Clinical remission at week 8 Upadacitinib 7.5 mg:4/47 (8.5%); $p = 0.052$ Upadacitinib 15 mg: 7/49 (14.3%); $p = 0.013$ Upadacitinib 30 mg: 7/52 (13.5%); $p = 0.011$ Upadacitinib 45 mg: 11/56 (19.6%); $p = 0.002$	Endoscopic improvement, endoscopic remission, clinical response, change in Mayo score from baseline, histologic improvement at week 8: Significant with all the doses	One event of herpes zoster and 1 participant with pulmonary embolism and deep venous thrombosis were reported in the group that received upadacitinib 45 mg once daily. Increases in	Sandborn WJ, et al. (2020)[58]

(Continues)

TABLE 1 (Continued)

Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Author
							PBO: 0/46 (0%)		serum lipid levels and creatine phosphokinase with upadacitinib were observed	
3NCT02819635	U-ACHIEVE induction (UC1)	Upadacitinib PO 45 mg versus PBO once daily	I	$n = 474$	Anti-TNF-naive and anti-TNF-experienced	8 weeks	Clinical remission at week 8 Upadacitinib 45 mg: 83/319 (26%); $p < 0.0001$ PBO: 7/154 (5%)	Endoscopic improvement, endoscopic remission, clinical response, histological-endoscopic mucosal improvement, no bowel urgency, no abdominal pain, histological improvement, change from baseline in IBDQ total score, mucosal healing, change from baseline in FACIT-F score: All significant in UC1 and UC2	The most commonly reported AEs in UC1 and UC2 were nasopharyngitis, creatine phosphokinase elevation and acne. SAEs and AEs leading to discontinuation of treatment were less frequent in the upadacitinib group than in the PBO group	Danese S, et al. (2022)[59]
3NCT03653026	U-ACCOMPLISH (UC2)		I	$n = 522$		8 weeks	Clinical remission at week 8 Upadacitinib 45 mg: 114/341 (34%); $p < 0.0001$ PBO: 7/174 (4%)			
3NCT02819635	UC3 or U-ACHIEVE maintenance	Upadacitinib PO (15 or 30 mg) versus PBO once daily	M	$n = 451$		52 weeks	Clinical remission at week 52 Upadacitinib 15 mg: 63/148 (42%); $p < 0.0001$ Upadacitinib 30 mg: 80/154 (52%); $p < 0.0001$ PBO: 18/149 (12%)	Endoscopic improvement, maintenance of clinical remission, CS-free remission, maintenance of endoscopic improvement, endoscopic remission, maintenance of clinical response, histological-endoscopic mucosal improvement, change from baseline in IBDQ total score, mucosal healing, no bowel urgency, no abdominal pain, change from baseline in FACIT-F score: All significant with the 2 doses of upadacitinib	The most frequently reported AEs were worsening of UC, nasopharyngitis, creatine phosphokinase elevation, arthralgia and upper respiratory tract infection. Proportion of SAEs and AEs leading to discontinuation was lower in both upadacitinib groups than in the PBO group. Events of cancer or venous thromboembolism were reported infrequently. There were no treatment-related deaths	

TABLE 1 (Continued)

	Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Author
Ivarmacitinib	2NCT03675477	AMBER2	SHR0302 PO (4 or mg once daily or 4 mg twice daily) versus PBO	I	*n* = 161	Anti-TNF-naive and anti-TNF-experienced	8 weeks +8 weeks	Clinical response at week 8 HR0302 8 mg QD: 46.3%; *p* = 0.066 4mg BID: 46.3%; 0.059 4mg QD: 43.9%; *p* = 0.095 PBO: 26.8%	Clinical remission, endoscopic remission: Significant for all the doses compared to PBO	SHR0302 was well tolerated and demonstrated a safety profile, consistent with the JAK class of medicine	Chen B, et al. (2021)[73]
Anti-integrins											
Etrolizumab	2NCT01336465	EUCALYPTUS	Etolizumab SC (100 mg/4 weeks or 420 mg at wk 0 followed by 300 mg at wks 2, 4, and 8) versus PBO	I	*n* = 124	Anti-TNF-naive and anti-TNF-experienced	10 weeks	Clinical remission at week 10 Etrolizumab 100 mg: 8/39 (21%); *p* = 0·0040 etrolizumab 300 mg + LD: 4/39 (10%); *p* = 0·048 PBO: 0/41 (0%)	Clinical response, endoscopic remission/rectal bleeding score of 0 in the mITT populatio at week 6 and 10: ns Proportions of patients with MCS subscores of 1 point or less, and those with subscores of 0 points, were, numerically, generally higher in patients in the etrolizumab groups than in those in the PBO group	AEs occurred in 61% patients in the etrolizumab 100 mg group, in 48% patients in the 300 mg plus LD group, and 72% in the PBO group	Vermeire S, et al. (2014)[186]
	3NCT02165215	LAUREL	Etolizumab SC (105 mg/4 weeks) versus PBO	M	*n* = 214	Anti-TNF-naïve	62 weeks	Remission at week 62: Etrolizumab: 32/108 (29.6%); *p* = 0.19 PBO:21/102 (20.6%)	At week 62, etrolizumab was superior to placebo in endoscopic improvement, histological remission and endoscopic remission	A greater proportion of patients reported one or more AEs in the PBO group (80%) than in the etrolizumab group (65%). The most common AE in both groups was UC. No difference in SAEs between groups. No deaths were reported in either treatment group	Vermeire S, et al. (2021)[91]
	3NCT02100696	HICKORY	Etolizumab SC (105 mg/4 weeks) versus PBO	I	*n* = 609	Anti-TNF-experienced	14 weeks	Remission at week 14: Etrolizumab: 71/384 (18.5%); *p* = 0.0033 PBO: 6/95 (6.3%)	Etrolizumab was superior to PBO in endoscopic improvement at week 14 and 66, histologic remission at week 66 and endoscopic remission at week 66	Four patients in the etrolizumab group reported treatment-related AEs leading to treatment discontinuation. The proportion of patients reporting at least AE was similar between treatment groups for induction and	Peyrin-Biroulet L, et al. (2022)[90]
			Etolizumab SC (105 mg/4 weeks) versus PBO	M	*n* = 232		66 weeks	Remission at week 66: Etrolizumab: 27/112 (24.1%); *p* = 0.5 PBO: 23/114 (20.2%)			

(Continues)

TABLE 1 (Continued)

	Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Author
										maintenance. The most common adverse event in both groups was UC flare	
	3NCT02163759	HIBISCUS I	Etrolizumab SC (105 mg/4 weeks) versus adalimumab versus PBO	I	$n = 358$	Anti-TNF-naive	10 weeks	Remission at week 10 Etrolizumab: 28/144 (19.4%); $p = 0.017$ compared to PBO PBO: 5/72 (6.9%)	On pooled analysis, etrolizumab was not superior to adalimumab in achieving induction of remission, endoscopic improvement, clinical response, histological remission, or endoscopic remission; however, similar numerical results were observed in both groups.	The most common AEs in all groups was UC flare. The incidence of SAEs in the pooled patient population was similar for etrolizumab (5%) and placebo (5%) and lower for adalimumab (2%). Two patients in the etrolizumab group died; neither death was deemed to be treatment related	Rubin DT, et al. (2022)[92]
	3NCT02171429	HIBISCUS II	Etrolizumab SC (105 mg/4 weeks) versus adalimumab versus PBO	I	$n = 358$	Anti-TNF-naive	10 weeks	Remission at week 10 Etrolizumab: 26/143 (18.2%); $p = 0.17$ compared to PBO PBO: 8/72 (11.1%)			
	3NCT02136069	GARDENIA	Etolizumab SC (105 mg/4 weeks) versus infliximab	M	$n = 397$	Anti-TNF-naive	54 weeks	Clinical remission at week 54: Etrolizumab: 37/199 (18.6%); $p = 0.81$ Infliximab: 39/198 (19.7%)	Proportion of patients who had both clinical response at week 10 and clinical remission at week 54	The number of patients reporting one or more AEs was similar between treatment groups. The most common AE in both groups was UC. More patients in the etrolizumab group reported SAEs (including serious infections) than did those in the infliximab group, the most common being UC	Danese S, et al. (2022)[87]
AJM300	2aJapicCTI-132293		AJM300 (960 mg PO) versus PBO 3 times daily	I	$n = 102$	Anti-TNF-naive	8 weeks	Clinical response at week 8: AMJ300: 32/51 (62.7%); $p = 0.0002$ PBO: 13/51 (25.5%)	Clinical remission, mucosal healing, improved of each subscore of the MCS, histologic improvement (Riley score): Significant Endoscopic subscore of 0 at week 8: Higher in the active treatment but not significant	No serious adverse event, including progressive multifocal leukoencephalopathy, was observed	Yoshimura N, et al. (2015)[97]
	3NCT03531892		AJM300 (960 mg PO) versus PBO 3 times daily	I	$n = 203$	Anti-TNF-naive and anti-TNF-experienced	8 weeks	Clinical response at week 8: AMJ300: 46/102 (45%); $p = 0{\cdot}00{,}028$	Statistically significant improvements were observed in the	No difference in the incidence of AEs between group. The	Matsuoka K, et al. (2022)[88]

TABLE 1 (Continued)

	Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Author
								PBO: 21/101 (21%)	secondary endpoints including mucosal remission rate and rectal bleeding disappearance rate	most common AE and treatment-related AE was nasopharyngitis. No deaths were reported. A SAE was reported in the AJM300 group (one patient with anal abscess), but this was judged to be unrelated to study drug	
S1P modulators											
Ozanimod	2NCT01647516	TOUCHSTONE	Ozanimod PO (0.5 or 1 mg once daily) versus PBO	I	$n = 197$	Anti-TNF-naive and anti-TNF-experienced	32 weeks	Clinical remission at week 8: Ozanimod 0.5 mg: 9/65 (14%); $p = 0.14$ Ozanimod 1 mg: 11/67 (16%); $p = 0.048$ PBO: 4/65 (6%) Clinical remission at week 32: Ozanimod 0.5 mg: 17/65 (26%); $p = 0.002$ Ozanimod 1 mg: 14/67 (21%); $p = 0.01$ PBO: 4/65 (6%)	Clinical response at week 8 and 32: Significant with the dose of 1 mg Mucosal healing at week 8 and 32: Significant with the 2 doses Histological remission ns at week 8 and significant with 1 mg at week 32	A decrease of absolute lymphocyte counts was observed at week 8 (49% from baseline in the group receiving 1 mg and 32% from baseline in the group that received 0.5 mg). The most common AEs overall were anemia and headache	Sandborn WJ, et al. (2016)[187]
	2NCT02531126	TOUCHSTONE OLE	Ozanimod 1 mg daily	OLE	$n = 170$	Anti-TNF-naive and anti-TNF-experienced	200 weeks	Partial Mayo score clinical response at week 56 (86.4%) and at week 200: 93.3%	Partial Mayo score [pMS] clinical remission at week 56 (66.4%) at week 200: 82.7% Histological remission at week 56 (46.3%) and at week 104 (38.5%) Endoscopic improvement at week 56 (46.4%) and at week 104 (46.5%)	No new safety signals were identified during ≥4 years of follow-up	Sandborn WJ, et al. (2021)[188]
	3NCT02435992	TRUE-NORTH	Ozanimod PO (1 mg per day) versus PBO	I	$n = 645$ (cohort 1) and $n = 367$ (cohort 2)	Anti-TNF-naive and anti-TNF-experienced	10 weeks	Clinical remission at week 10: Ozanimod 1 mg: 79/429 (18.4%); $p < 0.001$ PBO: 13/216 (6%)	Clinical response, endoscopic improvement, mucosal healing at week 10: Significant	The incidence of infection (of any severity) with ozanimod was similar to that with PBO during induction and higher than that with PBO during maintenance. Serious infection occurred in less than 2% of the patients in each group during the 52-week trial. Elevated liver	Sandborn WJ, et al. (2021)[101]
				M	$n = 457$		52 weeks	Clinical remission at week 52: Ozanimod 1 mg: 85/230 (37.0%) PBO: 42/227 (18.5%)	Clinical response, endoscopic improvement, maintenance of remission, CS-free remission, mucosal healing and durable		

(Continues)

TABLE 1 (Continued)

	Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Author
									remission: All significant	aminotransferase levels were more common with ozanimod	
	Real-world		Ozanimod 1 mg once daily	I	$n = 30$	Anti-TNF-naive and anti-TNF-experienced	10 weeks	8 patients (44%) had a clinical response, 6 (33%) were in clinical remission, and 6 patients (33%) achieved corticosteroids-free remission		Reduction in lymphocyte count, gastroenteritis, nausea, mild liver derangement	Cohen N, et al.[102]
Etrasimod	2NCT02447302	OASIS	Etrasimod PO (1 or 2 mg once daily) versus PBO	I	$n = 156$	Anti-TNF-naive and anti-TNF-experienced	12 weeks	Increase in the mean improvement in modified MCS from baseline to week 12 Etrasimod 1 mg: 1.94 (0.31); $p = 0.15$ Etrasimod 2 mg: 2.49 (0.31); $p = 0.009$ PBO: 1.50 (0.30)	Endoscopic improvement from baseline, clinical remission, clinical response, histologic improvement, histologic remission at week 12	Incidence of drug–related AEs and those leading to discontinuation were higher in the etrasimod groups than the PBO group. Three patients had a transient, asymptomatic, low-grade atrioventricular block that resolved spontaneously; all 3 patients had evidence of atrioventricular block before etrasimod exposure	Sandborn WJ, et al. (2020)
	2NCT02536404	OASIS OPEN	Etrasimod 2 mg	OLE	$n = 112$	Anti-TNF-naive and anti-TNF-experienced	52 weeks	Clinical response at end of treatment: 64%	Clinical remission: 33% Endoscopic improvement: 43% CS-free remission:22% Week 12 clinical response, clinical remission, or endoscopic improvement was maintained to end of treatment in 85%, 60%, or 69% of patients, respectively	Treatment-emergent AEs occurred in 60% of patients receiving etrasimod 2 mg at any time, most commonly worsening UC and anaemia; 94% of adverse events were mild/moderate	Vermeire S, et al. (2021)[113]
Anti-TLR9											
Cobitolimod	2bNCT03178669	CONDUCT	Cobitolimod versus PBO	I	$n = 211$	Anti-TNF-naive and anti-TNF-experienced	6 weeks	Clinical remission at week 6: Cobitolimod 2 × 31 mg: 5/40 (13%); $p = 0.18$ Cobitolimod 2 × 125 mg: 2/43 (5%); $p = 0.66$ Cobitolimod 2 × 250 mg: 9/42 (21%); $p = 0.025$	Secondary endpoints (Mayo clinical remission, symptomatic remission, clinical response, endoscopic	Ten patients (2 in the cobitolimod, 2 in the 4 × 125 mg, and 4 in the 2 × 250 mg group) had a total of 13 SAEs; these were worsening of UC (eight events)	Atreya R, et al. (2020)[189]

TABLE 1 (Continued)

Phase	Study name	Study design	I/M/ OLE/ RW	Cohort	Previous anti-TNF exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Author
							PBO: 3/44 (7%)	improvement and histological improvement): Non-significant whatever the dose	and pruritus, rash, abdominal hernia, fascia dehiscence, and deep vein thrombosis (one event each).	
	3NCT01493960 COLLECT	Cobitolimod versus PBO		n = 131	Anti-TNF-naive and anti-TNF-experienced	12 weeks	Clinical remission at week 12: Cobitolimod: 19/70 (27.9%); p = 0.214 PBO: 5/34 (15.2%)	Symptomatic remission at week 12, mucosal healing at week 4, histologic improvement at week 4: Significant	Not reported	Atreya R, et al. (2018)[123]

Abbreviations: AEs, adverse events; BID, twice daily; CS, corticosteroids, FACIT-F; Functional Assessment of Chronic Illness Therapy-Fatigue; GOL, golimumab; GUS, guselkumab; HEMR, endoscopic remission, histologic-endoscopic mucosal remission; I, induction; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; LD, loading dose; OLE, open-label extension; M, maintenance; MCS, Mayo Clinic Score; ns, non-significant; PBO, placebo; PO, per os; QD, once daily; RW, real-world (study); S1P, sphingosine-1-phosphate; SAE, serious adverse events; SC, subcutaneous; TEAE, treatment-emergent adverse events; TNF, tumour necrosis factor; vs, versus; Wks, weeks.

duration seemed to be the best responders.[25–28] Only one real-world study from a Belgian multicentric cohort of multi-refractory CD patients (95% had been exposed to more than 3 biologicals) has been published to date.[29] One third of these CD patients obtained a clinical remission and endoscopic response at week 24 with risankizumab and none of the patients experienced serious infections or intolerance.[29] Phase 2 and phase 3 studies are currently underway in UC and CD (including a phase 3 study comparing risankizumab to UST in moderate to severe CD patients, who have failed anti-TNF).[30]

Guselkumab (CNTO1959) is another IL-23 p19 inhibitor, already approved in plaque psoriasis[31] and psoriatic arthritis,[32] which has been shown to be effective in phases 2 studies in both CD and UC.[33–35] In the phase 2 GALAXI 1 study, CD patients were randomised 1:1:1:1:1 to receive guselkumab 200 mg, 600 mg, or 1200 mg IV at weeks 0, 4, and 8; UST 6 mg/kg IV at week 0 and 90 mg SC at week 8; or PBO.[33] A significantly higher proportion of CD patients met the primary endpoint (change from baseline in Crohn disease activity index or Crohn's disease activity index at week 12: −148 in combined guselkumab treatment vs. −36.2 on PBO; p = 0.006) and key secondary endpoints.[33] Guselkumab induction followed by SC maintenance (100 mg every 8 weeks for patients receiving 200 mg IV during induction or 200 mg every 4 weeks for patients receiving either 600 or 1200 mg IV during induction) achieved high rates of clinical efficacy at week 48 (with 63.9%, 73.0% and 57.4% of patients in clinical remission, respectively, compared to 58.7% in the UST group).[34] Guselkumab also appears to be an effective induction treatment in moderate to severe active UC, as a greater proportion of patients treated by guselkumab (200 or 400 mg administered IV at weeks 0,4 and 8) achieved primary and secondary endpoints in the QUASAR phase 2b induction study.[35] Clinical remission at week 12, which was the primary endpoint, was achieved by 61.4% and 60.7% of patients treated by guselkumab 200 and 400 mg, respectively, versus 27.6% of PBO-treated patients (p < 0.001).[35] Several studies are still ongoing (such as continuation of GALAXI and QUASAR studies, GRAVITI phase 3 study in moderately to severely CD,[36] including FUZION CD for perianal fistulising CD[37]).

Brazikumab (MEDI2070, formerly AMG139) is another IgG2 monoclonal antibody targeting p19 subunit of IL-23.[38] In a phase 2a randomised control trial (RCT) in patients with moderately to severely active CD who had failed at least one anti-TNF therapy, a significant proportion of MEDI2070-treated patients (700 mg IV at weeks 0 and 4) achieved a clinical response (49.2%) compared to PBO (26.7%; p = 0.01) at week 8, with a significant reduction of biomarkers.[14] Similar results were found at week 24 in the open-label period (with 210 mg of brazikumab SC every 4 weeks).[14] Patients with higher baseline IL-22 serum concentration (in particular above 15.6 pg/ml) had an increased probability of clinical response at week 8, suggesting that IL-22 could be used as a biomarker to predict treatment response and to target patients who might benefit.[14] Several phase 2 and phase 3 studies are currently underway in the UC and CD (Expedition in UC and INTREPID in CD).[39,40]

TABLE 2 Results of phase 2 and 3 studies for drugs currently being evaluated in phase 3 clinical trials (CTs), in Crohn's disease (CD)

	Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF/biologic exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Authors
Anti-IL-23											
Risankizumab	2 NCT02031276		Risankizumab IV (200 or 600 mg) versus PBO at weeks 0,4,8	I	$n = 121$	Anti-TNF-naive and anti-TNF-experienced	12 weeks	Clinical remission at week 12 Risankizumab 200 mg: 10/41 (24%); $p = 0.31$ Risankizumab 600 mg: 15/41 (37%); $p = 0.0252$ PBO: 6/39 (15%)	Clinical response: Significant with 600 mg Endoscopic remission: Significant with 200 and 600 mg Endoscopic response: Significant with 600 mg Mucosal healing: no Deep remission: Significant in pooled analysis	Most common adverse events: Nausea and most common SAE: Worsening of underlying CD. No deaths occurred	Feagan BG, et al. (2017)[17]
			Risankizumab 180 mg SC/8 weeks	OLE	$n = 62$	Anti-TNF-naive and anti-TNF-experienced	52 weeks	Clinical remission at week 52 Risankizumab: 71% of patients	Clinical response: 81% Endoscopic response: 55% Endoscopic remission: 35% Mucosal healing: 24% Deep remission: 29%	Risankizumab was well tolerated with no new safety signals	Feagan BG, et al. (2018)[19]
	3 NCT03105128	ADVANCE	Risankizumab IV (600 or 1200 mg) versus PBO at wks 0,4 and 8	I	$n = 850$	Biologic-naive and biologic-experienced	12 weeks	Clinical remission at week 12 Risankizumab IV 600 mg: 152/336 (45%); $p < 0.0001$ Risankizumab IV 1200 mg: 141/339 (42%); $p < 0.0001$ PBO: 43/175 (25%) Endoscopic response at week 12 Risankizumab IV 600 mg: 135/336 (40%); $p < 0.0001$ Risankizumab IV 1200 mg: 109/339 (32%); $p < 0.0001$ PBO: 21/175 (12%)	SF remission, AP remission, clinical response, endoscopic remission, ulcer free endoscopy: Significant with both doses	The overall incidence of treatment-AE was similar among the treatment groups in both trials. Three deaths occurred during induction (two in the placebo group and one in the risankizumab 1200 mg group, deemed unrelated to the study drug).	D'Haens G, et al. (2022)[18]
	3NCT03104413	MOTIVATE	Risankizumab IV (600 or 1200 mg) versus PBO at wks 0,4 and 8	I	$n = 569$	Biologic-experienced	12 weeks	Clinical remission at week 12 Risankizumab IV 600 mg: 80/191 (42%); $p < 0.0001$ Risankizumab IV 1200 mg: 77/191 (40%); $p < 0.0001$ PBO: 37/187(20%) Endoscopic response at week 12 Risankizumab IV 600 mg: 55/191 (29%); $p < 0.0001$	SF remission, AP remission, clinical response, endoscopic remission, ulcer free endoscopy: Significant with both doses		

TABLE 2 (Continued)

	Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF/biologic exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Authors
								Risankizumab IV 1200 mg: 65/191 (34%); $p < 0.0001$ PBO: 21/187 (11%)			
	3NCT03105102	FORTIFY	Risankizumab SC (180 or 360 mg) versus PBO every 8 weeks	M	$n = 298$	Anti-TNF-naive and anti-TNF-experienced	52 weeks	Clinical remission at week 52 Risankizumab 180 mg: 87/157 (55%); $p = 0.0031$ Risankizumab 360 mg: 74/141 (52%); $p = 0.0054$ PBO: 67/164 (41%) Endoscopic response at week 52 Risankizumab 180 mg: 74/157 (47%); $p < 0.0001$ Risankizumab 360 mg: 66/141 (47%); $p < 0.0001$ PBO: 36/164 (22%)	SF remission: Significant with 360 mg AP remission, clinical response, enhanced clinical response, ulcer-free endoscopy, endoscopic remission, dep remission: Significant with both doses	Treatment was well tolerated. AE rates were similar among groups. The most frequently reported adverse events in all treatment groups were worsening CD, arthralgia, and headache.	Ferrante M, et al. (2022)[21]
	Real-world study		Rizankisumab 180 mg/8 weeks	RW	$n = 19$	Anti-TNF experienced	24 weeks	CS-free remission at week 24 Risankizumab: 7/19 (37%)	Clinical remission: 7/19 (27%) Clinical response: 15/19 (79%) Endoscopic remission: 1/19 (5%) Endoscopic response: 7/19 (37%) Biological remission: 3/19 (16%) Biological response: 10/19 (53%) Need for CD-related hospitalization: 3/19 Need for CD-related surgery: 2/19	None of the patients experienced serious infections or intolerance	Alsoud D, et al. (2022)[29]
Guselkumab	2NCT03466411	GALAXI-1	Guselkumab IV (200, 600 or 1200 mg) at wks 0,4 and 8 versus ustekinumab (6 mg/kg at wk 0 and 90 mg SC at wk 8) versus PBO	I	$n = 309$	Anti-TNF-naive and anti-TNF-experienced	12 weeks	Change from baseline in CDAI at week 12 Guselkumab 200 mg: -160.4; $p = 0.001$ Guselkumab 600 mg: −138.9; $p = 0.115$ Guselkumab 1200 mg: -144.9; $p = 0.040$ Combined: −148; $p = 0.006$ Ustekinumab: −135.9 PBO: −36.2	Clinical remission, clinical response, PRO-2 remission, clinical-biomarker response, endoscopic response: Significant in the combined group	Safety event rates were generally similar across treatment groups	Sandborn WJ, et al. (2022)[33]
	2NCT03466411		Guselkumab SC (100 mg every 8 weeks or 200 mg every	M	$n = 248$	Anti-TNF-naive and anti-TNF-experienced	48 weeks	Clinical remission at week	CS-free clinical	Key safety event rates were similar among	Danese S, et al. (2022)[34]

(Continues)

TABLE 2 (Continued)

	Phase	Study name	Study design	I/M/ OLE/ RW	Cohort	Previous anti-TNF/ biologic exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Authors
			4 weeks) versus ustekinumab					48 Guselkumab 100 mg q8w < 200 mg IV: 63.9% Guselkumab 200 mg q4w < 600 mg IV: 73.0% Guselkumab 200 mg q4w < 1200 mg IV: 57.4% Ustekinumab: 58.7%	remission: 71.4% with 200 mg q4w < 600 mg IV PRO-2 remission: 69.8% with 200 mg q4w < 600 mg IV Clinical response: 84.1% with 200 mg q4w < 600 mg IV	guselkumab dose groups; no opportunistic infections, case of tuberculosis, or death were reported in any group	
Brazikumab	2aNCT01714726		Brazikumab IV (700 mg) versus PBO at wks 0 and 4	I	$n = 119$	Anti-TNF experienced	8 weeks	Clinical response at week 8 Brazikumab: 29/59 (49.2%); $p = 0.010$ PBO: 16/60 (26.7%)	Clinical remission: ns Clinical response and ≥50% reduction in fecal calprotectin or CRP concentration from baseline: Significant	The most common adverse events were headache and nasopharyngitis	Sands, B et al. (2017)[14]
			Brazikumab SC 210 mg/4 weeks	OLE	$n = 52$		112 weeks	Clinical response at week 24 Brazikumab: 28/52 (53.8%) PBO: 30/52 (57.7%)	Clinical remission: 22/52 (42.3%) Clinical response and ≥50% reduction in fecal calprotectin or CRP concentration from baseline: 24/52 (46.2%)		
Mirikizumab	2NCT02891226	SERENITY	Mirikizumab IV (200, 600 or 1000 mg) versus PBO every 4 weeks	I	$n = 191$	Anti-TNF-naive and anti-TNF-experienced	12 weeks	Endoscopic response at week 12 Mirikizumab 200 mg: 8/31 (25.8%); $p < 0.1$ Mirikizumab 600 mg: 12/32 (37.5%); $p < 0.01$ Mirikizumab 1000 mg: 28/64 (43.8); $p < 0.01$ PBO: 7/64 (10.9%)	Endoscopic remission, PRO response and remission, CDAI response and remission, CRP and FC change from baseline: Significant with 600 and 1000 mg	Frequencies of AE in the mirikizumab groups were similar to PBO	Sands BE, et al. (2022)[43]
			Mirikizumab 300 mg IV versus SC every 4 weeks	M	$n = 176$		52 weeks	Endoscopic response at week 52 (among responders at week 12) Mirikizumab IV: 16/23 (69.6%) Mirikizumab SC: 16/24 (66.7%)	Endoscopic remission at week 52:19.5% in mirikizumab IV and 32.6% in mirikizumab SC		
JAK inhibitors											
Filgotinib	2NCT02048618	FITZROY	Filgotinib 200 mg PO versus PBO once a day	I	$n = 174$	Anti-TNF-naive and anti-TNF-experienced	10 weeks	Clinical remission at week 10 Filgotinib: 60/128 (47%); $p = 0{\cdot}0077$ PBO: 10/44 (23%)	Clinical response: Significang Endoscopic remission, mucosal healing, deep remission: ns	Serious treatment-emergent AEs were reported in 14 (9%) of 152 patients treated with filgotinib	Vermeire S, et al. (2017)[54]

TABLE 2 (Continued)

	Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF/biologic exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Authors
										and 3 (4%) of 67 patients treated with PBO	
Upadacitinib	2NCT02365649	CELEST	Upadacitinib PO (3, 6, 12, 24 mg twice daily or 24 mg once daily) versus PBO	I	$n = 220$	Anti-TNF-naive and anti-TNF-experienced	16 weeks	Clinical remission at week 16 Upadacitinib 3 mg BID: 5/39 (13%); ns Upadacitinib 6 mg BID: 10/37 (27%); ns Upadacitinib 12 mg BID: 4/36 (11%); ns Upadacitinib 24 mg BID: 8/36 (22%); ns Upadacitinib 24 mg QD: 5/35 (14%); ns PBO: 4/37 (11%) Endoscopic remission at week 16 Upadacitinib 3 mg BID: 4/39 (10%); ns Upadacitinib 6 mg BID: 3/37 (8%); ns Upadacitinib 12 mg BID: 3/36 (8%); ns Upadacitinib 24 mg BID: 8/36 (22%); $p < 0.01$ Upadacitinib 24 mg QD: 5/35 (14%); $p < 0.5$ PBO: 0/37 (0%)	Endoscopic response 50%, CDAI <150, CS-free clinical remission, mean change (reduction) from baseline in hs-CRP: Higher with upadacitinib 24 mg twice daily	During the induction period, patients in the upadacitinib groups had higher incidences of infections and serious infections versus PBO. Patients in the twice-daily 12 and 24 mg upadacitinib groups had significant increases in total, high-density lipoprotein, and low-density lipoprotein cholesterol levels compared with patients in the PBO group	Sandborn WJ, et al. (2020)[61]
			Upadacitinib PO (3,6 or 12 mg twice daily)	M	$n = 178$		52 weeks	Clinical remission and endoscopic remission at week 52 The percentage of patients with clinical remission, endoscopic remission was highest among patients receiving 12 mg twice daily compared with the other	The percentage of patients with endoscopic response 50%, and CDAI <150, was highest among patients receiving 12 mg twice daily compared with the other dose groups, but these differences were not significant.		
	2NCT02782663	CELEST OLE	Upadacitinib PO 15 mg QD versus upadacitinib 30 mg QD	OLE	$n = 107$	Anti-TNF-naive and anti-TNF-experienced	30 months	Clinical remission at month 30 Upadacitinib 15 mg: 31/51 (60.8%) Upadacitinib 30 mg:15/28 (53.6%) Upadacitinib 15 mg → 30 mg QD: 11/20 (55.0%)	Endoscopic response was maintained in all groups (month 24: 68%, 67%, and 40%, respectively)	AEs, SAEs, AEs leading to discontinuation, infections, serious infections, herpes zoster, and creatine phosphokinase elevation were higher with upadacitinib 30 versus 15 mg	D'Haens G, et al. (2021)[83]
	Real-world		Upadacitinib PO 45 mg/day	RW	$n = 6$	Anti-TNF-experienced	12 weeks	At week 2, all patients presented with a		Treatment was well tolerated. One case	Pokryszka J, et al. (2022)[64]

(Continues)

TABLE 2 (Continued)

	Phase	Study name	Study design	I/M/OLE/RW	Cohort	Previous anti-TNF/biologic exposure	Treatment period	Primary endpoint	Key secondary endpoints	Safety	Authors
								decrease in FC and CRP, as well as at week 6 and 12 for those for whom data was available		of fever and paresthesia was reported but did not lead to drug discontinuation. No cases of infection or TE	
	Real-world		Upadacitinib PO 15 mg/day (except for one patient, which had 30 mg)	RW	*n* = 12	Anti-TNF-experienced		3/12 patients (25%) reported improvement in their CD-related symptoms Five patients (41.67%) had objective evidence of response; four had a decrease in one inflammatory biomarker and one had evidence of CD improvement on pelvic MRI		Upadacitinib was well-tolerated and the AE profile was similar to that of the phase II study. two patients developed DVT/PE while on therapy.	Traboulsi C, et al. (2022)[65]
Anti-integrins											
Etrolizumab	3NCT02394028	BERGAMOT	Etrolizumab SC (105 mg or 210 mg/4 weeks) versus PBO		*n* = 300	Anti-TNF-naive and anti-TNF-experienced	14 weeks	Clinical remission at week 14 Etrolizumab 105 mg: 20.8% Etrolizumab 210 mg: 24.8% PBO: 11.9% Endoscopic improvement at week 14 Etrolizumab 105 mg: 17.4% Etrolizumab 210 mg: 21.0% PBO: 3.4%	CDAI remission, PRO2-remission were achieved in a greater proportion of patients treated by etrolizumab than PBO	Etrolizumab was well tolerated. The frequency of adverse events was comparable with PBO, and no deaths, anaphylaxis, or PML occurred	Reinisch W, et al. (2021)[95]
S1P modulators											
Ozanimod	2NCT02531113	STEPSTONE	Ozanimod PO (1 mg once daily after a 7-day dose escalation)		*n* = 69	Anti-TNF-naive and anti-TNF-experienced	12 weeks	Change in SES-CD from baseline to week 12 Ozanimod: 16/69 (23.2%)	A reduction from baseline in CDAI, clinical remission, clinical response, histological improvement were also observed	AEs were most frequently those attributed to CD. The most commonly reported serious treatment-related AE were CD (6 or 9%) and abdominal abscess(2 or 3%)	Feagan BG, et al. (2020)[103]

Abbreviations: AE, adverse event; AP, abdominal pain; BID, twice daily; Crohn disease activity index ,CDAI, Crohn disease activity index; CRP, C-reactive protein; CS, corticosteroids; DVT, deep vein thrombosis; FC, fecal calprotectin; I, induction study; IV, intravenous; M, maintenance study; ns, non-significant; OLE, open-label extension; PBO, placebo; PML, progressive multifocal leukoencephalopathy; PO, per os; QD, once daily; S1P, sphigosine-1-phosphate; serious adverse events ,SAE, serious adverse event; SC, subcutaneous; SES-CD, Simple Endoscopic Score for CD; SF, Stool frequency; TE, thromboembolic event; TNF, tumour necrosis factor; RW, real-world (study); wks, weeks.

TABLE 3 Molecules currently under development in phase 1 and 2 in Inflammatory bowel diseases (IBD) clinical trials (CTs)

Molecule name	Molecule type and target	Mechanism	Indication	Route	Ongoing phase	Ongoing clinical trials	Reported results	Authors	Efficacy	Safety
Anti-interleukins										
Olamkicept (TJ301/ GPD301)	A soluble gp130-Fc fusion protein targeting IL-6/soluble IL-6R complex	TJ301, by binding the **IL-6/soluble IL-6R complex**, inhibits trans-signaling. IL-6 is an important driver cytokine in the propagataion and maintenance of chronic inflammation	UC: moderate to severe, with an inadequate response to at least conventional therapy	IV	2	In UC (NCT03235752) : recruitment completed	2 (n=91)	Chen B, et al. (2021)[190]	Significantly greater clinical response (58.6% vs 34.5% on PBO; P=0.032), clinical remission (20.7% versus 0% on PBO) and mucosal healing (34,5% versus 3.4% on PBO; p<0,001) at week 12. Patients receiving olamkicept had greater improvements in partial Mayo score and fecal calprotectin levels than placebo	Well tolerated with a favourable safety profile that differentiates it from pan-IL-6 inhibitors
PF-04236921	Fully human antibody that binds to and neutralizes the IL-6 ligand	PF-04236921 binds the **IL-6** ligand and neutralize its activity	CD: moderate to severe	SC	2	ANDANTE I and II in CD (NCT01287897 ; NCT01345318): recruitment completed	2 in CD (n=247)	Danese S, et al. (2019)[191]	(CDAI)-70 response rates were significantly greater with PF-04236921 50 mg than PBO at weeks 8 (49.3% vs 30.6%, P<0.05) and 12 (47.4% vs 28.6%, P<0.05) Week 12 CDAI remission rates with PF-04236921 50 mg and PBO were 27.4% and 10.9%, respectively (16.5% difference; P<0.05).	GI abscess and perforation were observed
OSE-127	Humanised monoclonal antibody targeting CD127 receptor (or IL-7Rα)	OSE-127 targets the α chain of the IL-7R, allowing a potent antagonistic effect on effector T cells; **IL-7** is a cytokine regulating tissue migration of CD4 and CD8 effector T cells	UC: moderate to severe	IV	2	Co TikiS in UC (NCT04882007): recruiting	Na data			
GSK1070806	Humanized IgG1/kappa anti-IL-18 monoclonal antibody	GSK1070806, neutralizes activated (mature) **IL-18** released from damaged cells following inflammasome activation; IL-18 induces IFN-γ expression	CD: moderate to severe	IV	1/2	CDAID in CD (NCT03681067) : recruitment completed	No data			
NNC0114-0006	IL-21 monoclonal antibody	NNC0114-0006, by blocking the **IL-21**, limits modulating IL-17/IFN-γ production in IBD[192]	CD: moderate to severe	IV	2	In CD (NCT01751152) : recruitment completed	No data			
IBI112	A selective anti-IL23p19 monoclonal antibody	**IL-23**, when binding to its receptor, induces signal transducer and activator of transcription 3 (STAT3) phosphorylation and induces downstream IL-17 production	UC : moderate to severe	IV/SC	2	In UC (NCT05377580) : not yet recruiting	No data			
Spesolimab (BI 655130)	Humanized anti–IL-36 receptor monoclonal antibody	Activation of IL-36R induces MYD-88-dependent activation of NF-κB and MAPKs, resulting in the production of various pro-inflammatory effectors by the target cells (including epithelial cells, lymphocytes and fibroblasts)[193]	UC: moderate to severe CD: stenosing and fistulizing	IV/SC	~~2/3~~	In UC (NCT03482635): recruitment completed In UC (long term treatment) (NCT03648541): active, not recruiting Fistulising CD (NCT04362254) : active, not recruiting	No data			
Interleukin agonists										
Aldesleukin	IL-2	At low dose, IL-2 promote the selective activation and expansion of Tregs	UC and CD: moderate to severe	SC	1/2	Low dose in CD (NCT04263831) (study completed in UC)	No data			

(Continues)

TABLE 3 (Continued)

Efavaleukin alfa (AMG 592)	IgG Fc-IL-2 mutein fusion protein	Efavaleukin alfa, is an IL-2 mutein fusion protein, that selectively expand Treg[194]	UC : moderate to severe	SC	2	In UC (NCT04987307) : recruiting	No data			
MK-6194 (PT101)	IgG Fc-IL-2 mutein fusion protein	MK-6194, an IL-2 mutein Fc fusion protein that promotes expansion of Treg cell	UC: mild to severe	SC	1	In UC (NCT04924114) : recruiting	No data			
LY3471851 (NKTR 358)	Polyethylene glycol (PEG) conjugate of recombinant human IL-2	It targets the interleukin (IL-2) receptor complex in the body in order to stimulate proliferation of inhibitory immune cells known as regulatory T cells	UC: moderate to severe	SC	2	INSTRUCT-UC in UC (NCT04677179) : recruiting	No data			
AMT-101	GI-selective, recombinant biologic fusion protein of human interleukin 10 (hIL-10)	MT-101 is an oral, gut selective, fusion protein of IL-10, an anti-inflammatory cytokine, and a carrier protein that mediates transcytosis through intestinal enterocytes into the lamina propria	UC: moderate to severe	PO	2	LOMBARD in UC (NCT04583358): recruiting MARKET in UC (NCT05372939) : combination of AMT-101 and adalimumab	1b in UC (n=16)	Posch m, et al. (2021)[138]	Histological improvements were observed in 60% of patients on AMT-101, compared with 0% patients treated with PBO	AMT-101 was safe and well tolerated; all AEs were mild to moderate and self-limiting
UTTR1147A	Fusion protein in which IL-22 is linked with the Fc portion of IgG4 to improve the pharmacokinetic (PK) characteristics[139]	IL-22 binding activates the transcription factor signal transducer and activator of transcription 3 (STAT3) and contributes to innate immunity in epithelial tissues by increasing epithelial tight junction integrity and promoting mucus production and secretion of antimicrobial peptides[195,196]	UC and CD: moderate to severe	IV	2	In UC (NCT03558152) : UTTR1147A versus vedolizumab	1b in UC (n=24)	Wagner F.D., et al. (2020)[139]	Clinical response was observed in 7/18 patients, and clinical remission in 5/18 patients treated with UTTR1147A compared with 1/6 and 0/6 placebo patients, respectively	Adequate safety
JAK inhibitors										
Brepocitinib (PF-06700841)	Selective tyrosine kinase 2 (TYK2) and janus kinase 1 (JAK1) inhibitor	Brepocitinib inhibits cytokines mediated by the TYK2 isoform, in particular IL-12 and IL-23, as well as those mediated by JAK1	UC and CD: moderate to severe	PO	2	In UC (NCT02958865): recruitment completed In CD: recruiting (NCT03395184)	No data			
Deucravacitinib (BMS-986165)	Small molecule selectively targeting tyrosine kinase 2	Tyrosine kinase 2 (TYK2) is an intracellular enzyme, mediating signaling of inflammatory cytokines of both innate (type I IFN) and adaptative (IL12, IL-23) immune response	CD: moderate to severe	PO	2	Active, not recruiting in UC (NCT03934216) Long term safety and efficacy in UC and CD (NCT04877990): recruiting	No data			
Ritlecitinib (PF-06651600)	Small molecule that selectively inhibits JAK3/TEC	Inhibits JAK3 by irreversibly blocking the ATP binding site and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family of kinases. TEC kinases are involved in immunologic regulation	UC and CD: moderate to severe	PO	2	In UC: recruitment completed (NCT02958865) In CD: recruiting (NCT03395184)	2b in UC (VIBRATO study)	Hassan-Zahrae M, et al. (2022)[197]		
OST-122	Gut-restricted, and subtype-selective JAK3/TYK2/AMPK-related protein kinase 5 (ARK5) inhibitor	Inhibits the inflammatory cascade upstream of the JAK-STAT pathway	UC: moderate to severe	PO	1b/2a	In UC (NCT04353791) : recuiting	No data			

TABLE 3 (Continued)

Peficitinib (ASP015K, JNJ-54781532)	Small molecule, pan-JAK inhibitor	Inhibits JAK1, JAK2, JAK3 and TYK2 enzyme activities	UC: moderate to severe	PO	2b	In UC (NCT01959282) : recruitment completed	No data			
TD-3504	Intestinally restricted pan-JAK inhibitor	TD-3504 inhibits locally these JAK enzymes, thus interferes with the JAK/STAT signaling pathway and, thus, modulates the activity of a wide range of pro-inflammatory cytokines	UC: active moderate	PO	1	In UC (NCT03103412) : recruitment completed	No data			
Anti-integrins										
Abrilumab (AMG181/MEDI7183	Fully human monoclonal antibody against a4b7	AMG181 blocks the interaction of the α4β7 integrin with its target ligand MAdCAM-1 and thus prevents adhesion, extravasation and homing of lymphocytes	UC and CD: moderate to severe	SC	2	In UC (NCT01694485) : recruitement completed In CD (NCT01696396) : recruitement completed	2b in UC (n=354)	Sandborn WJ, et al. (2019)[147]	Abrilumab induce higher remission (13,3% with 70 mg vs 4.3% on PBO; p<0.05) at week 8, as well as clinical response and mucosal healing. Higher baseline α4β7 levels on naïve CD4+ T cells were a prognostic indicator for overall outcome, but not a predictive biomarker of abrilumab response	Abrilumab has an accept-able safety and tolerability profile. There were no cases of progressive multifocal leukoencephalopathy or deaths
Milategrast (E 6007)	Integrin activation inhibitor	Inhibits the adhesion and infiltration of various leukocytes through the blockade of the interaction between calreticulin (CRT) and the leukocyte adhesion molecule integrin α by associating with CRT	UC: active moderate	PO	2	In Japanese UC patients (NCT03018054) : recruitment completed	No data			
PN-943	GI-restricted peptide antagonist of $\alpha_4\beta_7$ integrin	PN-943, by inhibiting locally in the intestine, the $\alpha_4\beta_7$ integrin on leukocytes, blocks leukocytes trafficking and activation in the gut, inhibiting intestinal inflammation	UC: moderate to severe	PO	2	In UC (NCT04504383) : active, not recruiting	No data			
S1P modulators										
Amiselimod (MT-1303)	Sphingosine 1-phosphate receptor-1 functional antagonist	S1P and the S1P1 receptor play an essential role in lymphocyte egress from secondary lymphoid organs[198,199]	UC: mild to moderate CD: moderate to severe	PO	2	In UC (NCT04857112) : recruiting In CD (NCT02378688) : recruitment completed; extension study (NCT02389790): recruitment completed	2a in CD (n=78)	D'Haens G, et al.[151]	Clinical response at w12: 48.7% vs. 54.1% on PBO (ns)	Safe and well tolerated
CBP-307	Small molecule modulator of the sphingosine-1-phosphate 1 receptor (S1P1)	A G-protein coupled receptor that plays a central role in regulating T cell movement	UC: moderate to severe	PO	2	In moderate to severe UC (NCT04700449): active, not recruiting	No data			
KRP203	Oral immunomodulator, Agonist of the S1P receptor subtype 1	Act on lymphocyte trafficking	UC: moderate	PO	2	In UC (NCT04857112): recruiting In CD (NCT02378688) : recruitement completed	2a	Radeke HH, et al. (2020)[152]	Higher rate of clinical remission at w8 (14% vs. 0% on PBO)	Safe and well tolerate
VTX002	A peripherally-restricted, potent, and selective, orally bioavailable small molecule modulator of the S1P1 receptor	Act on lymphocyte trafficking	UC: moderate to severe	PO	2	In UC (NCT05156125) : recruiting	No data			

(Continues)

TABLE 3 (Continued)

Anti-chemokines										
E6011	Humanized monoclonal antibody targeting fractalkine, a CX3C chemokine	CX3C regulates leukocytes trafficking during inflammation[200]	CD: moderate to severe	IV	2	Recruiting in active CD patients (NCT03733314)	1 in CD	Matsuoka K, et al. (2021)[155]	Clinical response and clinical remission were observed in 40% and 16% of active CD patients, at w12, respectively	Serious adverse events in 3 patients (progression of CD in two, and anemia in one)
Anti-CD										
Muromomab (OKT3)	Fully mouse IgG2a anti-CD3 monoclonal antibody	OKT3 recognizes the T3 antigen complex (CD3) on human T lymphocytes	UC: moderate to severe	PO	1/2	In UC (NCT01287195) : recruitment completed	1 in UC (n=6)	Boden EK, et al. (2019)[158]	OKT3 increases proliferation of peripheral blood mononuclear cells and anti-inflammatory gene expression profile in these cells	No serious adverse events
Foralumab	Fully human IgG1 anti-CD3 Monoclonal Antibody	Oral anti-CD3 is taken up by gut-associated lymphoid tissue, where it is associated with the induction of Tregs that reduce disease severity in a transforming growth factor β or interleukin (IL)-10-dependent manner[201]	CD: moderate to severe	PO	1	In CD (NCT05028946): not yet recruiting				
Ravagalimab (ABBV-323)	Humanized anti-CD40 mAb antagonist	Inhibition of cellular activation of lymphocytes, macrophages, and dendritic cells via interference between cluster of differentiation 40 (CD40) and its ligand (CD40L)	UC: moderate to severe who failed priori therapy	IV/SC	2	In UC who failed prior therapy (NCT03695185): recruitment completed	No data			
Neihulizumab (AbGn-168H)	Humanized anti CD162 (P-selectin glycoprotein 1 or PSGL-1) monoclonal antibody	Neihulizumab induces apoptosis of late stage activated T cells	UC: moderate to severe	IV	2	In UC, anti-TNFa and/or anti-Integrin refractory (NCT03298022) : recruitment completed	2 (n=21)	Rubin T, et al.[160]	56% exhibited clinical response, 22% showed clinical remission, and 22% showed mucosa healing at W12. 100% of patients fulfill the criteria of responders, and 40% of patients fulfill the criteria of remission at their best response	No drug-related SAEs were reported
VB-201	Oxidized phospholipid small molecule	VB-201 inhibits CD14-and TLR2-dependent innate cell activation	UC: mild to moderate	PO	2	In UC (NCT01839214 : recruitment completed	No data			
Anti-TL1A										
PRA023	Humanized IgG1 anti-TL1A monoclonal antibody	TL1A (tumor necrosis factor ligand-related molecule 1) drive inflammatory Th1, Th17, Th9, and group 2 innate lymphoid cell (ILC2) responses[202,203]	UC and CD: moderate to severe	IV	2	ARTEMIS UC: recruiting (NCT04996797) APOLLO-CD: recruiting (NCT05013905)	No data			
PF-06480605	Fully humanized IgG1 anti-TL1A monoclonal antibody	TL1A (tumor necrosis factor ligand-related molecule 1) drive inflammatory Th1, Th17, Th9, and group 2 innate lymphoid cell (ILC2) responses[202,203]	UC: moderate to severe	IV	2	Active, not recruiting in moderate to severe UC (NCT04090411)	2a in UC (n=50)	Danese S, et al. (2021)[204]	Endoscopic improvement observed in a statistically significant proportion of patients: 38.2% Minimal histologic disease was observed after treatment (Robarts Histopathology Index ≤5: 33.3%; Geboes Index ≤3.2: 47.6%)	Acceptable safety profile
Treatment acting on epigenetics										
ABX464	Small molecule, targets miR-124	ABX464 interacts with the cap binding complex, allowing specific splicing of anti-inflammatory miR-124, which is a crucial modulator of inflammation and innate immunity[163]	UC: moderate to severe	PO	2	In UC: Induction study (NCT03093259), recruitment completed maintenance study (NCT04023396) active, not recruiting and evaluation of long term efficacy and safety :active not recruiting	2a in UC (n=32)	Vermeire S, at al.[163]	Clinical remission and response were observed in 35.0% and 70.0% of patients in the ABX464 group vs 11.1% and 33.3% in the PBO group; Endoscopic improvement and remission were observed in 50.0% and 10.0% of patients receiving ABX464, respectively, vs 11.1% each for placebo High maintenance of remission rate: 71% of patients in remission on ABX464 at week 8 sustained clinical remission until week 52	Safe and well tolerate

TABLE 3 (Continued)

						(NCT03368118, NCT05177835)				
Protein kinase inhibitors										
TOP1288	Small molecule, narrow spectrum protein kinase inhibitors (NSKIs)	Selectively targets key kinases (p38apha, Src family kinases, and Syk) involved in inflammatory signalling in cells of the innate and adaptive immune systems	UC: moderate to severe	PO and topical	2	TOP2 in UC (NCT02888379) : recruitment completed	1 (n=36 healthy male volunteers)	Rowley A, et al. (2018)[205]	Pharmacologically relevant TOP1288 concentrations are delivered to the colon as measured by direct quantification in tissue samples and biomarker assays	Well tolerate with no safety concern
Tilpisertib (GS-4875)	Small molecule targeting TPL2 protein (also known as MAP3K8 protein) or serine/threonine kinase inhibitor	TLP2 is a mitogen-activated protein kinase and the primary regulator of ERK-mediated gene transcription downstream of multiple proinflammatory stimuli including bacterial products (eg, LPS and bacterial peptidoglycans), damage-associated molecular patterns (DAMPs), TNFα, and IL-1β[206]	UC: moderate to severe	PO	2	Falcon in UC (NCT04130919) : recruitment completed	No data			
Combined treatment										
ABBV-154	Anti-tumour necrosis factor (TNF) steroid conjugate	ABBV-154 allow precise targeting of activated immune cells while significantly dampening inflammation and minimizing the systemic side-effects associated with glucocorticoids	CD: moderate to severe	SC/IV	2	AIM-CD in CD (NCT05068284) : recruiting	No data			
BI 706321 (coupled to ustekinumab)	Kinase inhibitor	Inhibits the inflammatory cascade at these kinases	CD: moderate to severe	PO	2	In Charge in CD (NCT04978493): recruiting	No data			
Spesolimab (BI 655130) (coupled to infliximab)	Humanized anti–IL-36 receptor monoclonal antibody	Activation of IL-36R induces MYD-88-dependent activation of NF-κB and MAPKs, resulting in the production of various pro-inflammatory effectors by the target cells (including epithelial cells, lymphocytes and fibroblasts)[193]	UC: mild to moderate	IV	2	In UC (NCT03123120): recruitment completed	No data			
JNJ-78934804 (Golimumab + Guselkumab)	Monoclonal antibodies, TNFα inhibitor, IL-23 inhibitor	JNJ-78934804 inhibits 2 pro-inflammatory cytokines	UC: moderate to severe CD: moderate to severe	SC	2	DUET-UC in UC (NCT05242484):not yet recruiting DUET-CD in CD (NCT05242471) :not yet recruiting	No data			
Vorinostat + ustekinumab	Histone deacetylase inhibitor	HDAC inhibitors may have a beneficial effect in colitis by boosting levels of Foxp3+ (forkhead box P3+) Treg cells that dampen inflammation[207]	CD: moderate to severe	PO	1/2	In CD (NCT03167437) : recruiting	No data			
Other drugs										
Apremilast	Small molecule, inhibiting phosphodiesterase 4 (PDE4)	PDE4 modulates pro- and anti-inflammatory mediators[208]	UC	PO	2	In UC (NCT02289417) : recruitment completed	2 in UC (n=170)	Danese S, et al. (2018)[156]	Higher rate of clinical remission at w12 (31.6% vs 13.8% on PBO,P≤0.05	Safe and well tolerate

(Continues)

TABLE 3 (Continued)

BBT-401	Small molecule, Lipidated tetra-peptide, binding to Pellino-1	BBT-401 specifically binds to Pellino-1 and dissociates the multi-protein signalling complexes containing MyD88 and RIP1 kinase contributing to the innate immune response	UC: moderate to severe	PO	2	In UC (NCT04596293) : active, not recruiting	No data (preclinical models)			
BT051	Small molecule acting on local neutrophils	BT051 acts locally by inhibiting neutrophils trafficking and activation	UC: moderate to severe	PO	1	SCOUT study in UC (NCT05084261): recruiting	1	Murphy C, et al. (2021)	Not evaluated	Safe and well tolerated in healthy volunteers
Empagliflozin	Small molecule, sodium/glucose cotransporteur 2 (SGLT2) inhibitors	Empagliflozin could restore neutrophil function and normalisation of neutrophil apoptosis leads to improvement of wound healing and could ameliorate symptoms of IBD	UC	PO	2	In UC (NCT05058417) : recruiting	No data			
GLPG3970	Small molecule, salt-inducible kinase or (SIK)2/3 inhibitor	SIK2 and SIK3 play a role in the differentiation of macrophages into a potent and stable anti-inflammatory phenotype	UC: moderate to severe	PO	2	SEA TURTLE: completed in UC (NCT04577794), results pending	No data			
Hemay007	Active tumour necrosis factor alpha (TNF-α) inhibitor	Act on a pro-inflammatory cytokine	UC: active	PO	2	In UC (NCT03977480) : recruiting	No data			
Hydroxychloroquine	Small molecule, TLR7/9 antagonist	TLRs serve as the hub of immune responses to microbes in the gut, thereby inciting IBD[209]	UC: mild to severe CD	PO	1/2	In UC (NCT05119140) : recruiting In CD (NCT01783106): recruitment completed	No data			
KHK4083	Fully human anti monoclonal antibody specific for OX40	OX40, which maintains late T-cell proliferation and survival by suppressing apoptosis and by inducing T-cell memory formation	UC: moderate to severe	IV	2	In UC (NCT02647866): recruitment completed	1 in UC (n=8)	Furihata K, et al. (2021)[210]	Clinical response (37.5%) and remission (25%) at w6	No serious adverse events
LYS006	Small molecule, leukotriene A4 (LTA4) hydrolase inhibitor	Leukotrienes are mediators of inflammation	UC: mild to moderate	PO	2	In UC (NCT04074590) : recruiting	No data			
NX-13	Small molecule, gut-restricted, NLRX1 agonist	NX-13 (a NLRX1 agonist) can favourably modulate epithelial barrier integrity and interactions with the gut microbiome[211]	UC: active	PO	1b	In UC (NCT04862741) : active, not recruiting	1 in healthy volunteers (n=56)	Leber A, et al. (2021)	Not evaluated	Safe and well-tolerated with a wide therapeutic margin above anticipated therapeutic doses in healthy volunteers
Omilancor (BT-11)	Small molecule targeting lanthionine synthetase C-like 2 (LANCL2)	BT-11 is a gut-restricted LANCL2 agonist, which increases the suppressive capacity of regulatory immune cells, including regulatory CD4+ T cells (Tregs), locally within the intestinal mucosa	UC: mild to moderate CD: moderate to severe	PO	2	In UC (NCT03861143): recruitment completed In CD ((NCT03870334): active, not recruiting	1 in healthy volunteers (n=70) (results of phase 2 withdrawn)	Leber A, et al. (2022)[212]	Not evaluated	No increase in total AE or GI AE rates in individual dose cohorts and overall pooled active group. No SAEs were observed
PBF 677	Small molecule, adenosine A3 receptor antagonist	Adenosine regulates many biological responses, including inflammation	UC: mild to moderate	PO	2a	ADENOIBD in UC (NCT03773952) : recruitment completed	No data			

TABLE 3 (Continued)

PRV-6527	Small molecule inhibiting colony stimulating factor-1 receptor (CSF-1R)	CSF-1R play a role in macrophage recruitment. Inhibiting CSF-1R limits their recruitment	CD: moderate to severe	PO	2a	PRINCE in CD (NCT03854305): completed	No data			
SPH3127	Selective renine inhibitor	Circulating components of the alternative renin-angiotensin system are increased in patients with IBD[213]	UC: mild to moderate	PO	2	In UC (NCT05019742) : recruiting	No data			
Telotristat Etiprate (LX1606)	Small-molecule, inhibitor of tryptophan hydroxylase	Tryptophan hydroxylase 1 (Tph1) catalyzed intestinal 5-HT synthesis. Tph1 inhibition results in decreased inflammatory cytokine level	UC: mild to moderate	PO	2	In UC (NCT01456052) : recruitment completed	No data (only preclinical models)			
Tesnatilimab (JNJ-64304500 or NNC 0142-0000-0002)	Anti-natural killer group 2D (NKG2D) monoclonal antibody	Inhibit NKG2D leads to a decrease in cellular proliferation, cytokine production[214]	CD: moderate to severe	SC	2b	TRIDENT in CD (NCT02877134) : recruitment completed	No data			
Vidofludimus calcium (IMU-838)	Small molecule inhibitor of dihydroorotate dehydrogenase (DHODH)	IMU-838 induces Mregs and decreased secretion of IL-6 and TNF-α, inhibits proliferation of activated B and T cells, as well as inflammatory T cell cytokine secretion, IL-17A, IL-17F and IFNγ	UC: moderate to severe	PO	2	CALDOSE-1 in UC (NCT03341962): active, not recruiting	No data			
5-aminolevulinic acid in combination with blue-light and red-light photopheresis	Nonprotein amino acid	5-ALA possess anti-inflammatory and immunoregulatory properties through upregulation of heme oxygenase-1 via enhancement of porphyrin[215]	CD	PO	1/2	In CD (NCT04164849): recruiting	No data			
Enteric/topical release treatment										
IBD98-M	Delayed-release formulation of mesalamine (mesalazine) and sodium hyaluronate (a mucosa supplement)	Mesalamine activate peroxisome proliferator-activated receptor (PPAR)-gamma, a key receptor that transrepressing several key target genes such as nuclear factor B, signal transducers and activators of transcription[216]	UC: mild to moderate	PO	2	In UC (NCT02493712) : recruitment completed	2a (n=51)	Fiorino G, et al. (2019)[217]	IBD98-M did not meet the primary end point but had higher clinical response (1.2 g/day) and endoscopic improvement (0.8 g/day) compared to placebo.	Safe and well-tolerated
Niclosamide Enemas	Small molecule	Niclosamide, has anti-viral and anti-inflammatory properties	UC: mild to moderate ulcerative proctitis or proctosigmoiditis	Topical	1b/2a	In UC (NCT03521232) : recruiting	No data			
AVX 470	Anti-TNF polyclonal antibody, orally delivered	AVX-470 neutralizes TNF locally in the gastrointestinal tract, minimizing systemic exposure[218]	UC	PO	1	In UC (NCT01759056) : recruitment completed	1 in UC (n=33)	Harris MS, et al. (2016)[218]	A total of 25.9% of patients achieved clinical response with AVX-470, compared to 11.1% with PBO	Safe and well tolerate
V565	Intestinal release TNFα-neutralising single domain antibody	V565 is an engineered TNFα-neutralising single domain antibody formulated into enteric coated mini-tablets to enable release in the intestine after oral administration	CD	PO	2	HarbOR in CD (NCT02976129): completed	1 (n=5)	Nurbhai S, et al.[219]	Decreased phosphoproteins after 7 days, consistent with V565-TNFα engagement and neutralising activity	Safe and well tolerate
SB012	Oligonucleotide	SB012 is a novel GATA-3 specific DNAzyme that specifically binds and inactivates GATA-3 messenger RNA (mRNA) (GATA3 transcription factor)	UC : moderate disease	Topical	1/2	SECURE in UC (NCT02129439) : recruitment completed	2a (n=20)	Atreya R, et al. (2018)[220]	SB012 lead to a significant clinical Mayo score improvement at day 28 (p=0.004) and 56 (p=0.016). Patients achieved higher rate of clinical remission (42.9% versus 0% at day 56), clinical response (42.9% versus 0% on PBO) and mucosal healing (57.1% versus 0% on PBO) at day 56	Safe and well tolerate
Bacterial therapy										

(Continues)

TABLE 3 (Continued)

KBL697	Lactobacillus gasseri	Modulation of gut microbiota composition, metabolic pathways and immune systems of host[221]	UC: mild to moderate	PO	2	In UC (NCT04898348): recruiting	No data			
TSO	Trichuris suis ova	Studies suggest that helminth parasites may afford protection from, or even treat disorders of the immune system, including autoimmune disease and IBD[222]	UC: moderate CD	PO	2	PROCTO in UC (NCT03565939): recruitment completed TRUST-2 in CD (NCT01279577): recruitment completed	1 (n=36)	Sandborn WJ, et al. (2013)[222]	Not evaluated	Well tolerated; no short- or long-term treatment-related side effects
BGP-014	Lyophilised Lactobacillus reuteri	Modulation of gut microbiota	UC: mild to moderate	PO	1/2	In UC (NCT05118919) : recruiting	No data			
P28GST	A unique schistosome protein	This parasite enzyme molecule restoring the immunological balance between pro-inflammatory Th1 responses and both Th2 and regulatory responses	CD: moderate	SC	2	ACROHNEM in CD (NCT02281916) : recruitment completed	2a	Foligné B, et al.[223]	P28GST induced slight changes in the faecal bacterial composition in CD patients	Safe
RHB-104	A combination of clarithromycin 95 mg, rifabutin 45 mg, and clofazimine 10 mg	RHB-104 is a therapy anti-mycobacterium avium subspecies paratuberculosis (MAP), developed in view of the suspected role of MAP in CD[224]	CD: moderate to severe	PO	3	MAPUS in CD (NCT01951326): recruitment completed	3	Graham D, et al.[224]	A greater proportion of patients achieved primary endpoint (clinical remission) at week 26 (37% vs. 23%, p=0.007), as well as clinical response at week 26, durable remission at week 52	Any safety concerns
VE202	Clonal human commensal bacteria strains selected for their ability to impact the number and activity of Treg cells in the gut mucosa	These commensal bacteria help restore a healthy microbiome in UC patients (after 5 days of vancomycin pre-treatment at 125mg po QID)	UC: mild to moderate	PO	2	In UC (NCT05370885) : not yet recruiting	1 (n=31 healthy adults)	Silber J, et al.[225]	Provides robust, durable, abundant colonization of live biotherapeutic product strains	Well tolerated
TAK-018	Small molecule	Molecule having the potential to block a group of bacteria present in the gut that might be triggering inflammation seen in CD	CD	PO	2	In CD, to prevent recurrence after surgery (NCT03943446): recruiting	No clinical data			

Abbreviations: ATP, adenosine triphosphate; CD, Crohn's disease; CDAI, Crohn disease activity index; GI, gastrointestinal; IFN, interferon; IL, Interleukin; IV, intravenous; JAK-STAT, Janus-kinase/signal transducer and activator of transcription pathway; LPS, lipopolysaccharide; MAP, mycobacterium avium subspecies paratuberculosis; PBO, placebo; PDE4, phosphodiesterase 4; QID, quater in die; R, receptor; SC, subcutaneous; SGLT2, sodium/glucose cotransporteur 2; TEC, hepatocellular carcinoma; Treg, regulatory T cells; TSO, Trichuris suis ova; UC, ulcerative colitis.

Mirikizumab (LY3074828) is a humanised IgG4 monoclonal antibody. In patients with moderate to severe UC, higher proportion of patients achieved clinical remission (24.2% on mirikizumab vs. 13.3% on PBO; $p = 0.00006$), clinical response, endoscopic remission, symptomatic remission, clinical response in biologic-failed patients, histologic-endoscopic mucosal improvement and improvement in bowel urgency at week 12 with 300 mg mirikizumab IV administered every 4 weeks compared to PBO (LUCENT-1 phase 3 study).[41] In patients responding to mirikizumab induction therapy, the mirikizumab 200 mg SC every 4 weeks maintenance regimen (phase 3 maintenance LUCENT-2 study) allowed a significantly higher rate of patients to reach clinical remission at week 40 (49.9%) compared to PBO (25.1%).[42] In this study, all key secondary endpoints (CS-free remission, endoscopic remission, histologic-endoscopic mucosal remission, improvement in bowel urgency, bowel urgency remission and maintenance of clinical remission) were achieved (each: $p < 0.001$) at week 40[42]. Mirikizumab was also assessed in CD (SERENITY study).[43] Patients were randomized 2:1:1:2 to receive PBO, 200, 600, or 1000 mg mirikizumab IV every 4 weeks.[43] At week 12, a significantly higher proportion of patients treated by this anti-IL-23 achieved endoscopic response (especially with the 600 and 1000 mg dose, 37.5% and 43.8%, respectively, vs. 10.9% on PBO; $p < 0.01$ for both doses) as well as secondary endpoints.[43] In the maintenance study, the rate of endoscopic response were similar between IV and SC groups (300 mg every 4 weeks in both cases), with 69.6% and 66.7% of patients in endoscopic response at week 12, who were endoscopically responsive at week 52[43]. Phase 3 studies are currently underway in UC, CD as well as in paediatrics (including LUCENT-3, VIVID-1 and 2).[44–46]

In conclusion, four IL-23 inhibitors are currently under development in IBD and appear superior than PBO to achieve endpoints, including in patients with experience of biologics (except for guselkumab in UC where sub-analysis results are not yet available).[14,21,34,43,47] However, the rate of patients achieving primary and secondary endpoints was generally higher among the biologic-naive compared to biologic-experienced patients group.[14,21,34,43,47] They should be approved soon in IBD, in particular risankizumab, which is at the most advanced stage of development in CD. In studies comparing an anti-IL-23 to PBO, the adverse event rates were generally similar between groups.[21,43,47] The most frequently reported adverse events were IBD worsening, arthralgia, headache, nausea and nasopharyngitis.[14,17,21,47]

Janus kinase inhibitors

There are four isoforms of JAK (janus kinase 1 (JAK1), JAK2, JAK3 and tyrosine kinase 2 (TYK2)), whose expression varies according to the tissues. These tyrosine kinases are involved in the signal transmission induced by the binding of cytokines (including the aforementioned IL-23) to their receptor.[48–50] JAK inhibitors are small molecules, having the advantage of being per os and not associated with antidrug antibodies development, acting downstream of cytokines.[51] Tofacitinib (a pan-JAK inhibitor), already approved in UC,[9] showed disappointing results in the 2 phase 2b studies in CD, leading to its discontinuation in CD.[52,53] Filgotinib, upadacitinib and ivarmacitinib are three other JAK-inhibitors that have been developed in IBD.

Filgotinib (GLPG0634 or GS-6034) is an oral once-daily JAK1-selective inhibitor, also approved in UC, which is currently in evaluation in CD.[10] In FITZROY phase 2 study, assessing the safety and efficacy of filgotinib in CD, filgotinib (200 mg once a day per os [PO]) allow the achievement of clinical remission (primary endpoint) in significantly more patients compared to PBO at week 10 (47% vs. 23%; $p = 0.0077$). More striking difference were observed for anti-TNF naive patients (60% of clinical remission at week 10 with filgotinib vs. 13% with PBO for anti-TNF naïve; 37% with JAK-1 selective inhibitor vs. 29% on PBO for anti-TNF experienced patients).[54] In addition, preliminary results of the phase 2 DIVERGENCE study suggest that oral filgotinib 200 mg once daily may also be beneficial in perianal fistulizing disease.[55] Subsequently phase 3 studies have therefore been initiated (DIVERSITY1 and DIVERSTYLTE) and are currently underway in CD.[56,57]

Another selective JAK1 inhibitor, upadacitinib (ABT-494 or Rinvoq®), currently approved for the treatment of psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and atopic dermatitis, is also currently under evaluation in IBD.[53] The efficacy of upadacitinib in UC was demonstrated in a phase 2b study and confirmed in three phase 3 studies.[58,59] In the two phase 3 induction studies (U-ACHIEVE induction/UC1 and U-ACCOMPLISH/UC2), statistically significantly more patients achieved clinical remission with upadacitinib 45 mg PO once daily (26% in UC1 and 33% in UC2) than in the PBO group (5% in UC1 and 4% in UC2; $p < 0.0001$ for both UC1 and UC2), regardless baseline disease characteristics.[60] The rate of patients reaching primary endpoints at week 8 with upadacitinib 45 mg was greater in biologic-naive patients (35.2% in UC1 and 37.5% in UC2) than in biologic-experienced patients (17.9% in UC1 and 29.6% in UC2), but superior to PBO in all cases.[60] Patients who achieved clinical response at week 8 were randomly reassigned 1:1:1 for upadacitinib 15 mg, 30 mg or PBO for 52 weeks (U-ACHIEVE maintenance study/UC3). This study showed that clinical remission was achieved by statistically significantly more patients receiving upadacitinib (42% with 15 mg and 52% with 30 mg) than those receiving PBO (12%; $p < 0.0001$), whether they have a previous biologic failure or not.[60] Upadacitinib was also effective on extra-intestinal manifestations or EIMs (any EIM, arthropathy and classic EIM such as axial and/or peripheral arthropathy, episcleritis/uveitis/iritis, oral aphthous ulcers, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome).[61,62] According a sub-analysis, the dose of 15 mg was appropriate for UC patients with less severe inflammatory flare and the dose of 30 mg could be proposed to patients with more severe disease (with Mayo score >9 and extensive disease).[60] The efficacy and safety of upadacitinib in CD was evaluated in the CELEST phase 2 study.[63] While upadacitinib, as induction therapy, did not achieve a significantly greater rate of clinical remission than PBO at week 16, endoscopic remission (which was the

co-primary endpoint) and key secondary endpoints were observed with the dose of upadacitinib 24 mg twice daily group (22% of endoscopic remission vs. 0% on PBO; $p < 0.01$).[51] In addition, two recent real-world studies showed promising results with upadacitinib (with a decrease in faecal calprotectin already 2 weeks after initiation) in treatment-refractory CD patients.[64,65] Phase 3 studies are currently underway in CD[66–68] as well as studies evaluating long-term efficacy, safety, and tolerability of repeated administration of upadacitinib in UC and CD subjects are currently in progress.[69,70]

Ivarmacitinib (formely SHR0302) is another novel oral selective JAK1 inhibitor. Recruitment for four-arm (oral SHR0302 4 mg once daily, 8 mg once daily, 4 mg twice daily, and PBO) phase 2 RCT are completed in moderate to severe UC (AMBER2 or NCT03675477) and CD (NCT03677648).[71,72] While data are not yet available in CD, SHR0302 resulted in a higher rate of clinical response (46.3% vs. 26.8% on PBO; $p = 0.059$) and remission rate compared to PBO after 8 weeks of treatment in UC and was well tolerated.[73] A phase 3 study is currently underway to investigated the efficacy and safety in moderate to severe active UC.[74]

Studies show that using selective JAKs does not result in a loss of efficacy (compared to pan-JAK inhibitors), but there are still doubts about safety.[75] Indeed, not only very quickly effective (with symptoms improvements as early as day 1 with upadacitinib for example[76]), two recent systematic review and network meta-analysis comparing a series of small molecules and biologics have shown that upadacitinib was the best treatment to induce clinical remission in patients with moderate to severe UC,[77,78] whether or not the patient has been previously exposed to anti-TNFs.[78] However, it was also the treatment associated with the worst outcome in terms of side effects.[77] The safety of different JAK inhibitors (tofacitinib, filgotinib, peficitinib, upadacitinib, and TD-1473) in UC and CD patients compared with PBO was evaluated by Ma et al. in a systematic review and meta-analysis.[75] The use of different JAK inhibitors were overall not associated at a significantly higher risk for adverse events compared with PBO[75] but they nevertheless reported that JAK inhibitors were associated with a higher risk of infections, including herpes zoster and upper respiratory tract infections.[75] Another safety concern with this class is the risk of venous thromboembolism and major adverse cardiovascular events (MACE).[79] Indeed, in a post-authorization safety trial, patients with rheumatoid arthritis aged of 50 years or older with ≥1 cardiovascular risk factor treated by the pan-JAK inhibitor tofacitinib 10 mg twice daily have a higher incidence of MACE and a 5-fold increase in the risk of pulmonary thromboembolism compared to the anti-TNF-treated patients.[79] The role of JAK inhibitors selectivity of these drugs safety needs further clarification (in particular because JAK2 is the kinase whose inhibition is associated with increased platelet count and risk of thrombosis).[80] Sporadic pulmonary embolism and venous thromboembolic events have been described with upadacitinib, but some of these patients had thromboembolic risk factors and these events cannot be considered with certainty as a side effect of treatment given the inherent risk associated with IBD.[58,65,81] JAK inhibitors were also associated with increases in serum lipid levels possibly interfering with the risk of MACE. However, these changes are dose-dependent, reversible, generally complied the ratio total/high-density lipoprotein cholesterol and not related to a higher risk of MACE in a pooled analysis of 22 RCT assessing JAK inhibitors.[82] Other commonly reported side effects include arthralgia, nasopharyngitis and increases in creatine phosphokinase.[58,61,65,83] There are also concerns about the testicular toxicity of filgotinib and its impact on sperm count, warranting dedicated studies (MANTA and MANTA-Ray).[51] However, preliminary data appear reassuring and show that at week 13, 6.7% of filgotinib-treated patients and 8.3% of PBO-treated patients had ≥50% decline in sperm concentration, out of a total of 248 randomised patients followed-up for active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis).[84] Further studies are needed to answer these safety questions, but JAK inhibitors remain a promising class of treatment in IBD.

Anti-integrin and anti-adhesion molecules

The success of vedolizumab in IBD in recent years demonstrates that interfering with immune cell trafficking, particularly T lymphocytes, is an effective mechanism of action to reduce disease burden.[6,7] This lymphocyte gut homing occurs through interactions between selectin, $\alpha_4\beta_7$, $\alpha_4\beta_1$ on T cells, attracted by tissue-secreted chemokines (i.e. CCL25, CXCL10), and adhesion molecules present on endothelial cells, including mucosal addressin cell adhesion molecule-1 (MAdCAM-1).[85] The development of ontamalimab, an anti- MAdCAM-1, has recently been stopped[86] but 2 other anti-integrins (etrolizumab and AJM300) are currently being evaluated in phase 3 CTs in IBD.[87–89]

Etrolizumab (PRO145223) is a humanized monoclonal antibody that selectively binds the β_7 subunit of the heterodimeric integrins $\alpha_4\beta_7$ and $\alpha_E\beta_7$. Phase 3 studies HICTORY (assessing etrolizumab as induction and maintenance treatment in anti-TNF-experienced patients with evaluation at week 14 and 66) and LAUREL (assessing etrolizumab as maintenance treatment in anti-TNF naïve patients with evaluation at week 62) showed that etrolizumab SC (105 mg every 4 weeks) was superior to PBO to induce remission at week 14 (18.5% with etrolizumab vs. 6.3% with PBO; $p = 0.0033$), endoscopic improvement at weeks 14 and 62–66 as well as endoscopic and histological remission at week 62–66 (in both anti-TNF naïve and experienced patients).[90,91] Etrolizumab was well tolerated and no safety signals were identified.[90,91] The efficacy and safety of etrolizumab appears to be equivalent to that of anti-TNFs based on phase 3 studies comparing anti-β_7 to anti-TNF agents (the latter being used as an active comparator).[87,92] The pooled analysis of HIBISCUS 1 and 2 studies showed that etrolizumab was not superior to adalimumab but similar in terms of efficacy and safety.[92] Similar results were found in the GARDENIA phase 3 study comparing etrolizumab to IFX as maintenance treatment in moderate to severe UC (18.6% of clinical remission at week 54 with etrolizumab vs. 19.7% with IFX;

$p = 0.81$).[87] Phase 3 studies are underway in the UC: open-label extension (COTTONWOOD)[93] and a phase I has just been initiated in paediatrics (FENNEL).[94] In CD, the induction/maintenance BERGAMOT phase 3 trials, showed a clinically meaningful endoscopic improvement, with rapid symptomatic remission as early as week 6, which was sustained through week 14, indicative of the efficacy of etrolizumab in treating CD.[95] Enrolment into subsequent induction cohorts and into the maintenance phase of BERGAMOT is ongoing as well as in the open-label extension and safety study for CD patients previously enrolled (JUNIPER).[96]

AJM300 (carotegrast methyl) is a new small molecule, α4-integrin antagonist, being evaluated in UC.[88] In the phase III study (NCT03531892), AJM300-treated patients (960 mg three times daily orally) had a significantly higher rate of clinical response (45%; $p = 0.00028$) than PBO group (21%) at week 8[88,89]. Statistically significant improvements were also observed in the secondary endpoints including mucosal remission rate and rectal bleeding disappearance rate.[88] These results were consistent with those obtained in phase 2a in UC.[97] There was no difference in the incidence of adverse events between the groups.[88]

These anti-integrins were generally well tolerated.[87,95,97] In the study comparing etrolizumab to IFX, there was slightly more infections in the etrolizumab group.[87] No cases of progressive multifocal leukoencephalopathy (PML) were reported, either with etrolizumab or with AJM300 (with the limitation that the number of subjects in this CT was small and the study period was short).[87,95,97,98] Although sharing a common mechanism of action with natalizumab (another monoclonal anti-α4 integrin antibody whose development has been halted due to the PML risk), fewer systemic adverse events are expected with AJM300 since it is an oral formulation, with a shorter duration of action than natalizumab.[98] Larger scale and longer term studies are needed.

S1P receptor agonists/sphingosine-1-phosphate modulators

The sphingosine-1-phosphate (S1P) subtype 1 (S1P1) receptor is a member of a family of 5 receptors (S1P1–S1P5) implicated in multiple cellular processes including immunological pathways.[99,100] S1P1 receptor agonists leads to internalization and degradation of the S1P1 receptor, therefore blocking the B and T lymphocytes migration, potentially decreasing the number of lymphocytes circulating to the gastrointestinal tract.[100] Ozanimod and etrasimod are two S1P modulators currently being evaluated in phase 3 CTs in IBD.

Ozanimod (RPC1063) is an S1P1 and S1P5 receptor modulator approved since 2021 in US for UC.[101] Indeed, the incidence of clinical remission at week 10 was significantly higher among patients who received oral ozanimod hydrochloride at a dose of 1 mg (equivalent to 0.92 mg of ozanimod) than among those who received PBO during both induction (18.4% on ozanimod vs. 6% on PBO; $p < 0.001$) and maintenance (37% on ozanimod and 18.5% on PBO; $p < 0.001$) in TRUE-NORTH phase 3 study and all key secondary endpoints were significantly improved with ozanimod compared with PBO in both periods.[101] Experienced anti-TNF patients had a higher percentage of clinical remission with ozanimod compared to PBO, but a lower percentage compared to anti-TNF-naive patients.[101] One study reporting real-world data from a large tertiary center has just been published by Cohen and colleague.[102] Ozanimod was well-tolerated but had modest effectiveness in a relatively treatment-refractory cohort of UC patients.[102] STEPSTONE was the phase 2 study assessing ozanimod in 69 moderate to severe CD patients.[103] Clinical, endoscopic and histological improvements were seen within 12 weeks of initiating ozanimod in patients with moderately to severely active CD.[103] Ozanimod is currently being studied in a phase 3 studies in UC[104–106] and CD,[107–110] as well as in phase 2/3 in UC in pediatrics.[111]

Etrasimod (APD334) is an oral S1P1, S1P4 and S1P5 receptor modulator. The efficacy and safety of etrasimod in patients with moderate to severe active UC was evaluated in the phase 2 OASIS trial (NCT02447302).[112] At week 12, etrasimod 2 mg was significantly more effective than PBO in producing clinical ($p = 0.009$ for etrasimod 2 mg) and endoscopic improvements.[112] The results of subgroup analyses showed similar improvement in patients with prior exposure to anti–TNF-α therapy.[112] Regarding tolerance, three patients, known to have an atrioventricular block before initiation, presented a transient, asymptomatic, low-grade new episode that resolved spontaneously.[112] The OASIS open-label extension study confirmed the long-term efficacy and safety profile of this drug with 85%, 60% and 60% of patients with clinical response, clinical remission, and endoscopic improvement at week 12, respectively, that maintained that status to end of treatment.[113] Phase 2 and 3 studies are currently underway in UC,[114–117] especially among the Japanese population[115,118] as well as in CD (CULTIVATE study).[119]

Ozanimod and etrasimod are lymphocytes migration inhibitors that appear to be active in both UC (for which it is already approved in the US) and CD for ozanimod and in UC for etrasimod. The adverse events described with this class of treatment are risk of lymphopenia, bradycardia, macula edema, herpes zoster infection and elevated liver aminotransferase level.[101–103,112] Furthermore, it should be noted that a case of PML has been reported with ozanimod.[120] As the risk of PML increases under S1P modulators seems to increase with treatment duration, the occurrence of this type of complication under long-term treatment should be carefully monitored.[120,121]

Toll like receptor agonists

Cobitolimod (DIMS0150 or Kappaproct®) is an oligonucleotide currently under evaluation in UC.[122–124] It is a single stranded DNA-based immunomodulatory sequence, containing an unmethylated CpG motif (mimicking DNA bacterial), which activate TLR-9 on target immune cells (including intestinal T and B lymphocytes and antigen-presenting cells).[125,126] These TLR-9 agonist alleviate intestinal inflammation by suppressing Th17 cells and inducing Treg cells as well as secretion of anti-inflammatory cytokines (IL-10 and

interferon).[125] In the COLLECT phase 3 study, the topical administration of cobitolimod, although not meeting the primary endpoint, induced PRO-based symptomatic remission, mucosal healing and histological improvement.[122,123] No safety signals were detected.[122,123] The efficacy and safety of cobitolimod as induction and maintenance therapy is currently under investigation (phase 3 CONCLUDE study or NCT04985968) in patients with moderate to severe active left-sided UC.[124]

DRUG BEING EVALUATED IN A PHASE 1 OR 2 CLINICAL TRIAL

All molecules currently being evaluated in phase I and II CTs, with promising results, are listed in Table 2. Some treatments target interleukins, including IL-23 IV/SC (IBI112)[127] but also IL-6 (olamkicept IV, PF-04236921 SC),[128,129] IL-7 IV (OSE-127),[130] IL-18 IV (GSK1070806),[131] IL-21 IV (NNC0114-0006)[132] and IL-36 (Spesolimab).[133,134] Some interleukins, instead of being inhibited, can also be boosted. It is the case of IL-2 (by recombinant protein such as LY3471851 SC,[135] or fusion protein such as efavaleukin alfa SC or MK-6194 SC[136,137]), oral IL-10 (AMT-101[138]) or IL-22 (UTTR1147 A IV for example which is also a fusion protein in which IL-22 is linked with the Fc portion of IgG4 allowing improvement of pharmacokinetic characteristics).[139] New oral JAK inhibitors are also being developed such as brepocitinib (JAK1 and TYK2 inhibitor),[140,141] deucravacitinib (TYK2 inhibitor),[142–144] ritlecitinib and OST-122 (JAK-3 inhibitors)[140,141,145] and peficitinib (pan-JAK inhibitor).[146] Regarding anti-integrins, abrilumab SC (AMG181) is an anti-integrin $\alpha_4\beta_7$ with proven effectiveness in a phase 2b study in UC[147–149] and PN-943 is a new oral gastro-intestinal-restricted peptide antagonist of α4β7 integrin being evaluated in a phase 2 study.[150] Amiselimod, CBP-307, KRP203 and VTX002 are four oral S1P modulators actually under investigation in UC, and in CD for amiselimod.[151–154] Other mechanisms of action include anti-chemokines (also playing a pivotal role in T cells recruitment in the gut),[155] oral anti-CD3, anti-CD40 IV/SC, anti-CD162 IV, inhibitor of phosphodiesterase 4 (apremilast PO),[156] oral active TNF-α inhibitor (hemay007)[157] but also anti-TL1A IV.[158–162] ABX464 and Vorinostat are drugs that act on epigenetic mechanisms.[163–168] Other treatments, with more specific mechanisms, or bacterial therapies, are also being evaluated and are listed in Table 3.

ANTI-FIBROTIC THERAPIES

The humanized antagonistic monoclonal IgG1 antibody that blocks human IL36 R signalling, spesolimab (BI 655130), is a treatment with possible anti-fibrotic action that has recently been tested in a CT in patients with fibrostenotic CD (NCT05013385). IL-36 is a group of 3 cytokines (IL-36α, ß and γ) that are overexpressed in the gut mucosa from fibrostenotic CD patients and that are known to activate myofibroblasts, one of the key players of intestinal fibrosis.[169,170] The purpose of this phase 2a study was to demonstrate that spesolimab was effective in maintaining symptomatic and/or inducing radiographic stenosis response in patients with symptomatic CD-related small bowel stricture, who have achieved symptomatic stenosis response after standard medical therapy. Patients received, in addition to this standard treatment, either an infusion of spesolimab 1200 mg (every 4 weeks until week 8 then every 8 weeks) or a PBO. However, the CT was stopped due to a decision by the sponsor (neither the primary endpoint was met nor a clinical benefit was observed at the interim analysis).[171] However, the molecule is still being evaluated in phase 2 in CD (patients with fistulising CD who took part in previous trials)[172,173] and in the phase 2/3 CT in UC.[133,134] New findings on the molecular mechanisms involved in intestinal fibrosis have led to the identification of several anti-fibrotic therapeutic targets.[174] Several molecules have shown promising results in pre-clinical studies conducted in vivo, ex vivo, and in vitro (recently reviewed by Santacroce G, et al.) and may soon lead to human CTs (some of which are already being evaluated in luminal disease such as anti-TL1A[162]).[174]

COMBINATION THERAPY

However, when looking at the efficacy of currently available treatments, approximately 1/3 of patients are primary non-responders and 50% of patients become secondary non-responders.[175,176] It is unlikely that this ceiling will be broken by the arrival of these new molecules (since their clinical remission rates at the end of the induction and maintenance phases are close to those obtained with currently available treatments).[176] Combination therapy has been proposed as a promising IBD management strategy to try to overcome this plateau.[176,177] Several combination therapies are currently being evaluated (Table 3). Stalgis et al. have proposed four different types of combinations, depending on the degree of overlap and crosstalk in their mechanisms of action[176]: (1) combination of 2 molecules with independent mechanism of action and no direct anti-IBD activity when combined; (2) combination of high overlapping mechanism of action, high crosstalk; (3) medium overlapping activity, medium crosstalk; and (4) combination of complementary mechanism of action and direct anti-IBD activity).[175,176] The concomitant use of two biologics and/or small molecules, known as dual targeted therapy. An example of an ongoing dual targeted therapy CT is the phase 2a VEGA study comparing efficacy and safety of a combination induction therapy with guselkumab and GOL (JNJ-78934804) in moderate to severe active UC. Patients naïve to anti-TNFα and refractory or intolerant to immunomodulators and/or CS were randomly assigned to receive guselkumab 200 mg IV at weeks 0, 4, and 8; GOL 200 mg SC at week 0 then 100 mg SC at weeks 2, 6, and 10; or combination with guselkumab 200 mg IV and GOL 200 mg SC at week 0, GOL 100 mg SC at weeks 2, 6, and 10, and guselkumab 200 mg IV at weeks 4 and 8. Combination more effectively induced clinical response (83.1% in patients treated by combination therapy vs. 61.1% on GOL (p = 0.003) versus 74.6% on guselkumab

($p = 0.215$)), clinical remission, symptomatic remission, endoscopic improvement, normalized faecal calprotectin at week 12 than either monotherapy alone.[178] Adverse events rate were comparable among the treatment groups in these studies (compared to PBO or compared to guselkumab or GOL in VEGA study).[34,35,178] The evaluation of guselkumab in combination therapy with GOL in UC and CD is currently in phase 2b CTs (DUET-UC and DUET-CD).[179,180] Other combination therapies are being evaluated such as anti-TNF steroid conjugate (ABBV-154),[181] BI 706321 coupled with UST,[182] vorinostat (a histone deacetylase inhibitor) coupled with UST,[168] BI655130 (spesolimab) coupled with IFX.[183] Finally, a little beyond the scope of this review (since it is not new drugs or therapeutic targets), another CT also assess the efficacy and safety of a triple combination therapy of anti-integrin (vedolizumab IV), a TNF-α antagonist (adalimumab SC), and an immunomodulator (oral methotrexate) in high risk CD (EXPLORER trial).[184] Given that the immune-mediated inflammatory processes are driven by multiple pathways and that the use of a single agent leads to a limited rate of remission, it is possible that we are moving towards the search for rational and ideal treatment combinations (in addition to the search for new mechanisms of action) to try to overcome the plateau drug efficacy as recently reviewed by Danese et al.[185] These combination therapies should be subject to controlled CTs in the future.[185]

FUTURE DIRECTIVES AND CONCLUSION

Several new therapies have been shown to be effective and safe in IBD and will probably strengthen our therapeutic arsenal in the next few years. The anti-IL-23 drugs appear to be safe and effective, but the question of safety is less clear for the JAK inhibitors (in particular for long-term safety data) and the S1P modulators (for which it is too early to judge safety). Despite all the available molecules, there is a plateau of drug efficacy that cannot be surpassed today. Although no treatment is currently available to overcome this plateau, this therapeutic armamentarium (in addition to measuring drug levels, performing biomarkers for tight control and identifying biomarkers/factors to predict which patients are likely to respond to a given treatment) could nevertheless make it possible to improve the control of the disease by allowing multiple drug sequencing and/or new combination therapy. These emerging drugs will also allow the patient to have a more appropriate treatment according to his needs (according to age, to the presence of EIM or perianal disease, to the preference for route of administration, to speed to obtain a clinical remission, to pregnancy desire, among other things), the type of disease (with perianal involvement or extraintestinal manifestations) and according its past medical history (including personal cancer or thrombosis history). However, these new treatment options will also raise questions such as the most appropriate treatment according to the patient's profile, the search for predictors of response to a particular treatment, and also the need to determine the ideal therapeutic sequence to offer the patient the best chance of responding to each treatment.

AUTHOR CONTRIBUTIONS

Sophie Vieujean wrote the article and created tables. Ferdinando D'Amico, Patrick Netter, Silvio Danese and Laurent Peyrin-Biroulet critically reviewed the content of the paper. The manuscript was approved by all authors.

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CONFLICT OF INTEREST

Sophie Vieujean declares no conflict of interest.

Ferdinando D'Amico declares no conflict of interest.

Silvio Danese has served as a speaker, consultant, and advisory board member for Schering-Plough, AbbVie, Actelion, Alphawasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson and Johnson, Millenium Takeda, MSD, Nikkiso Europe GmbH, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma and Vifor.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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