nature reviews gastroenterology & hepatology

https://doi.org/10.1038/s41575-023-00768-1

Review article

Check for updates

IL-12 and IL-23 pathway inhibition in inflammatory bowel disease

In the format provided by the authors and unedited

Supplementary Box 1

Competing interests of Alimentiv Translational Research Consortium Member Authors

Silvio Danese reports consultancy fees from AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Dr Falk Pharma, Eli Lilly, Enthera, Ferring Pharmaceuticals Inc., Gilead, Hospira, Inotrem, Janssen, Johnson & Johnson, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB Inc., and Vifor; and lecture fees from Abbvie, Amgen, Ferring Pharmaceuticals Inc., Gilead, Janssen, Mylan, Pfizer, and Takeda.

Geert D'Haens reports consultancy fees from Abbvie, Agomab, AstraZeneca, AM Pharma, AMT, Arena Pharmaceuticals, Bristol Meiers Squibb, Boehringer Ingelheim, Celltrion, Eli Lilly, Exeliom Biosciences, Exo Biologics, Galapagos, Index Pharmaceuticals, Kaleido, Roche, Gilead, Glaxo Smith Kline, Gossamerbio, Pfizer, Immunic, Johnson and Johnson, Origo, Polpharma, Procise Diagnostics, Prometheus laboratories, Prometheus Biosciences, Progenity, and Protagonist; and speaker's fees from Abbvie, Arena, Galapagos, Gilead, Pfizer, BMS, and Takeda.

Lars Eckmann has nothing to disclose.

William A. Faubion reports consulting fees from Apple Tree Life Sciences Inc, Apertor Pharmaceuticals, Boehringer Ingelheim; and serves on advisory board fees for Janssen Pharmaceuticals Inc, AbbVie Inc and Lilly USA LLC.

Brian G. Feagan reports grant/research support from AbbVie Inc., Amgen Inc., AstraZeneca/MedImmune Ltd., Atlantic Pharmaceuticals Ltd., Boehringer-Ingelheim, Celgene Corporation, Celltech, Genentech Inc/Hoffmann-La Roche Ltd., Gilead Sciences Inc., GlaxoSmithKline (GSK), Janssen Research & Development LLC., Pfizer Inc., Receptos Inc./Celgene International, Sanofi, Santarus Inc., Takeda Development Center Americas Inc., Tillotts Pharma AG, and UCB; consulting fees from Abbott/AbbVie, Akebia Therapeutics, Allergan, Amgen, Applied Molecular Transport Inc., Aptevo Therapeutics, Astra Zeneca, Atlantic Pharma, Avir Pharma, Biogen Idec, BioMx Israel, Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, Galapagos, GiCare Pharma, Gilead, Gossamer Pharma, GSK, Inception IBD Inc, JnJ/Janssen, Kyowa Kakko Kirin Co Ltd., Lexicon, Lilly, Lycera BioTech, Merck, Mesoblast Pharma, Millennium, Nestle, Nextbiotix, Novonordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Progenity, Protagonist, Receptos, Salix Pharma, Shire, Sienna Biologics, Sigmoid Pharma, Sterna Biologicals, Synergy Pharma Inc., Takeda, Teva Pharma, TiGenix, Tillotts, UCB Pharma, Vertex Pharma, Vivelix Pharma, VHsquared Ltd., and Zyngenia; speakers bureau fees from Abbott/AbbVie, JnJ/Janssen, Lilly, Takeda, Tillotts, and UCB Pharma; is a scientific advisory board member for Abbott/AbbVie, Allergan, Amgen, Astra Zeneca, Atlantic Pharma, Avaxia Biologics Inc., Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Centocor Inc., Elan/Biogen, Galapagos, Genentech/Roche, JnJ/Janssen, Merck, Nestle, Novartis, Novonordisk, Pfizer, Prometheus Laboratories, Protagonist, Salix Pharma, Sterna Biologicals, Takeda, Teva, TiGenix, Tillotts Pharma AG, and UCB Pharma; and is the Senior Scientific Officer of Alimentiv, Inc.

Vipul Jairath reports consulting/advisory board fees from AbbVie, Alimentiv, Inc., Arena Pharmaceuticals, Asieris, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Janssen, Merck, Mylan, Pandion, Pendopharm, Pfizer, Reistone Biopharma, Roche, Sandoz, Takeda, and Topivert; speaker's fees from, Abbvie, Ferring, Galapagos, Janssen Pfizer Shire, Takeda.

Christopher Ma reports consulting fees from AbbVie, Amgen, AVIR Pharma Inc, Bristol Myers Squibb, Ferring, Fresenius Kabi, Janssen, McKesson, Mylan, Takeda, Pfizer, Roche, and Alimentiv, Inc.; speaker's fees from AbbVie, Amgen, AVIR Pharma Inc, Janssen, Takeda, and Pfizer; research support from Pfizer.

Saurabh Mehandru reports receiving research grants from Genentech and Takeda; receiving payment for lectures from Takeda, Genentech, Morphic; and receiving consulting fees from Takeda, Morphic and Arena Pharmaceuticals.

Julian Panes reports grants from AbbVie and Pfizer; reports consultancy fees/honorarium from AbbVie, Arena, Athos, Boehringer-Ingelheim, Celgene, Galapagos, Genentech/Roche, GlaxoSmithKline, Janssen, Mirum, Morphic, Nestlé, Origo, Pandion, Pfizer, Progenity, Protagonist, Takeda, Theravance and Wasserman; and reports payment for lectures including service on speaker bureau from Abbott, Janssen, Pfizer and Takeda.

Florian Rieder reports consulting or advisory board for Adnovate, Agomab, Allergan, AbbVie, Arena, Boehringer-Ingelheim, Celgene/BMS, CDISC, Cowen, Ferring, Galapagos, Galmed, Genentech, Gilead, Gossamer, Guidepoint, Helmsley, Horizon Therapeutics, Image Analysis Limited, Index Pharma, Jannsen, Koutif, Mestag, Metacrine, Morphic, Organovo, Origo, Pfizer, Pliant, Prometheus Biosciences, Receptos, RedX, Roche, Samsung, Surmodics, Surrozen, Takeda, Techlab, Theravance, Thetis, UCB, Ysios, 89Bio.

William J. Sandborn reports research grants from Abbvie, Abivax, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol Meyers Squibb, Genentech, Gilead Sciences, Glaxo Smith Kline, Janssen, Lilly, Pfizer, Prometheus Laboratories, Seres Therapeutics, Shire Pharmaceuticals, Takeda, Theravance Biopharma; consulting fees from Abbvie, Abivax, Alfasigma, Alimentiv (previously Robarts Clinical Trials, owned by Alimentiv Health Trust), Allakos, Amgen, Arena Pharmaceuticals, AstraZeneca, Atlantic Pharmaceuticals, Beigene, Boehringer Ingelheim, Bristol Meyers Squibb, Celltrion, Clostrabio, Forbion, Galapagos, Genentech (Roche), GlaxoSmithKline, Gossamer Bio, Index Pharmaceuticals, Iota Biosciences, Janssen, Lilly, Morphic Therapeutics, Novartis, Oppilan Pharma (now Ventyx Biosciences), Pfizer, Pharm Olam, Polpharm, Progenity, Prometheus Biosciences, Protagonist Therapeutics, PTM Therapeutics, Seres Therapeutics, Shoreline Biosciences, Sublimity Therapeutics, Surrozen, Takeda, Theravance Biopharma, Vedanta Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivreon Gastrosciences, Xencor, Zealand Pharmaceuticals; stock or stock options from Allakos, BeiGene, Gossamer Bio, Oppilan Pharma (now Ventyx Biosciences), Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonists Therapeutics, Shoreline Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivreon Gastrosciences; and employee at Shoreline Biosciences. Spouse: Iveric Bio - consultant, stock options; Progenity - stock; Oppilan Pharma (now Ventyx Biosciences) – stock; Prometheus Biosciences - employee, stock, stock

options; Prometheus Laboratories – stock, stock options, consultant; Ventyx Biosciences – stock, stock options; Vimalan Biosciences – stock, stock options.

Mark S. Silverberg reports research support, speaker fees, consulting fees, advisory Board fees from Abbvie, Janssen, Takeda, Pfizer, Gilead, Amgen.

Marisol Veny has nothing to disclose.

Severine Vermeire has received grants from AbbVie, J&J, Pfizer, Galapagos, and Takeda; and consulting and/or speaking fees from AbbVie, AbolerIS Pharma, AgomAb, Alimentiv, Arena Pharmaceuticals, AstraZeneca, Avaxia, BMS, Boehringer Ingelheim, Celgene, CVasThera, Dr Falk Pharma, Ferring, Galapagos, Genentech-Roche, Gilead, GSK, Hospira, Imidomics, Janssen, J&J, Lilly, Materia Prima, MiroBio, Morphic, MrMHealth, Mundipharma, MSD, Pfizer, Prodigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Surrozen, Takeda, Theravance, Tillots Pharma AG, and Zealand Pharma. Stefania Vetrano has nothing to disclose.

Supplementary Table 1. Phase II and III trials of therapies targeting IL-12 and/or IL-23 in clinical development for the treatment of Crohn's disease

Investigational agents	Trial	Treatment phase and trial design	Patients and treatment arms	Primary outcome	Endoscopic or histological outcomes
Targeting p40					
Ustekinumab	UNITI-1[1]	Phase III RCT induction	Primary non-response or intolerant to TNF inhibitors 130 mg IV (n=245) ~6mg/kg IV (n=249) Placebo (n=247)	Clinical response[a] at Week 6 130 mg: 34.3% (p≤0.003 compared to placebo) ~6mg/kg: 33.7% (p≤0.003 compared to placebo) Placebo: 21.5%	None reported in primary study
Ustekinumab	UNITI-2[1]	Phase III RCT induction	Failure or unacceptable side effects with conventional therapy 130 mg IV (n=209) ~6mg/kg IV (n=209) Placebo (n=210)	Clinical response[a] at Week 6 130 mg: 51.7% (p<0.001 compared to placebo) ~6mg/kg: 55.5% (p<0.001 compared to placebo) Placebo: 28.7%	None reported in primary study

Ustekinumab	IM-UNITI[1]	Phase III RCT maintenance	Clinical response[a] to ustekinumab induction therapy in UNITI-1/2 90 mg SC Q8W (n=132) 90 mg SC Q12W (n=132) Placebo (n=133)	Clinical remission[b] at maintenance Week 44 90 mg Q8W: 53.1% (p=0.005 compared to placebo) 90 mg Q12W: 48.8% (p=0.04 compared to placebo) Placebo: 35.9%	None reported in primary study
Ustekinumab	SEAVUE[2]	Phase III randomised, head-to-head trial	Biologic-naïve failing or intolerant to conventional therapy with an ulcer of any size Ustekinumab ~6mg/kg IV at baseline then 90 mg SC Q8W (n=191) Adalimumab 160 mg/80 mg SC at baseline/Week 2, then 40 mg SC Q2W (n=195)	Clinical remission[b] at Week 52 Ustekinumab: 65% Adalimumab: 61% (p=0.417)	Endoscopic remission[c] at Week 52 Ustekinumab: 28.5% (p=0.631 compared to adalimumab) Adalimumab: 30.7 % Endoscopic response[d] at Week 52 Ustekinumab: 41.9% (p=0.349 compared to adalimumab) Adalimumab: 36.9 %
Ustekinumab	STARDUST[3]	Phase IIIb RCT comparing T^2T vs. SoC maintenance strategy	Failure with conventional therapy and/or one biologic and a 70-point reduction in baseline CDAI score following ustekinumab induction therapy (single 6mg/kg IV dose at Week 0 followed by 90 mg SC at Week 8)	Endoscopic response[e] at Week 48 T^2T: 37.7% (p=0.0933 compared to SoC) SoC: 29.9%	See primary outcome

			T^2T: ustekinumab SC Q8W or Q12W depending on endoscopic improvement at Week 16, followed by clinical and biomarker-directed dose escalation up to Q4W from Week 16 to Week 48 (n=220) SoC: ustekinumab SC Q8W or Q12W based on EU summary of product characteristics (n=221)		
Briakinumab	N/A[4]	Phase IIb RCT induction	Moderate-severe CD stratified by prior TNF-inhibitors use and response IV 400 mg Q4W (n=45) IV 700 mg Q4W (n=139) Placebo (n=46)	Clinical remission[b] at Week 6 400 mg: 13.3% (p=0.455 compared to placebo) 700 mg: 17.3% (p=0.157 compared to placebo) Placebo: 8.7%	None reported
Briakinumab	N/A[4]	Phase IIb RCT maintenance	Clinical responders[m] to placebo or briakinumab at Week 12 Responders in IV 400 mg (n=21) and placebo (n=14) induction group received same regimen in maintenance Responders in IV 700 mg induction group were re-randomised to:	Clinical remission[b] at Week 24 Continued IV 400 mg: 48% (p=ns compared to placebo) Continued placebo: 29% Re-randomised IV 200 mg: 43% (p=ns compared to re-randomised placebo)	None reported

			Placebo (n=22) IV 200 mg Q4W (n=21) IV 700 mg Q4W (n=21)	Re-randomised IV 700 mg: 57% (p=ns compared to re-randomised placebo) Re-randomised placebo: 46%	
Targeting p19					
Risankizumab	ADVANCE[5]	Phase III RCT induction	Inadequate response or intolerance to biologic and/or conventional therapy IV 600 mg Q4W (n=336) IV 1200 mg Q4W (n=339) Placebo (n=175)	Co-primary of clinical remission[b,f] and endoscopic response at Week 12 CDAI remission[b]: 600 mg: 45.2% (p<0.001 compared to placebo) 1200 mg: 41.6% (p<0.001 compared to placebo) Placebo: 25.2% SF/AP remission[f]: 600 mg: 43.5% (p<0.001 compared to placebo) 1200 mg: 41.0% (p<0.001 compared to placebo) Placebo: 21.7% Endoscopic response[g] at Week 12:	See primary outcome

				600 mg: 40.3% (p<0.001 compared to placebo) 1200 mg: 32.2% (p<0.001 compared to placebo) Placebo: 12%	
Risankizumab	MOTIVATE[5]	Phase III RCT induction	Inadequate response or intolerance to biologic therapy 600 mg IV Q4W (n=191) 1200 mg IV Q4W (n=191) Placebo (n=187)	Co-primary of clinical remission[b,f] and endoscopic response at Week 12 CDAI remission[b]: 600 mg: 42.5% (p≤0.001 compared to placebo) 1200 mg: 40.3% (p≤0.001 compared to placebo) Placebo: 19.8% SF/AP remission[f]: 600 mg: 34.6% (p≤0.001 compared to placebo) 1200 mg: 39.3% (p≤0.001 compared to placebo) Placebo: 19.3% Endoscopic response[g] at Week 12:	See primary outcome

				600 mg: 28.8% (p≤0.001 compared to placebo) 1200 mg: 34.2% (p≤0.001 compared to placebo) Placebo: 11.2%	
Risankizumab	FORTIFY[6]	Phase III RCT maintenance	Response to risankizumab induction therapy in ADVANCE and MOTIVATE 180 mg SC Q8W (n=157) 360 mg SC Q8W (n=141) Placebo Q8W (n=164)	Co-primary of clinical remission[b,f] and endoscopic response at Week 52 CDAI remission[b]: 180 mg: 55% (p<0.01 compared to placebo) 360 mg: 52% (p<0.01 compared to placebo) Placebo: 41% SF/AP remission[f]: 180 mg: 46% (p=ns) 360 mg: 52% (p<0.01 compared to placebo) Placebo: 40% Endoscopic response[g] at Week 52: 180 mg: 47% (p<0.001 compared to placebo) 360 mg: 47% (p<0.001 compared to placebo) Placebo: 22%	Endoscopic remission[h] at Week 52[6] 180 mg: 30% (p<0.01 compared to placebo) 360 mg: 39% (p<0.01 compared to placebo) Placebo: 13% Deep remission[b,h] at Week 52[6] 180 mg: 25% (p<0.001 compared to placebo) 360 mg: 29% (p<0.001) compared to placebo Placebo: 10%

Guselkumab	GALAXI 1[7]	Phase II dose ranging RCT induction	Inadequate response/ intolerance to conventional therapies and/or biologics Guselkumab IV 200 mg Q4W (n=61) Guselkumab IV 600 mg Q4W (n=63) Guselkumab IV 1200 mg Q4W (n=61) Ustekinumab IV ~6mg/kg at Week 0 and SC 90 mg at Week 8 (n=63) Placebo (n=61)	Change from baseline in CDAI score at Week 12 Significantly greater reductions from baseline CDAI reported in the 200mg, 600mg, and 1200mg guselkumab groups compared to placebo (LS means: -160.4, -138.9, -144.9 vs. -36.2, respectively; p<0.05 for all comparisons with placebo)	Endoscopic response[i] at Week 12 Guselkumab 200 mg: 37.7% (p<0.05 compared to placebo) Guselkumab 600 mg: 36.5% (p<0.05 compared to placebo) Guselkumab 1200 mg: 32.8% (p<0.05 compared to placebo) Ustekinumab: 28.6% (p<0.05 compared to placebo) Placebo: 11.5% Endoscopic remission[j] at Week 12[8] Guselkumab 200 mg: 16.0% (p=0.064 compared to placebo) Guselkumab 600 mg: 10.0% (p=0.255 compared to placebo) Guselkumab 1200 mg: 16.0% (p=0.041 compared to placebo) Ustekinumab: 14.3% Placebo: 3.9%
Guselkumab	GALAXI 1[9]	Phase II RCT maintenance	GALAXI 1 induction Guselkumab IV 200 mg induction → SC 100 mg Q8W maintenance (n=61) Guselkumab IV 600 mg induction → SC 200 mg Q4W maintenance (n=63)	Clinical remission[b] at Week 48 Guselkumab IV 200 mg → SC 100 mg: 63.9% (95% CI: 51.9, 76.0)	None reported

			Guselkumab IV 1200 mg induction → SC 200 mg Q4W maintenance (n=61) Ustekinumab IV 6mg/kg induction → SC 90 mg Q8W maintenance (n=63)	Guselkumab IV 600 mg → SC 200 mg: 73.0% (95% CI: 62.1, 84.0) Guselkumab IV 1200 mg → SC 200 mg: 57.4% (95% CI: 45.0, 69.8) Ustekinumab: 58.7% (95% CI: 46.6, 70.9)	
Brazikumab	N/A[10]	Phase IIa double-blind induction and open- label maintenance	Failure with TNF inhibitors IV 700 mg at Weeks 0 and 4 followed by open-label Brazikumab SC 210 mg Q4W from Week 12 to 112 (n=59 in double blind; n=52 in open-label) Placebo at Weeks 0 and 4 followed by open-label Brazikumab SC 210 mg Q4W from Week 12 to 112 (n=60 in double blind; n=52 in open-label)	Clinical response[a] at Week 8 700 mg: 49.2% (p=0.010 compared to placebo) Placebo: 26.7%	None reported
Mirikizumab	SERENITY[11]	Phase II RCT induction	Inadequate response or failure to ≥1 of the following: aminosalicylates, budesonide, systemic corticosteroids, immunosuppressants	Endoscopic response[k]**Error! Bookmark not defined.** at Week 12 200 mg: 25.8% (95% CI: 10.4- 41.2;	Endoscopic remission[l] at Week 12 200 mg: 6.5% (p=0.241 compared to placebo) 600 mg: 15.6% (p=0.032 compared to placebo)

			(azathioprine, 6-MP, methotrexate); or prior exposure to biologics IV 200 mg Q4W (n=31) IV 600 mg Q4W (n=32) IV 1000 mg Q4W (n=64) Placebo (n=64)	p=0.079 compared to placebo) 600 mg: 37.5% (95% CI: 20.7- 54.3; p=0.003 compared to placebo) 1000 mg: 43.8% (95% CI: 31.6- 55.9; p<0.001 compared to placebo) Placebo: 10.9% (95% CI: 3.3-18.6)	1000 mg: 20.3% (p=0.009 compared to placebo) Placebo: 1.6%
Mirikizumab	SERENITY[12]	Phase II RCT maintenance	Patients who achieved ≥1 point improvement in SES-CD score at Week 12 in response to mirikizumab IV at dose received during induction Q4W (IV-C; n=41) SC 300 mg Q4W (SC; n=46)	Previously reported in SERENITY induction	Endoscopic response[k] at Week 52 IV-C: 58.5% (69.6% among Week 12 responders) SC: 58.7% (66.7% among Week 12 responders) Endoscopic remission[l] at Week 52 IV-C:19.5% (50% among Week 12 remitters) SC: 32.6% (64.3% among Week 12 remitters)

[a] ≥100 decrease in CDAI score from baseline or CDAI<150

[b] CDAI <150

[c] SES-CD ≤ 3, or SES-CD=0 for participants who entered the study with a SES-CD=3

[d] Reduction of ≥50% from baseline in SES-CD score or SES-CD ≤ 3, or SES-CD=0 for participants who entered the study with a SES-CD=3

[e] ≥50% reduction in SES-CD score vs. baseline

[f] Average daily SF ≤2.8 and average daily AP score ≤1, not worse than baseline for both

[g] Decrease in SES-CD >50% from baseline or ≥2-point reduction in SES-CD score from baseline for those with isolated ileal disease and baseline SES-CD of 4

[h] SES-CD ≤4 and ≥2-point reduction vs. baseline with no individual subscore greater than 1

[i] ≥50% improvement from baseline in SES-CD or SES-CD score ≤2
[j] SES-CD score ≤2
[k] 50% reduction from baseline in SES-CD
[l] SES-CD score <4 for ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1
[m] Decrease in CDAI score of ≥70 points compared to Week 0

Abbreviations: AP, abdominal pain; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; IV, intravenous; ns, non-significant; LS, least squares; RCT, randomised controlled trial; SC, subcutaneous; SES-CD, simple endoscopic score for Crohn's disease; SF, stool frequency; SOC, standard of care; TNF, tumor necrosis factor; T^2T, treat-to-target

Supplementary Table 2. Phase II and III trials of therapies targeting IL-12 and/or IL-23 in clinical development for the treatment of ulcerative colitis

Investigational agents	Trial	Treatment phase and trial design	Patients and treatment arms	Primary outcome	Endoscopic or histological outcomes
Targeting p40					
Ustekinumab	UNIFI[13]	Phase III RCT induction	Inadequate response to or unacceptable side effects with TNF inhibitors, vedolizumab, or conventional (nonbiologic) therapy IV 130 mg (n=320) IV ~6mg/kg (n=322) Placebo (n=319)	Clinical remission[a] at Week 8 130 mg: 15.6% (P<0.001 compared to placebo) ~6mg/kg: 15.5% (P<0.001 compared to placebo) Placebo: 5.3%	Endoscopic improvement[b] at Week 8 130 mg: 26.3% (P<0.001 compared to placebo) 6mg/kg: 27.0% (P<0.001 compared to placebo) Placebo:13.8% Histo-endoscopic mucosal healing[b,c] at Week 8 130 mg: 20.3% (P<0.001 compared to placebo) 6mg/kg: 18.4% (P<0.001 compared to placebo) Placebo: 8.9%
Ustekinumab	UNIFI[13]	Phase III RCT maintenance	Clinical responders[d] to ustekinumab induction therapy at Week 8 and those who did not have a response to IV placebo and who then received ustekinumab IV 6mg/kg at Week 8 and had a response at Week 16 SC 90 mg Q12W (n=172) SC 90 mg Q8W (n=176)	Clinical remission[a] at maintenance Week 44 90 mg Q12W: 38.4% (P=0.002 compared to placebo) 90 mg Q8W: 43.8% (P<0.001 compared to placebo) Placebo: 24.0%	Endoscopic improvement[b] at Week 44 90 mg Q12W: 43.6% (P=0.002) compared to placebo) 90 mg Q8W: 51.1% (P<0.001 compared to placebo) Placebo: 28.6% Histo-endoscopic mucosal healing[b,c] at Week 44 90 mg Q12W: 38.8%

			Placebo (n=175)		90 mg Q8W: 45.9% Placebo: 24.1%
Targeting p19					
Mirikizumab	LUCENT-1[14]	Phase III RCT induction	Inadequate response, loss of response, or intolerance to corticosteroids, immunosuppressants, biologic therapies, or tofacitinib IV 300 mg Q4W (n=868) Placebo (n=294)	Clinical remission[e] at Week 12 300 mg: 24.2% (p=0.00006 compared to placebo) Placebo: 13.3%	Endoscopic remission[b] (excluding friability) at Week 12 300 mg: 36.3% (p<0.00001 compared to placebo) Placebo: 21.1% Histologic-endoscopic mucosal improvement[b,c] at Week 12 300 mg: 27.1% (p<0.00001 compared to placebo) Placebo: 13.9%
Guselkumab	QUASAR[15]	Phase IIb RCT dose-ranging induction	Inadequate response or intolerance to conventional (thiopurines or corticosteroids) or advanced therapy (TNF alpha inhibitors, vedolizumab, or tofacitinib) IV 200 mg Q4W (n=101) IV 400 mg Q4W (n=107) Placebo (n=105)	Clinical response[f] at Week 12 200 mg: 61.4% (p<0.001 compared to placebo) 400 mg: 60.7% (p<0.001 compared to placebo) Placebo: 27.6%	Endoscopic improvement[b] with no friability on endoscopy at Week 12 200 mg: 30.7% (p<0.05 compared to placebo) 400 mg: 30.8% (p<0.001 compared to placebo) Placebo: 12.4% Endoscopic normalisation[g] at Week 12 200 mg: 17.8% (p<0.05 compared to placebo) 400 mg: 14.0% (p=ns compared to placebo) Placebo: 6.7%

					Histo-endoscopic mucosal improvement[b,c] at Week 12 200 mg: 19.8% (p<0.05 compared to placebo) 400 mg: 27.1% (p<0.001 compared to placebo) Placebo: 8.6%
Guselkumab + golimumab	VEGA[16]	Phase IIa RCT induction	TNFα inhibitors naïve and refractory or intolerant to conventional therapy (immunomodulators and/or corticosteroids) Guselkumab IV 200 mg Q4W (n=71) Golimumab SC 200 mg at Week 0 then SC 100 mg at Week 2, 6 and 10 (n=72) Combination with guselkumab IV 200 mg + golimumab SC 200 mg at Week 0, golimumab SC 100 mg at Week 2, 6, and 10, and guselkumab IV 200 mg at Week 4 and 8 (n=71)	Clinical response[d] at Week 12 Golimumab and guselkumab combination: 83.1% (p=0.003 compared to golimumab alone and p=0.215 compared to guselkumab alone) Golimumab alone: 61.1% Guselkumab alone: 74.6%	Endoscopic improvement[b] with no friability present on endoscopy at Week 12 Golimumab and guselkumab combination: 49.3% (p=0.003 compared to golimumab alone and p=0.016 compared to guselkumab alone) Golimumab alone: 25.0% Guselkumab alone: 29.6% Endoscopic normalisation[g] with no friability on endoscopy at Week 12 Golimumab and guselkumab combination: 18.3% (p=0.140 compared to golimumab alone and p=0.084 compared to guselkumab alone Golimumab alone: 9.7% Guselkumab alone: 8.5% Histologic remission[h] at Week 12

					Golimumab and guselkumab combination: 56.3% (p=0.003 compared to golimumab alone and p=0.403 compared to guselkumab alone) Golimumab alone: 31.9% Guselkumab alone: 49.3% Histologic remission[h] and endoscopic improvement[b] at Week 12 Golimumab and guselkumab combination: 40.8% (p<0.001 compared to golimumab alone and p=0.077 compared to guselkumab alone Golimumab alone: 15.3% Guselkumab alone: 26.8% Histologic remission[h] and endoscopic normalisation[g] at Week 12 Golimumab and guselkumab combination: 15.5% (p=0.023 compared to golimumab alone and p=0.113 compared to guselkumab alone Golimumab alone: 4.2 % Guselkumab alone: 7.0%

[a] Total score of ≤2 on the Mayo scale and no subscore >1 on any of the four Mayo scale components. [b] Mayo endoscopic subscore of 0 or 1. [c] Neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue. [d] Decrease in the total Mayo score of ≥30% and of ≥3 points from baseline, with an accompanying decrease ≥1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1. [e]

Stool frequency subscore = 0 or 1 with a ≥1-point decrease from baseline, and rectal bleeding subscore = 0, and endoscopic subscore = 0 or 1 (excluding friability). [f] Decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1. [g] Endoscopy subscore of 0. [h] Absence of neutrophils from the mucosa (both lamina propria and epithelium), no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system. Abbreviations: IV, intravenous; ns, non-significant; RCT, randomised controlled trial; SC, subcutaneous; TNF, tumor necrosis factor

Supplementary references

1. Feagan BG, Sandborn WJ, Gasink C*, et al.* Ustekinumab as induction and maintenance therapy for crohn's disease. *N Engl J Med* 2016;**375**:1946-60.
2. Sands BE, Irving PM, Hoops T*, et al.* Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active crohn's disease: A multicentre, randomised, double-blind, parallel-group, phase 3b trial. *Lancet* 2022;**399**:2200-11.
3. Danese S, Vermeire S, D'Haens G*, et al.* Treat to target versus standard of care for patients with crohn's disease treated with ustekinumab (stardust): An open-label, multicentre, randomised phase 3b trial. *Lancet Gastroenterol Hepatol* 2022;**7**:294-306.
4. Panaccione R, Sandborn WJ, Gordon GL*, et al.* Briakinumab for treatment of crohn's disease: Results of a randomized trial. *Inflamm Bowel Dis* 2015;**21**:1329-40.
5. D'Haens G, Panaccione R, Baert F*, et al.* Risankizumab as induction therapy for crohn's disease: Results from the phase 3 advance and motivate induction trials. *Lancet* 2022;**399**:2015-30.
6. Ferrante M, Panaccione R, Baert F*, et al.* Risankizumab as maintenance therapy for moderately to severely active crohn's disease: Results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 fortify maintenance trial. *Lancet* 2022;**399**:2031-46.
7. Sandborn WJ, D'Haens GR, Reinisch W*, et al.* Guselkumab for the treatment of crohn's disease: Induction results from the phase 2 galaxi-1 study. *Gastroenterology* 2022.
8. Sandborn WJ, Chan D, Johanns J*, et al.* The efficacy and safety of guselkumab induction therapy in patients with moderately to severely active crohn's disease: Week 12 interim analyses from the phase 2 galaxi 1 study. *United European Gastroenterol* 2020;**8**:64.
9. Danese S, Panaccione R, Rubin DT*, et al.* Op24 clinical efficacy and safety of guselkumab maintenance therapy in patients with moderately to severely active crohn's disease: Week 48 analyses from the phase 2 galaxi 1 study. *J Crohns Colitis* 2022;**16**:i026-i7.
10. Sands BE, Chen J, Feagan BG*, et al.* Efficacy and safety of medi2070, an antibody against interleukin 23, patients with moderate to severe crohn's disease: A phase 2a study. *Gastroenterology* 2017;**153**:77-86.
11. Sands BE, Sandborn WJ, Peyrin-Biroulet L*, et al.* 1003 – efficacy and safety of mirikizumab (ly3074828) in a phase 2 study of patients with crohn's disease. *Gastroenterology* 2019;**156**:S-216.
12. Sands BE, Sandborn WJ, Peyrin-Biroulet L*, et al.* Efficacy and safety of mirikizumab after 52-weeks maintenance treatment in patients with moderate-to-severe crohn's disease *Gastroenterology* 2021;**160**:S-37.
13. Sands BE, Sandborn WJ, Panaccione R*, et al.* Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2019;**381**:1201-14.
14. D'Haens G, Kobayashi T, Morris N*, et al.* Op26 efficacy and safety of mirikizumab as induction therapy in patients with moderately to severely active ulcerative colitis: Results from the phase 3 lucent-1 study. *J Crohns Colitis* 2022;**16**:i028-i9.
15. Dignass A, Rubin D, Bressler B*, et al.* Op23 the efficacy and safety of guselkumab induction therapy in patients with moderately to severely active ulcerative colitis: Phase 2b quasar study results through week 12. *J Crohns Colitis* 2022;**16**:i025-i6.
16. Sands BE, Feagan BG, Sandborn WJ*, et al.* Op36 efficacy and safety of combination induction therapy with guselkumab and golimumab in participants with moderately-to-severely active ulcerative colitis: Results through week 12 of a phase 2a randomized, double-blind, active-controlled, parallel-group, multicenter, proof-of-concept study. *J Crohns Colitis* 2022;**16**:i042-i3.