

SYSTEMATIC REVIEW OPEN ACCESS

Asian Pacific Association of Gastroenterology (APAGE) Clinical Practice Guidelines on the Use of Small Molecules and IL-23 p19 Inhibitors in Ulcerative Colitis and Crohn's Disease

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ABSTRACT

Ulcerative colitis (UC) and Crohn's disease (CD) are increasingly prevalent in the Asia Pacific region, necessitating updated, region-specific guidance on advanced therapies. Targeted small molecule agents, such as filgotinib, tofacitinib, upadacitinib, etrasimod, and ozanimod; and the IL-23 p19 inhibitors (guselkumab, mirikizumab, risankizumab) are the newest advanced therapies in our armamentarium for the treatment of IBD. The aim of the Asia-Pacific consensus statements is to provide context-specific recommendations integrating real-world evidence specific to our region. The Asian-Pacific Association of Gastroenterology (APAGE) Committee on Inflammatory Bowel Disease, with the participation of Asian Education Network in Inflammatory Bowel Disease (AEN-IBD), convened a forum of 34 IBD experts from 12 countries to develop consensus guidelines on the best practices on the use of these new advanced therapies using the modified Delphi method. IL-23 p19 inhibitors have shown good efficacy in biologic-naïve and experienced patients in both UC and CD, with clinical and endoscopic superiority over ustekinumab and an excellent safety profile. JAK inhibitors (tofacitinib and filgotinib) are efficacious in UC, and upadacitinib is efficacious in both UC and CD. They have a rapid time to response, and emerging data on acute severe UC appears promising. However, careful screening and monitoring is needed for known side effects, and prophylactic vaccination for herpes zoster should be considered. S1P modulators (ozanimod, etrasimod) are efficacious in UC with a favorable side effect profile.

1 | Introduction

The therapeutic landscape for IBD has undergone a transformative evolution over the past two decades [1]. Traditional management relied heavily on corticosteroids and conventional immunosuppressants such as thiopurines and methotrexate. The introduction of biologic therapies marked a paradigm shift,

beginning with anti-tumor necrosis factor (anti-TNF) agents like infliximab, adalimumab, golimumab, and certolizumab pegol, followed by vedolizumab and ustekinumab. Despite these advances, a significant minority of patients do not respond at all (primary non-responders), or have an incomplete response, or lose response over time. Some develop serious adverse events necessitating treatment discontinuation. In addition, the

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parenteral administration of biologic therapy remains a limitation in terms of patient preference and convenience. This has led to the development of novel small molecules that are similar to biologics in that they target specific inflammatory pathways, but are administered orally rather than parenterally. Another main limitation of our current advanced therapies is that there remains a therapeutic ceiling. Therefore, in parallel with the development of targeted small molecules, there continues to be ongoing research and development of biologic therapies with different mechanisms of action.

1.1 | Novel Therapeutic Classes

1.1.1 | IL-23 p19 Inhibitors

Interleukin-23 (IL-23) is a heterodimeric cytokine comprising p40 and p19 subunits [2]. The IL-23/IL-17 axis plays a pivotal role in IBD pathogenesis by promoting the expansion and maintenance of pathogenic Th17 cells, which produce pro-inflammatory cytokines including IL-17A, IL-21, and IL-22. Selective IL-23 p19 inhibitors target the p19 subunit unique to IL-23.

Three IL-23 p19 inhibitors have received regulatory approval for IBD: guselkumab (approved for UC and CD), mirikizumab (approved for UC and CD), and risankizumab (approved for UC and CD) [3]. These agents demonstrate superior efficacy compared with placebo in both biologic-naïve and biologic-experienced patients, with excellent safety profiles and absence of boxed warnings.

1.1.2 | JAK Inhibitors

Janus kinase (JAK) inhibitors represent the first oral small molecules approved for IBD, targeting the JAK–STAT pathway crucial for signal transduction of multiple pro-inflammatory cytokines involved in IBD pathogenesis [4]. The JAK family consists of four members (JAK1, JAK2, JAK3, TYK2) that mediate signaling for various cytokines including interferons, interleukins, and growth factors.

Three JAK inhibitors are approved for IBD: tofacitinib (pan-JAK inhibitor, approved for UC), upadacitinib (selective JAK1 inhibitor, approved for UC and CD), and filgotinib (selective JAK1 inhibitor, approved for UC) [5]. These agents offer rapid symptom relief, with clinical improvements observed as early as 1–7 days of initiation. However, they carry boxed warnings regarding increased risks of serious infections, cardiovascular events, thrombosis, and malignancies, particularly in high-risk populations [6].

In view of the fact that generic tofacitinib and upadacitinib are available in some parts of Asia, JAK inhibitors are positioned to become one of the most important advanced therapies with resource-constrained healthcare systems.

1.1.3 | Sphingosine-1-Phosphate (S1P) Modulators

S1P modulators represent a novel oral therapeutic class that modulates lymphocyte trafficking by targeting the S1P pathway.

S1P regulates lymphocyte egress from secondary lymphoid organs through interaction with S1Ps, particularly S1P1 [7].

S1P modulators act as functional antagonists by binding to S1P1 receptors on lymphocytes, causing receptor internalization and degradation [8]. This prevents lymphocytes from responding to S1P gradients, effectively sequestering them in lymphoid organs and reducing their migration to inflamed tissues.

Two S1P modulators are approved for UC: ozanimod (selective S1P1 and S1P5 receptor modulator) and etrasimod (selective S1P1 receptor modulator with partial S1P4/S1P5 activity). These agents demonstrate favorable safety profiles with low rates of serious infections and absence of immunogenicity concerns, though they require cardiac monitoring.

1.1.4 | Advanced Combined Therapies (ACT)

The concept of Advanced Combined Targeted Therapy (ACT) has emerged as a strategy to overcome the therapeutic ceiling of current IBD treatments, where maximum remission rates plateau around 40%–50% even with optimal monotherapy [9]. ACT involves the simultaneous use of two or more advanced therapies—biologics and/or small molecules—with complementary mechanisms of action to address the multifactorial pathogenesis of IBD [10].

The biological rationale for ACT stems from the complex, redundant inflammatory pathways in IBD that may require multi-target approaches for optimal disease control. Early clinical evidence suggests potential benefits in highly refractory patients, those with extraintestinal manifestations (EIMs), or concurrent immune-mediated inflammatory diseases, though this approach requires careful patient selection and enhanced safety monitoring [11].

1.2 | Asia-Pacific Specific Considerations

The APAGE Committee on Inflammatory Bowel Disease developed this consensus to guide physicians in the use of the newest available therapies in IBD.

Although these consensus statements are grounded in the same pivotal randomized controlled trials that inform Western guidelines, their recommendations are tailored for the Asia-Pacific context. In particular, this guideline places emphasis on real-world data from Asian cohorts, infections of special interest such as tuberculosis (TB), chronic hepatitis B and herpes zoster as well as cost and accessibility in resource-limited countries.

A summary of the major trials reviewed is listed in Appendix 1.

2 | Methods

Global randomized controlled trials formed the primary evidentiary base, whereas real-world cohort data from Asia-Pacific populations were specifically sought to validate the efficacy and safety in patients in the Asia-Pacific.

TABLE 1 | Quality of evidence, classification of recommendation, and voting on recommendation.^a

Category and grade	Description
Quality of evidence	
I	Evidence obtained from at least 1 RCT
II-1	Evidence obtained from well-designed control trials without randomization
II-2	Evidence from well-designed cohort or case-control study
II-3	Evidence obtained from comparison between time or places with or without intervention
III	Opinion of respected authorities, based on clinical experience and expert committees
Classification of recommendation	
A	There is good evidence to support the statement
B	There is fair evidence to support the statement
C	There is poor evidence to support the statement but recommendation made on other ground
D	There is fair evidence to refute the statement
E	There is good evidence to refute the statement
Voting on recommendation	
a	Accept completely
b	Accept with some reservation
c	Accept with major reservation
d	Accept with major reservation
e	Reject completely

Note: Statement for which more than 80% of participants voted a and b are accepted.

^aFor recommendations graded as Quality of Evidence III and Classification C, the evidence base is limited and consensus-driven; clinicians should apply these recommendations with careful clinical judgment, taking into account local resources, comorbidities, and patient preferences.

The consensus was developed using the modified Delphi method and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to ensure a rigorous and transparent process. The issues are determined according to perceived clinical importance particular to the Asia-Pacific region.

A planning group panel (C.J.O., I.H., K.L.L.) generated a list of 27 statements and circulated them electronically to Consensus Group members. These statements were proposed to the Consensus Group panel for discussion, revision and voting. A password-secured website was populated with relevant literature assembled by the literature review team (C.J.O., I.H., K.L.L., G.M., H.Y.L., J.L., J.M., M.T.W., R.L., S.C.W., T.K., V.A., W.C.O.). Systematic literature reviews, with defined inclusion and exclusion criteria, were conducted to identify and grade the available evidence to support each statement. Literature searches were conducted in English language publications in MEDLINE, EMBASE, and the Cochrane Trials Register in human subjects. All national and international guidelines on UC and Crohn's disease (CD) were solicited. Relevant literature from the Asia-Pacific region was of particular interest. Categorization of evidence, classification of recommendation and voting schema is modified from the Canadian Task Force on the Periodic Health

Examination [Barkun] (Table 1). Consensus was considered to be achieved when 80% or above of voting members indicated "accept completely" or "accept with reservation." A statement was refuted when 80% or above of voting members "reject completely" or "reject with reservation." Every statement was then graded to indicate the level of evidence available and the strength of recommendation.

2.1 | Membership of the Consensus Group

Voting members of the Consensus Group were selected using the following criteria:

1. Demonstration of knowledge and expertise in IBD through publication/research or participation in national or regional guideline development.
2. Geographical representation of the Asia-Pacific countries.
3. Diversity of views and expertise in the healthcare system (including colorectal surgeon, pathologist, pharmacist, nurse practitioners, patient support group representatives). Voting was limited, however, to clinicians.

A total of 34 representatives from Australia, China, Hong Kong, India, Indonesia, Malaysia, the Philippines, Singapore, Japan, South Korea, Taiwan, Thailand, and Vietnam were involved.

2.2 | Voting, Delphi Process and General Organization of the Consensus

Voting was conducted anonymously at all times. The first vote was conducted by the entire Consensus Group electronically via online voting. Relevant literature was then made available on a secured web site for review by all voters. Modification of first round votes after access to the literature, if required, constituted the second round of voting. A face-to-face meeting of the entire Consensus Group was then held to discuss any suggested modifications to the wording of the statements and to discuss openly the evidence for and against each specific statement. A third vote was held thereafter. Statements that could not reach consensus were discussed and modified or rejected. Each statement was graded to indicate the level of evidence available and the strength of recommendation by using the Canadian Task Force on the Periodic Health Examination Guidelines. A face-to-face Consensus Conference was held on May 15, 2025 in Penang, Malaysia on the sidelines of the 6th APAGE Clinical Forum on Inflammatory Bowel Disease.

3 | Results

Twenty-seven consensus statements were generated (Table 2).

Statement 1

IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) can be used as induction and maintenance therapy in advanced therapy-naïve and experienced adult patients with moderate-to-severe UC and Crohn's disease (CD).

Level of agreement: 100%

Quality of evidence: I

Classification of recommendation: A

Guselkumab, mirikizumab, and risankizumab provide substantial clinical and endoscopic remission benefits as induction and maintenance therapy for moderate-to-severe UC and CD in adults, including patients previously treated with other biologics or small molecules. Key phase 3 trials demonstrate statistically robust increases in remission and response rates over placebo [12–18]. Phase 3 trials also demonstrate the efficacy of guselkumab subcutaneous induction and maintenance therapy for moderate-to-severe UC and CD [19, 20].

Subgroup analyses from all the landmark trials (although some not yet published) confirm that the efficacy of these therapies is similar in Asian populations. Guselkumab achieved similar induction and maintenance efficacy in East Asian patients with moderate-to-severe UC compared with

TABLE 2 | Consensus statements.

Statement		Level of agreement	Quality of evidence	Classification of recommendation
IL-23 p19 inhibitors				
1	IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) can be used as induction and maintenance therapy in advanced therapy-naïve and experienced adult patients with moderate-to-severe Ulcerative Colitis (UC) and Crohn's disease (CD).	100%	I	A
2a	For moderate to severe CD patients who have inadequate response/intolerance to oral corticosteroids or 6-MP/AZA/MTX, or biologic therapies, guselkumab provides comparable clinical remission but higher endoscopic response and remission rates compared with ustekinumab.	96.88%	I	A
2b	For moderate to severe CD patients who have inadequate response/intolerance to oral corticosteroids or 6-MP/AZA/MTX, or biologic therapies, mirikizumab provides comparable clinical and endoscopic response and remission rates compared with ustekinumab.	90.63%	I	A
2c	For moderate to severe CD patients, who have failed or are intolerant to anti-TNF therapy, risankizumab provides comparable clinical remission but higher endoscopic remission rate compared with ustekinumab.	93.75%	I	A

(Continues)

TABLE 2 | (Continued)

Statement		Level of agreement	Quality of evidence	Classification of recommendation
3	All IL-23 p19 inhibitors (guselkumab, mirikizumab, risankizumab) show efficacy in CD patients who are refractory to ustekinumab	90.63%	II-3	B
4	There are limited data on the efficacy of IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) in IBD-related extraintestinal manifestations (EIMs).	100%	III	C
5	There are limited data on the efficacy of IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) in perianal fistulising CD.	100%	III	C
6a	There are currently no data on the use of IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) in the pediatric population.	100%	III	C
6b	IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) can safely be used in IBD patients who are pregnant or attempting conception.	100%	III	C
6c	IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) can safely be used during breastfeeding.	100%	III	C
7	IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) have demonstrated favorable safety profiles, with minimal side effects and no boxed warnings.	100%	I	A
JAK inhibitors				
8	JAK inhibitors (filgotinib, tofacitinib, and upadacitinib) can be used for induction and maintenance in moderate-to-severe UC patients who are refractory or intolerant to conventional or advanced therapies.	100%	I	A
9	Upadacitinib can be used as induction and maintenance therapy in moderate-to-severe CD patients who are refractory or intolerant to conventional or advanced therapies.	100%	I	A
10	Upadacitinib can be considered in UC patients who are refractory to tofacitinib.	100%	II-3	B
11	There are emerging data on the efficacy of upadacitinib in fistulizing and perianal CD.	83%	III	C
12	Upadacitinib can be used in IBD-related axial and peripheral arthropathy.	100%	I	A
13	JAK inhibitors (filgotinib, tofacitinib, upadacitinib) should be used cautiously in patients at risk for major adverse cardiovascular events (MACE), venous thromboembolism (VTE), and a history of malignancy.	97%	II-2	C
14	Vaccination with the recombinant HZV vaccine is recommended for patients considering JAK inhibitors (filgotinib, tofacitinib, and upadacitinib).	100%	II-3	B
15	There are emerging data on the role of JAK inhibitors (filgotinib, tofacitinib, and upadacitinib) in pediatric IBD patients.	100%	III	C

(Continues)

TABLE 2 | (Continued)

Statement		Level of agreement	Quality of evidence	Classification of recommendation
16	JAK inhibitors (filgotinib, tofacitinib, and upadacitinib) should be avoided in IBD patients who are considering pregnancy and breastfeeding.	97%	II-C	C
17	Tofacitinib and upadacitinib may be considered for patients with acute severe UC (ASUC).	88%	II-2	B
S1P modulators				
18	S1P modulators (etrasimod and ozanimod) can be used for both induction and maintenance therapy in adults with moderate to severe UC, who have had inadequate response, loss of response, or are intolerant to conventional or advanced therapies.	100%	I	A
19	S1P modulators (etrasimod and ozanimod) should be avoided in patients who are considering pregnancy and breastfeeding.	100%	II-3	C
20	There are limited data for the use of etrasimod and ozanimod in IBD-related extraintestinal manifestations (EIMs).	100%	III	C
21	S1P modulators (etrasimod and ozanimod) have a low risk of serious infections, including herpes zoster and tuberculosis reactivation.	100%	I	B
22	S1P modulators (etrasimod and ozanimod) have not been associated with progressive multifocal leukoencephalopathy in IBD patients, but long-term data are required.	100%	III	C
23	Patients considered for S1P modulators (etrasimod and ozanimod) should undergo a cardiac evaluation to exclude significant cardiovascular disease, brady-arrhythmias and/or heart block.	94%	I	C
24	Withdrawal of 5-ASA can be considered in UC patients in remission on small molecules or IL-23 p19 inhibitors.	83%	III	C
25	Immunomodulators should not be used in combination with JAK inhibitors and S1P modulators.	96%	III	C
26	There is no evidence of additional benefit or increased harm when combining IL-23 p19 inhibitors with immunomodulators (in IBD patients).	91%	III	C
27	Concurrent use of two or more advanced treatments (i.e., biologic therapies and/or small molecules) may be considered for selected patients with (a) refractory IBD (b) active extraintestinal manifestations (EIMs), or (c) other immune-mediated inflammatory disease (IMIDs)	96%	III	C

the overall QUASAR population [21]. Mirikizumab provides robust induction and maintenance efficacy with a consistent safety profile in Japanese patients with moderately to severely active UC, supporting its use in East Asian populations [22]. Subgroup analysis of Asian patients within the ADVANCE, MOTIVATE, and FORTIFY CD studies, and the INSPIRE study for UC showed no significant differences in efficacy and safety compared with non-Asian subjects [23, 24]. Real-world data from Asia also supports the use of risankizumab in Asian CD patients [25].

Statement 2a

For moderate to severe CD patients who have inadequate response/intolerance to oral corticosteroids or 6-MP/AZA/MTX, or biologic therapies, guselkumab provides comparable clinical remission but higher endoscopic response and remission rates compared with ustekinumab.

Level of agreement: 96.88%

Quality of evidence: I

Classification of recommendation: A

In GALAXI 2&3, compared with ustekinumab, the clinical remission rate at Week 48 was 65% in the group receiving guselkumab 100 mg SC every 8 weeks and 70% in the group receiving guselkumab 200mg SC every 4weeks; these rates were not significantly higher than the clinical remission rate of 63% in the UST group [12]. However, the endoscopic remission rate at Week 48 was significantly higher in the guselkumab group (33% and 37% in the groups receiving guselkumab 100mg SC every 8 weeks and 200mg SC every 4 weeks, respectively) compared with the UST group (24%).

The higher guselkumab dose of 200 mg SC 4-weekly achieved superior week-48 clinical and endoscopic outcomes versus 100 mg every 8 weeks for those with more marked disease burden by baseline clinical (CDAI > 300) or endoscopic (SES-CD > 12) severity, higher post-induction inflammatory burden (CRP > 5 mg/L), or lack of endoscopic response after induction [26].

Statement 2b

For moderate to severe CD patients who have inadequate response/intolerance to oral corticosteroids or 6-MP/AZA/MTX, or biologic therapies, mirikizumab provides comparable clinical and endoscopic response and remission rates compared with ustekinumab.

Level of agreement: 90.63%

Quality of evidence: I

Classification of recommendation: A

In CD, in the VIVID-1 Phase 3 trial, patients with moderately to severely active CD with inadequate response, loss of response, or intolerance to conventional or biologic therapies were randomized to receive mirikizumab 900 mg IV followed by 300 mg SC every 4 weeks, ustekinumab ~6 mg/kg IV then 90 mg SC every 8 weeks, or placebo [15]. Mirikizumab demonstrated non-inferiority to ustekinumab for clinical remission by CDAI at Week 52. In patients who had previously failed biological therapy, mirikizumab showed numerically higher clinical remission rates (49% vs. 42% with ustekinumab) and endoscopic response rates (45% vs. 40% with ustekinumab).

Statement 2c

For moderate to severe CD patients who have failed or are intolerant to anti-TNF therapy, risankizumab provides comparable clinical remission but a higher endoscopic remission rate compared with ustekinumab.

Level of agreement: 93.75%

Quality of evidence: I

Classification of recommendation: A

In the SEQUENCE Phase 3b trial, patients with moderate-to-severe CD who had previously failed or were intolerant to anti-TNF therapy were randomized to receive risankizumab or ustekinumab [27]. Risankizumab demonstrated non-inferior clinical remission compared with ustekinumab at Week 24 (58.6% vs. 39.5%) and significantly higher endoscopic remission at Week 48 (31.8% vs. 16.2%; $p < 0.001$).

Statement 3

All IL-23 p19 inhibitors (guselkumab, mirikizumab, risankizumab) show efficacy in CD patients who are refractory to ustekinumab.

Level of agreement: 90.63%

Quality of evidence: II-3

Classification of recommendation: B

All three IL-23 inhibitors show promise in patients with ustekinumab failure. Guselkumab achieved 52.9% clinical remission at 16 weeks and 35% endoscopic remission at 1 year in 17 ustekinumab-nonresponders [28]. Mirikizumab demonstrated over 40% endoscopic response at Week 52 in 92 patients who had not responded to ustekinumab [29]. Risankizumab showed numerically superior clinical and endoscopic remission rates versus placebo in patients with ustekinumab failure history in Phase 3 trials [30]. Real-world studies confirm risankizumab's effectiveness remains intact regardless of prior ustekinumab exposure, with similar clinical remission rates between ustekinumab-naïve and ustekinumab-experienced patients [31].

Statement 4

There are limited data on the efficacy of IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) in IBD-related extraintestinal manifestations (EIMs).

Level of agreement: 100%

Quality of evidence: III

Classification of recommendation: C

Evidence for IL-23 inhibitors in treating EIMs remains limited. As of now, more data is required before clear recommendations can be made on the use of these therapies in EIM.

Statement 5

There are limited data on the efficacy of IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) in perianal fistulising CD.

Level of agreement: 100%

Quality of evidence: III

Classification of recommendation: C

Evidence for IL-23 inhibitors in perianal fistulizing CD is limited. Guselkumab has no robust data, though a trial is ongoing [32]. As of now, more data is required before clear recommendations can be made on the use of these therapies for perianal fistulizing CD.

Statement 6a

There are currently no data on the use of IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) in the pediatric population.

Level of agreement: 100%

Quality of evidence: III

Classification of recommendation: C

IL-23 inhibitors lack established efficacy and safety data in pediatric IBD patients. Guselkumab has ongoing trials MACARONI-23 (pediatric CD) and QUASAR Jr (pediatric UC), with PROTOSTAR showing similar adverse event rates to placebo in pediatric psoriasis patients aged 6–18 years [33–35]. Mirikizumab's clinical program (LUCENT-1/2/3, VIVID-1) enrolled only adults aged 18–80 years, with no pediatric IBD trials completed or ongoing as of April 2025. No pediatric efficacy, safety, pharmacokinetic, or pharmacodynamic data exist for mirikizumab in IBD. Risankizumab has limited pediatric data from small case series, lacks pediatric IBD approval, and has unknown dosing requirements for children [36]. All three agents require caution in pediatric IBD patients until dedicated studies establish appropriate efficacy, safety profiles, and dosing regimens for this population.

Statement 6b

IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) can safely be used in IBD patients who are pregnant or attempting conception.

Level of agreement: 100%

Quality of evidence: III

Classification of recommendation: C

IL-23 p19 inhibitors safety data in pregnancy remains limited, though emerging evidence suggests potential safety. Guselkumab shows promising safety signals from WHO pharmacovigilance data analyzing 214 pregnancies, with low overall adverse outcomes (ROR 0.09) compared with TNF- α inhibitors,

including reduced risks for abortion/stillbirth, pregnancy complications, and delivery complications [37]. Mirikizumab clinical trials excluded pregnant patients, providing no published safety data on pregnancy use or fetal outcomes. Risankizumab's EMA Summary recommends avoiding pregnancy use, though recent case series noted lower infant drug levels versus maternal levels at birth [38]. Despite limited human data, the Global Consensus Group for pregnancy and IBD states all three IL-23 inhibitors can be continued during pregnancy based on placental transfer mechanics and class safety profile [39]. However, insufficient data exist for definitive recommendations, and caution remains advised pending more comprehensive pregnancy safety studies.

Statement 6c

IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) can safely be used during breastfeeding.

Level of agreement: 100%

Quality of evidence: III

Classification of recommendation: C

No data are available on breastfeeding while being treated with guselkumab, mirikizumab or risankizumab. However, given that they are all monoclonal antibodies, they are considered low risk during breastfeeding based on pharmacokinetics of transfer into breast milk and minimal to no absorption through the infant gut.

Statement 7

IL-23 p19 inhibitors (guselkumab, mirikizumab, and risankizumab) have demonstrated favorable safety profiles, with minimal side effects and no boxed warnings.

Level of agreement: 100%

Quality of evidence: I

Classification of recommendation: A

All three IL-23 p19 inhibitors demonstrate favorable safety profiles in IBD clinical trials. Guselkumab shows similar adverse event rates to placebo in QUASAR and GALAXI studies, with consistent safety through 5-year follow-up in psoriatic disease studies, including comparable rates of discontinuation, serious infections, cancer, and cardiovascular events [2, 3, 40]. Long-term pooled VOYAGE 1 and 2 data demonstrate a consistent guselkumab safety profile with up to 5 years of continuous treatment in psoriasis, without emergent safety signals, supporting favorable long-term tolerability of this IL-23 inhibitor class [41]. Real-world surveillance from Japan and the EARLY study confirm that guselkumab remains effective and generally well tolerated through at least 52 weeks and in patients with infectious comorbidities, prior malignancy, or cardiovascular disease, without new safety concerns [42]. Psoriasis studies in Asian patients show durable clinical response and stable safety

over 5 years and indicate that guselkumab can be used safely in individuals with latent TB receiving appropriate prophylaxis [43, 44]. Mirikizumab exhibited low serious adverse event rates across LUCENT and VIVID trials with minimal treatment discontinuations [14, 15]. Antidrug antibodies decreased from 23.6% in Year 1 to 3.2% in Year 3, with no boxed warnings required. Risankizumab showed comparable adverse event rates to placebo in ADVANCE/MOTIVATE/FORTIFY trials; in fact, serious infections were slightly higher in the placebo groups [16, 17]. In UC trials, serious adverse events were lower with risankizumab (2.3%–5.2%) versus placebo (8.2%–10.2%) [18].

TB is endemic in many parts of Asia and the use of advanced therapies, particularly anti-TNFs, is of particular concern in view of the high risk of reactivation. Therefore, the use of IL-23 p19 inhibitors, which are efficacious but with essentially no increased risk of reactivation of TB, confers a significant advantage in this part of the world [23]. In addition, there were no safety signals with regards to reactivation of chronic hepatitis B.

3.1 | JAK Inhibitors

Statement 8

JAK inhibitors (filgotinib, tofacitinib, and upadacitinib) can be used for induction and maintenance in moderate-to-severe UC patients who are refractory or intolerant to conventional or advanced therapies.

Level of agreement: 100%

Quality of evidence: I

Classification of recommendation: A

JAK inhibitors demonstrate efficacy in moderate-to-severe UC. Filgotinib 200mg achieved higher clinical remission rates versus placebo at Week 10 (26.1% vs. 15.3% in Study A, 11.5% vs. 4.2% in Study B) and Week 58 maintenance (37.2% vs. 11.2%) [45]. Tofacitinib 10mg twice daily showed superior remission rates at 8 weeks versus placebo in OCTAVE trials, with both 5 and 10mg twice daily maintaining superior clinical remission and mucosal healing at 52 weeks [46]. Asian data reported 40%–50.5% clinical remission at 8 weeks and 43.5%–55.1% at 48–52 weeks [47]. Long-term extension data from OCTAVE Open further confirm sustained efficacy and an acceptable safety profile of tofacitinib in East Asian patients with UC, supporting its use beyond the induction–maintenance trial period [48]. Real-world cohort data from Asia further demonstrate that tofacitinib is effective and generally well tolerated in routine practice, with high clinical response and remission rates and no unexpected safety signals in Asian UC populations [49]. Upadacitinib demonstrated significantly higher clinical remission at Week 8 (26% vs. 5% in U-ACHIEVE, 33% vs. 4% in U-ACCOMPLISH) with rapid symptom relief within 1–3 days [50, 51]. Maintenance therapy

achieved clinical remission in 40% (15 mg) and 53.6% (30 mg) versus 10.8% placebo [52].

Statement 9

Upadacitinib can be used as induction and maintenance therapy in moderate-to-severe CD patients who are refractory or intolerant to conventional or advanced therapies.

Level of agreement: 100%

Quality of evidence: I

Classification of recommendation: A

Upadacitinib demonstrated significant efficacy in moderate-to-severe CD across pivotal Phase 3 trials. In U-EXCEL and U-EXCEED induction studies, upadacitinib 45 mg daily achieved superior clinical remission rates versus placebo (in U-EXCEL, 49.5% vs. 29.1%; in U-EXCEED, 38.9% vs. 21.1%) and endoscopic response (in U-EXCEL, 45.5% vs. 13.1%; in U-EXCEED, 34.6% vs. 3.5%) [53]. Rapid symptom relief occurred within 5–6 days, with clinical improvements evident at Week 2 [54]. In U-ENDURE maintenance trial, clinical remission was achieved with 15 mg (37.3%) and 30 mg (47.6%) versus placebo (15.1%), with endoscopic response rates of 27.6% and 40.1% versus 7.3% placebo at 52 weeks [48]. Post hoc analysis confirmed efficacy regardless of prior biologic exposure [55]. Real-world data from the West and from Asia show similar rates of response and remission in both bio-naïve and bio-experienced patients [56–58].

Statement 10

Upadacitinib can be considered in UC patients who are refractory to tofacitinib.

Level of agreement: 100%

Quality of evidence: II-3

Classification of recommendation: B

Real-world studies demonstrate upadacitinib's effectiveness as a second-line JAK inhibitor following tofacitinib exposure in UC. A Japanese multicentre study showed upadacitinib induced clinical responses in 64.6% of tofacitinib-naïve versus 86.4% of tofacitinib-exposed patients at Week 8, with clinical remission rates of 60.4% and 77.3%, respectively [59]. A prospective study reported similar rapid effectiveness, with 77.8% of tofacitinib-experienced patients achieving remission at 8 weeks [60]. An Australian multicentre data including 152 UC patients (28% with prior tofacitinib exposure) showed no significant difference in clinical remission rates by week 16 between tofacitinib-experienced and naïve patients (86% vs. 84%), supporting its use as an effective therapeutic option after tofacitinib failure [61].

Statement 11

There are emerging data on the efficacy of upadacitinib in fistulizing and perianal CD.

Level of agreement: 83%

Quality of evidence: III

Classification of recommendation: C

Upadacitinib shows promising efficacy for perianal fistulizing CD in both clinical trials and real-world settings. Post hoc analysis of Phase 3 trials (U-EXCEL, U-EXCEED, U-ENDURE) demonstrated significantly higher rates of perianal fistula drainage resolution with upadacitinib 45 mg versus placebo during induction (44.7% vs. 5.6%, $p=0.003$) and closure of external openings (22.1% vs. 4.8%, $p=0.013$) [62]. Maintenance therapy with 15 and 30 mg showed numerical improvements in fistula closure versus placebo (18.8% and 16.0% vs. 0%, respectively). Real-world retrospective analysis of 81 perianal Crohn's patients across 10 centers showed 17.3% achieved clinical response (≥ 3 -point PDAI reduction) at 4 months, with 17.7% achieving MRI healing [63]. Network meta-analysis identified upadacitinib 45 mg among the highest-ranked treatments for fistula remission alongside infliximab and adipose-derived stem cells, supporting its role in perianal fistulizing disease management [64].

Statement 12

Upadacitinib can be used in IBD-related axial and peripheral arthropathy.

Level of agreement: 100%

Quality of evidence: I

Classification of recommendation: A

Upadacitinib demonstrates significant efficacy for EIMs in IBD patients, particularly arthropathy. In ankylosing spondylitis, 52% of patients on upadacitinib 15 mg achieved Assessment of SpondyloArthritis international Society 40 (ASAS40) response versus 26% of those on placebo at Week 14 [65]. For non-radiographic axial spondyloarthritis, ASAS40 response was 45% versus 23% placebo [66]. In psoriatic arthritis, ACR20 response rates were 78.5% (30 mg) and 70.6% (15 mg) versus 36.2% placebo at Week 12 [67]. For rheumatoid arthritis, upadacitinib showed superior efficacy over methotrexate (68%–71% vs. 41% ACR20 response) and abatacept in biologic-refractory patients [68]. In UC patients with baseline arthropathy, upadacitinib 30 mg significantly increased resolution rates at Week 52 [69]. A Spanish multicenter study of IBD patients with EIMs showed 64.2% improvement at Weeks 8–12, with 80% improvement in patients treated specifically for active EIMs [70]. At 6 months, 70.7% maintained EIM improvement alongside 62.2% IBD clinical remission.

Statement 13

JAK inhibitors (filgotinib, tofacitinib, upadacitinib) should be used cautiously in patients at risk for major adverse cardiovascular events (MACE), venous thromboembolism (VTE), and a history of malignancy.

Level of agreement: 97%

Quality of evidence: II-2

Classification of recommendation: C

JAK inhibitors carry increased safety risks in high-risk populations, particularly older patients with cardiovascular risk factors. Filgotinib shows low overall incidence of MACE, VTE, and malignancies but demonstrates modest increases in patients ≥ 65 years with pre-existing risk factors [71]. Tofacitinib significantly elevated MACE and malignancy risk in rheumatoid arthritis patients ≥ 50 years with cardiovascular risk factors compared with TNF inhibitors, though UC studies showed lower incidence rates [72–74]. Network meta-analysis reveals JAK inhibitors increase MACE risk (OR 2.64) compared with placebo across immune-mediated diseases [75]. However, IBD-specific data suggests no increased MACE or VTE risk, with decreased all-cause mortality in high-risk patients [76, 77]. Consistent with global trial data, long-term observational cohorts from Korea and Japan report no new safety signals with tofacitinib over several years of use, reinforcing its overall tolerability in real-world East Asian UC populations [78, 79]. Integrated safety analyses across more than 27 000 patient-years in immune-mediated inflammatory diseases indicate that upadacitinib has a predictable and manageable safety profile, with event rates consistent with class expectations when used with appropriate risk stratification [80]. Post hoc analyses of phase 2b/3 UC and CD trials show that the overall benefit-risk profile of upadacitinib remains favorable in appropriately selected patients, with efficacy gains outweighing safety risks in those without major contraindications [81]. Cancer risk remains controversial—IBD studies show no increased malignancy risk, whereas rheumatoid arthritis data demonstrated higher rates versus anti-TNF therapy [63, 82, 83].

FDA mandated boxed warnings for both tofacitinib and upadacitinib regarding MACE, VTE, malignancy, and death [84].

Statement 14

Vaccination with the recombinant herpes zoster vaccine is recommended for patients considering JAK inhibitors (filgotinib, tofacitinib, and upadacitinib).

Level of agreement: 100%

Quality of evidence: II-3

Classification of recommendation: B

JAK inhibitors significantly increase herpes zoster risk and this appears to be even higher in the Asian population [85]. Tofacitinib demonstrates dose-dependent risk of herpes zoster infection in UC patients [46, 85]. Upadacitinib also shows an increased risk of herpes zoster across multiple conditions, though without clear dose-dependence, whereas filgotinib demonstrates a lower but present risk [45, 86, 87]. The recombinant zoster vaccine (RZV, Shingrix®) is recommended before initiating JAK inhibitor therapy, particularly for patients ≥ 50 years, without requiring varicella zoster virus antibody testing [88]. The vaccine can be administered during ongoing treatment, though pre-treatment vaccination is preferred. In rheumatoid arthritis patients on upadacitinib plus methotrexate, RZV achieved humoral responses in 64.4% at Week 4 and 71.4% at Week 60, with comparable rates across age groups and corticosteroid use [89]. IBD-specific studies demonstrate RZV effectiveness: TriNetX database showed significantly lower herpes zoster risk in vaccinated versus unvaccinated IBD patients (aOR 0.44) [90]. Veterans Affairs data revealed reduced crude incidence rates across age groups (0.00 vs. 3.93 per 1000 person-years in 50–60 years; 1.80 vs. 4.57 in > 60 years) [91]. However, vaccinated IBD patients remain 3-times more likely to develop herpes zoster despite vaccination [92].

Statement 15

There are emerging data on the role of JAK inhibitors (filgotinib, tofacitinib, and upadacitinib) in pediatric IBD patients.

Level of agreement: 100%

Quality of evidence: III

Classification of recommendation: C

JAK inhibitor evidence in pediatric IBD remains limited but shows promising results for upadacitinib. Filgotinib has an ongoing clinical trial evaluating patients aged 8–18 with moderate-to-severe UC [93]. Tofacitinib evidence is limited in pediatric UC, with most trials conducted in adults and only preliminary pediatric data available, preventing definitive recommendations [94, 95]. Upadacitinib demonstrated the strongest pediatric evidence: a multicenter retrospective study of 100 children with UC/IBD-U showed clinical response in 84%, clinical remission in 62%, and corticosteroid-free remission in 56% at 8 weeks [96]. A multicentre cohort of pediatric CD results showed 75% clinical response, 56% clinical remission, and 52% corticosteroid- and exclusive enteral nutrition-free remission at Week 8 [97]. Similarly, an Asian cohort of pediatric CD patients achieved clinical remission with upadacitinib [57].

These findings suggest upadacitinib as an effective induction therapy for refractory pediatric IBD, though larger prospective studies are needed to establish definitive safety and efficacy profiles across all JAK inhibitors in pediatric populations.

Statement 16

JAK inhibitors (filgotinib, tofacitinib, and upadacitinib) should be avoided in IBD patients who are considering pregnancy and breastfeeding.

Level of agreement: 97%

Quality of evidence: II-C

Classification of recommendation: C

JAK inhibitor safety in pregnancy remains poorly characterized with limited human data. Animal studies show tofacitinib can cause teratogenicity at high doses, and its small molecular size enables placental transfer [98, 99]. Current guidelines recommend avoiding JAK inhibitors during pregnancy: ECCO advises against use in pregnant CD patients, whereas the Global Consensus Consortium and the AGA Pregnancy Study Group recommends discontinuing JAK inhibitor 4 weeks before conception and avoiding use during pregnancy/lactation [39, 100, 101]. However, emerging real-world data provides reassurance: a systematic review of 256 JAK inhibitor exposed pregnancies found spontaneous abortion and malformation rates similar to the general population [102]. Tofacitinib clinical program data from 40 pregnancies reported no fetal deaths or malformations [103]. A case series of six tofacitinib-exposed UC pregnancies showed no negative outcomes, though tofacitinib demonstrated 74% placental transfer and breast milk detection [101]. Emerging pregnancy data for upadacitinib from clinical trials and postmarketing reports have not identified a clear teratogenic signal, but numbers remain small, so current recommendations still advise avoiding JAK inhibitors during conception and pregnancy [104].

Statement 17

Tofacitinib and upadacitinib may be considered for patients with acute severe UC (ASUC).

Level of agreement: 88%

Quality of evidence: II-2

Classification of recommendation: B

JAK inhibitors show promising efficacy in ASUC, offering rapid symptom improvement within 3–7 days [105]. Tofacitinib demonstrates strong evidence: the TACOS trial showed significantly higher response rates with tofacitinib plus IV steroids versus steroids alone (83% vs. 58.2%, $p=0.007$) and reduced need for rescue therapy or colectomy at 90 days (13% vs. 38%, $p=0.003$) [106]. Multiple studies report 90-day colectomy-free survival rates of 79.9%–86% and response rates ranging 43%–100% (weighted mean 82%) [107, 108]. Its favorable pharmacokinetics with reduced albumin dependence make it

suitable for ASUC patients with hypoalbuminemia [109]. In addition, a Japanese cost-effectiveness analysis suggests that tofacitinib is a cost-effective option compared with several biologics for biologic-naïve patients with moderate-to-severe UC, supporting its consideration as an early advanced therapy [110]. Upadacitinib data, though limited, shows similar promise with systematic review reporting 25.99% colectomy rates, 81.55% initial clinical response, and 63.09% corticosteroid-free remission [111]. A Phase 3 Canadian trial (NCT06660693) is ongoing to compare upadacitinib-first versus infliximab strategies [112]. Both agents represent valuable options for ASUC, particularly in biologic-experienced patients.

3.2 | S1P Modulators

Statement 18

S1P modulators (etrasimod and ozanimod) can be used for both induction and maintenance therapy in adults with moderate to severe UC, who have had inadequate response, loss of response, or are intolerant to conventional or advanced therapies.

Level of agreement: 100%

Quality of evidence: I

Classification of recommendation: A

S1P modulators demonstrate significant efficacy in moderate-to-severe UC. Etrasimod showed superior clinical remission rates versus placebo in both ELEVATE trials during induction (27% vs. 7% in ELEVATE UC 52, 25% vs. 15% in ELEVATE UC 12 at Week 12) and maintenance (32% vs. 7% at Week 52) [113]. In addition, an East Asian Phase 3 trial (ENLIGHT UC) demonstrated that etrasimod is superior to placebo for induction and maintenance of clinical and endoscopic remission in patients with moderately to severely active UC [114]. Ozanimod achieved higher clinical remission rates compared with placebo in the True North trial during induction (18.4% vs. 6.0% at Week 10) and maintenance (37.0% vs. 18.5% at Week 52) [115]. Post hoc analysis of advanced therapy-naïve patients revealed numerically greater and earlier symptomatic responses with ozanimod, including 39% achieving symptomatic response by Week 2 [116]. Long-term data showed sustained efficacy with 91% of patients maintaining clinical response through week 94 in open-label extension [117]. A Japanese phase 2/3 study (J-True North) showed that oral ozanimod is superior to placebo for induction and maintenance of clinical and endoscopic remission with a good safety profile [118].

Statement 19

S1P modulators (etrasimod and ozanimod) should be avoided in patients who are considering pregnancy and breastfeeding.

Level of agreement: 100%

Quality of evidence: II-3

Classification of recommendation: C

Etrasimod is contraindicated during pregnancy and breastfeeding based on animal studies showing fetal harm and detection in offspring plasma via milk excretion [39, 119]. Women of childbearing potential need effective contraception during treatment and for 7 days after stopping etrasimod due to the drug's washout period [120]. The Global Consensus Group recommends discontinuing etrasimod 1–2 weeks before conception unless no effective alternatives exist [37, 39]. For ozanimod, AGA guidelines recommend stopping 6 months before conception, whereas the Global Consensus Group suggests stopping 3 months pre-conception [39, 121]. Despite restrictive guidelines, clinical data shows no increased fetal abnormalities or adverse pregnancy outcomes with ozanimod exposure during early pregnancy [122]. Both agents are highly protein-bound, potentially limiting breast milk transfer, but breastfeeding remains contraindicated due to unknown infant toxicity risks [39, 123]. Expert consensus advises against breastfeeding during S1P modulator therapy [39].

Statement 20

There are limited data for the use of S1P modulators (etrasimod and ozanimod) in IBD-related extraintestinal manifestations (EIMs).

Level of agreement: 100%

Quality of evidence: III

Classification of recommendation: C

Etrasimod lacks any published information on EIM efficacy, with no relevant data identified in medical literature searches through April 2025. A trial evaluating etrasimod for active skin EIMs in IBD patients (NCT03139032) was terminated, leaving no clinical evidence for EIM treatment [120]. Ozanimod has minimal evidence consisting of only one case series in abstract form reporting EIM outcomes [124]. In this small study, 78% (7/9) of patients with baseline EIMs experienced resolution of arthralgia and aphthous ulcers during ozanimod treatment. Overall, insufficient data exists to recommend either S1P modulator for EIM treatment. Clinicians should consider alternative therapies with established EIM efficacy when EIMs are a primary treatment concern in IBD patients.

Statement 21

S1P modulators (etrasimod and ozanimod) have a low risk of serious infections, including herpes zoster and tuberculosis reactivation.

Level of agreement: 100%

Quality of evidence: I

Classification of recommendation: B

S1P modulators demonstrate favorable infection safety profiles in UC trials. Etrasimod showed comparable infection rates to placebo in ELEVATE trials: overall infections (24.9% vs. 22.2% in UC 52, 11.3% vs. 12.1% in UC 12) and serious infections (1.0% vs. 3.5% in UC 52, none in either group in UC 12) [125]. Urinary tract infections were most common. Herpes zoster occurred in 0.7% of etrasimod patients versus none with placebo in UC 52, whereas UC 12 showed reverse pattern (none vs. 1.7%). Pooled analysis revealed one mild CMV infection in etrasimod group detected by stool testing, one TB case in placebo group, and three treatment discontinuations due to infections [126]. Ozanimod showed similar infection incidence as placebo during induction but higher rates during maintenance, with serious infections <2% in each group [115]. Herpes zoster occurred in 0.4% during induction and 2.2% during maintenance. Neither agent showed concerning infection signals, though routine monitoring remains appropriate.

Statement 22

S1P modulators (etrasimod and ozanimod) have not been strongly associated with progressive multifocal leukoencephalopathy in IBD patients, but long-term data are required.

Level of agreement: 100%

Quality of evidence: III

Classification of recommendation: C

S1P modulators carry a risk of progressive multifocal leukoencephalopathy (PML), though reported cases remain limited. Etrasimod has no reported PML cases in its clinical development program, but the prescribing information warns of PML risk based on experience with other S1P modulators in multiple sclerosis patients [119]. Risk factors include immunocompromised status and concurrent immunosuppressive therapy.

Ozanimod has one documented PML case in multiple sclerosis [127, 128]. Similar risk factors apply, particularly polytherapy with immunosuppressants and severe immunocompromise.

Physicians must remain vigilant for unexplained neurologic symptoms or findings suggestive of PML, requiring immediate treatment suspension pending diagnostic evaluation and permanent discontinuation if PML is confirmed. Both agents require careful patient selection, avoiding use in severely immunocompromised patients when possible, and maintaining high clinical suspicion for PML development. Regular neurologic monitoring and patient education about PML symptoms are essential safety measures for S1P modulator therapy in IBD patients.

Statement 23

Patients considered for S1P modulators (etrasimod and ozanimod) should undergo a cardiac evaluation to exclude significant cardiovascular disease, brady-arrhythmias and/or heart block.

Level of agreement: 94%

Quality of evidence: I

Classification of recommendation: C

S1P modulators require comprehensive cardiac evaluation and monitoring due to their effects on heart rate and conduction. Patients with significant QT prolongation, arrhythmias requiring antiarrhythmic drugs, unstable cardiac conditions, resting heart rate <50 bpm, or symptomatic bradycardia history should have a cardiology consultation prior to treatment with etrasimod [119]. Pre-treatment ECG is mandatory, and first-dose monitoring includes 4-h pulse, blood pressure, and ECG assessments for high-risk patients with bradycardia, second-degree AV block, or cardiac disease history. Caution is required with concurrent beta-blockers or calcium channel blockers due to additive cardiac effects.

Ozanimod has more extensive cardiac contraindications, including myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure, or NYHA Class III/IV heart failure within 6 months [128]. It is contraindicated in Mobitz type II second-degree or third-degree AV block, sick sinus syndrome, or sinoatrial block without functioning pacemaker. Cardiologist consultation is recommended for patients on Class Ia/III antiarrhythmics, QTc-prolonging drugs, or other cardiac medications with potential additive effects.

Statement 24

Withdrawal of 5-ASA can be considered in UC patients in remission on small molecules or IL-23 p19 inhibitors.

Level of agreement: 83%

Quality of evidence: III

Classification of recommendation: C

The role of 5-aminosalicylic acid (5-ASA) in combination with advanced IBD therapies remains controversial. For colorectal cancer chemoprevention, adding 5-ASA to regimens already achieving mucosal healing through biologics or small molecules appears questionable, as persistent intestinal inflammation is the key CRC risk factor. Seven consecutive meta-analyses have yielded conflicting results regarding 5-ASA chemoprevention effectiveness, explaining why not all IBD guidelines support this usage [129].

A Japanese retrospective study of 1213 UC patients found concomitant 5-ASA reduced relapse risk in patients on tofacitinib 5 mg twice daily, suggesting benefit at lower JAK inhibitor doses [130]. However, no benefit was observed with tofacitinib 10 mg twice daily plus 5-ASA. Conversely, a Chinese study of 156 UC patients found no differences in clinical or endoscopic relapse rates between JAK inhibitors alone versus combination with 5-ASA, highlighting the inconsistent evidence for combination therapy benefits [131]. There is no data to date on the efficacy of combination therapy of 5-ASAs and IL-23 p19 inhibitors.

Statement 25

Immunomodulators should not be used in combination with JAK inhibitors and S1P modulators.

Level of agreement: 96%

Quality of evidence: III

Classification of recommendation: C

Advanced IBD therapies show varying approaches to immunomodulator combination. Etrasimod requires thiopurine discontinuation at least 2 weeks before treatment initiation in regulatory studies, indicating these agents should not be used concomitantly [113]. Filgotinib represents a unique exception among JAK inhibitors, being the only one allowing concomitant immunomodulator use in clinical trials [132]. Post hoc analysis of the SELECTION study found no evidence of additional therapeutic benefit or increased adverse events when combining filgotinib with thiopurines. Despite the safety profile suggesting no enhanced risk, the lack of demonstrated efficacy benefit means routine combination therapy is not supported by current evidence.

This pattern reflects broader uncertainty about immunomodulator combinations with advanced therapies. Although some agents explicitly prohibit combination use due to safety concerns or study design requirements, filgotinib data suggests combination may be safe but offers no clear advantage. Clinicians should consider individual patient factors when determining whether to continue or discontinue immunomodulators when initiating advanced therapies.

Statement 26

There is no evidence of additional benefit or increased harm when combining IL-23 p19 inhibitors with immunomodulators (in IBD patients).

Level of agreement: 91%

Quality of evidence: III

Classification of recommendation: C

IL-23 inhibitors demonstrate negligible neutralizing antibody formation rates, eliminating the primary rationale used for anti-TNF combination therapy where immunomodulators reduce immunogenicity [133]. Further research focusing on specific patient subgroups might identify potential benefits, but present evidence does not support routine combination use of IL-23 inhibitors with immunomodulators in IBD management.

Statement 27

Concurrent use of two or more advanced treatments (i.e., biologic therapies and/or small molecules) may be considered for selected patients with:

- a. refractory IBD
- b. active extraintestinal manifestations (EIMs) or
- c. other immune-mediated inflammatory diseases (IMIDs)

Level of agreement: 96%

Quality of evidence: III

Classification of recommendation: C

Advanced combination therapy (ACT) shows promising efficacy in medically refractory IBD patients. Real-world studies demonstrate significant clinical improvements: Yang et al. found 50% of dual therapy patients achieved clinical and endoscopic improvements, with 41% clinical remission and 43% endoscopic improvement in high-risk CD patients who had failed a median of 4 biologics [134]. Multiple retrospective studies report clinical remission rates of 50%–60% and endoscopic improvement in 34%–54% of patients with refractory disease [135–138].

Common effective combinations include vedolizumab plus ustekinumab, tofacitinib with biologics, and anti-TNF agents with vedolizumab or ustekinumab. The COMBIO study of 143 patients showed 77% mild–moderate improvement [139].

Controlled trials provide mixed results: The infliximab–natalizumab study showed no significant efficacy difference, whereas the VEGA trial demonstrated superior clinical response, remission, and endoscopic improvement with guselkumab plus golimumab (versus monotherapy) [140, 141]. The EXPLORER study showed triple combination therapy (vedolizumab, adalimumab, methotrexate) effectively induced remission in biologic-naïve early CD patients [142]. Safety profiles remain acceptable across studies, supporting further investigation of combination strategies.

Nevertheless, in view of the limited evidence and lack of long-term safety data, ACT should be used selectively in carefully chosen patients and is best considered an emerging, investigational strategy rather than a routine standard of care.

4 | Conclusion

As therapeutic options expand, these consensus statements provide a comprehensive, evidence-based framework to inform clinical practice and guideline development in the Asia-Pacific region. Ongoing surveillance, real-world studies, and future clinical trials will be essential to refine these recommendations and address remaining knowledge gaps pertinent to the Asia-Pacific region, ensuring optimal and equitable care for regional patients with IBD.

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Conflicts of Interest

Dr. Choon Jin Ooi has received honoraria as a speaker for Johnson and Johnson, AbbVie, Takeda Pharmaceuticals, Celltrion, Everest Medicines, Menarini, Ferring, and Falk Pharmaceuticals. He has served as an advisory board member for Johnson and Johnson, Pfizer, Takeda Pharmaceuticals, and Celltrion.

Dr. Rupert Leong is on the advisory boards of AbbVie, Aspen, BMS, Celgene, Celltrion, Chiesi, Ferring, Glutagen, Hospira, Janssen, Lilly, MSD, Novartis, Pfizer, Prometheus Biosciences, Takeda Pharmaceuticals, Roche, and Spyre; research grant recipient: Joanna Tiddy University of Sydney, McCusker Charitable Foundation, Celltrion, Shire, Janssen, Takeda Pharmaceuticals, Gastroenterological Society of Australia, NHMRC, Gutsy Group, and Pfizer.

Dr. Siew-Chen Ng has served as an advisory board member for Pfizer, Ferring, Janssen, and Abbvie and received honoraria as a speaker for Ferring, Tillotts, Menarini, Janssen, Abbvie, and Takeda Pharmaceuticals. She has received research grants through her affiliated institutions from Olympus, Ferring, and Abbvie; is a founder member, non-executive Board director and non-executive scientific advisor of MicroSigX Biotech Diagnostic Limited and its holding company which is non-remunerative; is a shareholder of MicroSigX Diagnostic Holdings Limited; and receives patent royalties through her affiliated institutions.

Dr. Wai-Keung Leung has served as an advisory board member for Johnson and Johnson and Takeda Pharmaceuticals. He has received honoraria as a speaker for Abbvie, Ferring, Johnson and Johnson, and Takeda Pharmaceuticals. He has received a research grant from Takeda Pharmaceuticals.

Dr. Jose Sollano is a Member of Speaker Bureau for AstraZeneca, Takeda Pharmaceuticals, A Menarini, Johnson and Johnson, Ferring, and Eisai.

Dr. Ida Hilmi has received consulting and speaking honoraria from AbbVie, Johnson and Johnson, Ferring, DCH Auriga, Pfizer, and Takeda, and has served on advisory boards for AbbVie, Johnson and Johnson, Ferring, DCH Auriga, Pfizer, and Takeda.

Dr. Nazri Mustaffa has received speaking honoraria from AbbVie, AstraZeneca, EP Plus, Johnson and Johnson, Ferring, and Takeda; and has served on advisory boards for AbbVie, Johnson and Johnson, Ferring, DCH Auriga, Pfizer, and Takeda.

Dr. Khoon Lin Ling has received consulting and speaking honoraria from Abbvie, Johnson and Johnson, Ferring, and Takeda Pharmaceuticals.

Dr. Byong Duk Ye has consulted and/or served on advisory boards for AbbVie Korea, BMS Pharmaceutical Korea, Celltrion, Chong Kun Dang Pharm, CJ Red BIO, Curacle, Daewoong Pharmaceutical, Dong-A ST, Ferring Korea, Hanmi, Im Scout, IQVIA, Johnson & Johnson, Johnson & Johnson Korea, Jeil Pharmaceutical, Kangstem Biotech, Korea Otsuka Pharm, Korea United Pharm, Lilly Korea, Medtronic Korea, NanoEntek, ORGANOIDSCIENCES, Pfizer Korea, Samsung Bioepis, Takeda Pharmaceuticals, Takeda Korea, and Yuhan; has received speaking fees from AbbVie Korea, BMS Pharmaceutical Korea, Celltrion, Cornerstones Health, Curacle, Daewoong Pharmaceutical, Eisai Korea, Ferring Korea, IQVIA, Johnson & Johnson Korea, Pfizer

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Data Availability Statement

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

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Appendix 1

Pivotal Phase 3 Trials

A. IL-23 p19 Inhibitors

Trial	Disease	Induction regimen	Maintenance regimen	Primary endpoint	Primary results	Publication
QUASAR (Induction)	UC	Guselkumab 200 mg IV Weeks 0, 4, 8 vs. placebo	—	Clinical remission at Week 12	23% (guselkumab) vs. 8% (placebo)	Lancet 2025 (13)
QUASAR (Maintenance)	UC	—	200mg SC q4w OR 100 mg SC q8w vs. placebo (withdrawal)	Clinical remission at Week 44	50% (200 mg); 45% (100 mg); 19% (placebo)	Lancet 2025 (13)
ASTRO (Treat-through)	UC	Guselkumab 400 mg SC Weeks 0, 4, 8 vs. placebo	200mg SC q4w OR 100 mg SC q8w vs. placebo (treat-through)	Clinical remission at Week 12	28% (guselkumab) vs. 6% (placebo)	Lancet Gastroenterol Hepatol 2026 (20)
GALAXI-2,3 (Treat-through)	CD	Guselkumab 200 mg IV Weeks 0, 4, 8 vs. placebo	200mg SC q4w OR 100 mg SC q8w vs. Ustekinumab Vs placebo (treat-through)	Clinical remission composite endpoint (Week 12 clinical response and week 48 clinical remission) Endoscopic response composite endpoint (Week 12 clinical response and week 48 endoscopic response)	GALAXI-2 48.8% (guselkumab) vs. 9.2% (placebo) GALAXI-3 45.1% (guselkumab) vs. 12.5% (placebo) GALAXI-2 29.7% (guselkumab) vs. 3% (placebo) GALAXI-3 23.2% (guselkumab) vs. 6% (placebo)	Lancet 2025 (12)
GRAVITI (Treat-through)	CD	Guselkumab 400 mg SC Weeks 0, 4, 8 vs. placebo	200mg SC q4w OR 100 mg SC q8w vs. placebo (treat-through)	Clinical remission at Week 12 Endoscopic response at Week 12	56% (guselkumab) vs. 21% (placebo) 41% (guselkumab) Vs 21% (placebo)	Gastroenterology 2025 (19)
LUCENT-1 (Induction)	UC	Mirikizumab 300 mg IV Weeks 0, 4, 8 vs. placebo	—	Clinical remission at Week 12	24.2% (mirikizumab) vs. 13.3% (placebo)	NEJM 2023 (14)
LUCENT-2 (Maintenance)	UC	—	Mirikizumab 200 mg SC q4w vs. placebo	Clinical remission at Week 40	49.9% (mirikizumab) vs. 25.1% (placebo)	NEJM 2023 (14)
VIVID-1 (Treat-through)	CD	Mirikizumab 900 mg iv Weeks 0, 4, 8 vs. ustekinumab ≈6 mg/kg vs. placebo	Mirikizumab 300 mg SC q4w vs. ustekinumab 90 mg sc q8w vs. placebo (treat through)	Week 52 Endoscopic response composite endpoint (Week 12 clinical response by PRO and week 52 endoscopic response) Week 52 Clinical remission composite endpoint (Week 12 clinical response by PRO and week 52 clinical remission by CDAI)	38% (mirikizumab) vs. 9% (placebo) 54.1% (mirikizumab) vs. 19.6% (placebo)	Lancet 2024 (15)

Trial	Disease	Induction regimen	Maintenance regimen	Primary endpoint	Primary results	Publication
ADVANCE (Induction)	CD	Risankizumab 600 mg or 1200 mg IV Weeks 0, 4, 8 vs. placebo	—	Clinical remission (non US protocol) at Week 12 Endoscopic response at week 12	43% (600 mg); 41% (1200 mg); vs. 22% (placebo) 40% (600 mg); 32% (1200 mg) vs. 12% (placebo)	Lancet 2022 (16)
MOTIVATE (Induction)	CD	Risankizumab 600 mg or 1200 mg IV Weeks 0, 4, 8 vs. placebo	—	Clinical remission (non US protocol) at Week 12 Endoscopic response at week 12	35% (600 mg); 40% (1200 mg) vs. 19% (placebo) 29% (600 mg); 34% (1200 mg) vs. 11% (placebo)	Lancet 2022 (16)
FORTIFY (Maintenance)	CD	—	180mg OR 360 mg SC q8w vs. placebo (withdrawal)	Clinical remission (non US protocol) at Week 52 Endoscopic response at week 52	46% (180 mg); 52% (360 mg) vs. 40% (placebo) 47% (180 mg) 47% (360 mg) vs. 22% (placebo)	Lancet 2022 (17)
INSPIRE (Induction)	UC	Risankizumab 1200 mg IV Weeks 0, 4, 8 vs. placebo	—	Clinical remission at Week 12	20.3% (risankizumab) vs. 6.2% (placebo)	JAMA 2024 (18)
COMMAND (Maintenance)	UC	—	Risankizumab 180mg OR 360 mg SC q8w vs. placebo (withdrawal)	Clinical remission at Week 52	40.2% (180 mg); 37.6% (360 mg) vs. 25.1% (placebo)	JAMA 2024 (18)
SEQUENCE (Head-to-head)	CD	Risankizumab 600 mg IV Weeks 0, 4, 8 vs. ustekinumab ~6 mg/kg IV	Risankizumab 360mg SC q8w vs. ustekinumab 90mg SC q8w	Clinical remission at Week 24 Endoscopic remission at week 48	58.6% (risankizumab) vs. 39.5% (ustekinumab) 31.8% (risankizumab) vs. 16.2% (ustekinumab)	NEJM 2024 (27)

B. JAK Inhibitors

Trial	Disease	Induction regimen	Maintenance regimen	Primary endpoint	Primary results	Publication
SELECTION (Induction)	UC	Filgotinib 200mg PO daily OR 100 mg PO daily vs. placebo	—	Clinical remission at Week 10	18.5% (filgotinib 200 mg); 14.2% (filgotinib 100 mg) vs. 9.7% (placebo)	Lancet 2021 (45)
SELECTION (Maintenance)	UC	—	Filgotinib 200 mg PO daily vs. placebo OR 100 mg PO daily vs. placebo	Clinical remission at Week 58	23.8% (filgotinib 100 mg) vs. 13.5% (placebo) 37.2% (filgotinib 200 mg) vs. 11.2% (placebo)	Lancet 2021 (45)
OCTAVE Induction 1 and 2 (Induction)	UC	Tofacitinib 10 mg PO BID vs. placebo	—	Clinical remission at Week 8	18.5% and 16.6% (tofacitinib) vs. 8.2% and 3.6% (placebo)	NEJM 2017 (46)
OCTAVE Sustain (Maintenance)	UC	—	Tofacitinib 5 mg OR 10 mg PO BID vs. placebo	Clinical remission at Week 52	34% (5 mg); 41% (10 mg) vs. 11% (placebo)	NEJM 2017 (46)
U-ACHIEVE (Induction)	UC	Upadacitinib 45 mg PO daily vs. placebo	—	Clinical remission at Week 8	26% (upadacitinib) vs. 5% (placebo)	Lancet 2022 (50)

Trial	Disease	Induction regimen	Maintenance regimen	Primary endpoint	Primary results	Publication
U-ACCOMPLISH (Induction)	UC	Upadacitinib 45 mg PO daily vs. placebo	—	Clinical remission at Week 8	34% (upadacitinib) vs. 4% (placebo)	Lancet 2022 (51)
U-ACHIEVE (Maintenance)	UC	—	Upadacitinib 15 mg OR 30 mg PO daily vs. placebo	Clinical remission at Week 52	40.4% (15 mg); 53.6% (30 mg) vs. 10.8% (placebo)	Lancet Gastroenterol Hepatol 2023 (52)
U-EXCEL (Induction)	CD	Upadacitinib 45 mg PO daily vs. placebo	—	Clinical remission at Week 12 Endoscopic response at week 12	49.5% (upadacitinib) vs. 29.1% (placebo) 45.5% (upadacitinib) vs. 13.1% (placebo)	NEJM 2023 (53)
U-EXCEED (Induction)	CD	Upadacitinib 45 mg PO daily vs. placebo	—	Clinical remission at Week 12 Endoscopic response at week 12	38.9% (upadacitinib) vs. 21.1% (placebo) 34.6% (upadacitinib) vs. 3.5% (placebo)	NEJM 2023 (53)
U-ENDURE (Maintenance)	CD	—	Upadacitinib 15 mg OR 30 mg PO daily vs. placebo	Clinical remission at Week 52 Endoscopic response at week 52	37.3% (15 mg); 47.6% (30 mg) vs. 15.1% (placebo) 27.6% (15 mg); 40.1% (30 mg) vs. 7.3% (placebo)	NEJM 2023 (53)

C. S1P Modulators						
Trial	Disease	Induction regimen	Maintenance regimen	Primary endpoint	Primary results	Publication
True North (Induction)	UC	Ozanimod 0.92 mg PO daily vs. placebo	—	Clinical remission at Week 10	18.4% (ozanimod) vs. 6.0% (placebo)	NEJM 2021 (115)
True North (Maintenance)	UC	—	Ozanimod 0.92 mg PO daily vs. placebo	Clinical remission at Week 52	37% (ozanimod) vs. 18.5% (placebo)	NEJM 2021 (115)
J True North (Treat-through)	UC	Ozanimod 0.92 mg PO or ozanimod 0.46 mg daily vs. placebo	Ozanimod 0.92 mg PO or ozanimod 0.46 mg daily vs. placebo	Clinical response at week 12	52.9% (ozanimod 0.46 mg), 61.5% (ozanimod 0.92 mg) vs. 32.3% (placebo)	Gastro Hep Adv 2026 (118)
ELEVATE UC 12 (Induction)	UC	Etrasimod 2 mg PO daily vs. placebo	—	Clinical remission at Week 12	25% (etrasimod) vs. 15% (placebo)	Lancet 2023 (113)
ELEVATE UC 52 (Treat through)	UC	Etrasimod 2 mg PO daily vs. placebo	Etrasimod 2 mg PO daily vs. placebo	Clinical remission at Week 52	32% (etrasimod) vs. 7% (placebo)	Lancet 2023 (113)
ENLIGHT UC (Induction)	UC	Etrasimod 2 mg PO daily vs. placebo	—	Clinical remission at Week 12	25% (etrasimod) vs. 6% (placebo)	Lancet Gastroenterol Hepatol 2025 (114)
ENLIGHT UC (Maintenance)	UC	—	Etrasimod 2 mg PO daily vs. placebo	Clinical remission at Week 52	48.1% (etrasimod) vs. 12.5% (placebo)	Lancet Gastroenterol Hepatol 2025 (114)