Table 1. Executive summary of recommendations for the management of adult outpatients with moderate-to-severe Crohn's disease

USE AND POSITIONING OF ADVANCED THERAPIES
1. In adult outpatients with moderate-to-severely active Crohn's disease, the AGA *recommends* the use of infliximab, adalimumab, ustekinumab, risankizumab, guselkumab, mirikizumab or upadacitinib*, over no treatment [*Strong recommendation, moderate to high certainty of evidence*] **2. In adult outpatients with moderate-to-severely active Crohn's disease, the AGA *suggests* the use of certolizumab pegol or vedolizumab, over no treatment** [*Conditional recommendation, moderate certainty of evidence*] ***Implementation considerations:*** • ***Biosimilars** of **infliximab, adalimumab, and ustekinumab** can be considered equivalent to their originator drug in their efficacy in terms of therapy selection.* • ***Subcutaneous formulations of infliximab and vedolizumab** have shown comparable efficacy to the respective intravenous maintenance doses.* • *In some patients, particularly those with more severe disease, **extended induction regimens or dose escalation** may be beneficial for certain agents.* • *There are **two dosing options available for maintenance therapy** for risankizumab, guselkumab and upadacitinib. Higher maintenance doses may be preferred in patients with high burden of inflammation and/or more severe disease, and those who have previously failed TNF antagonists.* * FDA recommendations in the United States recommends reserving use of JAK inhibitors in patients with failure or intolerance to TNF antagonist therapy
3. **In adult outpatients with moderate-to-severely active Crohn's disease who are <u>naïve</u> to advanced therapies, the AGA suggests using a HIGHER efficacy medication (infliximab, adalimumab, vedolizumab, ustekinumab, risankizumab, mirikizumab, guselkumab), rather than a LOWER efficacy medication (certolizumab pegol, upadacitinib). [***Conditional recommendation, low to high certainty of evidence***]** ***Implementation considerations:*** • *Individual patient factors (e.g., age, comorbidities, frailty, pregnancy, adherence) and preferences (e.g., route of administration, ease of access) should be incorporated within a shared decision framework in selection of advanced therapies.* • *There are limited data on the safety of JAK inhibitors in pregnancy. These drugs should generally be avoided in women contemplating pregnancy in the near future.*

4. **In adult outpatients with moderate-to-severely active Crohn's disease who have previously been exposed to one or more advanced therapies, particularly TNF antagonists, the AGA suggests using a HIGHER efficacy medication (adalimumab, risankizumab, guselkumab, upadacitinib) OR an INTERMEDIATE efficacy medication (ustekinumab, mirikizumab), rather than a LOWER efficacy medication (vedolizumab, certolizumab pegol).** *[Conditional recommendation, low to moderate certainty of evidence]*

Implementation considerations:

- *Second-line TNF antagonists (especially infliximab or adalimumab) are effective in patients who discontinued their first TNF antagonist either due to secondary loss of response due to immunogenicity or intolerance. They may not be effective in patients with primary non-response to TNF antagonists, and alternative mechanisms of action should be considered.*
- *Individual patient factors (e.g., age, comorbidities, frailty, pregnancy, adherence) and preferences (e.g., route of administration, ease of access) should be incorporated within a shared decision framework in selection of advanced therapies.*
- *Some patients, such as those with multiple prior biologic failures, may require longer duration of treatment for response.*
- *JAK inhibitors may be associated with higher risk of major adverse cardiovascular events and cancer than TNF antagonists in older adults with cardiovascular risk factors (smoking, prior cardiovascular disease).*
- *There is limited data on the safety of JAK inhibitors in pregnancy. These drugs should be avoided in women of childbearing age contemplating pregnancy.*

USE OF IMMUNOMODULATORS

5. **In adult outpatients with moderate-to-severely active Crohn's disease, the AGA suggests AGAINST using thiopurines monotherapy over no treatment for inducing remission. [***Conditional recommendation, very low certainty evidence***]**

6. **In adult outpatients with moderate-to-severely active Crohn's disease who have achieved remission, the AGA SUGGESTS using thiopurine monotherapy over no treatment for maintaining remission. [***Conditional recommendation, low certainty evidence***]**

7. **In adult outpatients with moderate-to-severely active Crohn's disease, the AGA SUGGESTS using subcutaneous or intramuscular methotrexate monotherapy over no treatment. [***Conditional recommendation, moderate certainty evidence***]**

8. **In adult outpatients with moderate-to-severely active Crohn's disease, the AGA suggests AGAINST using oral methotrexate monotherapy over no treatment. [***Conditional recommendation, very low certainty evidence***]**

Implementation considerations:

- *The typical dose of thiopurines is 2-2.5mg/kg/day for azathioprine and 1-1.5mg/kg/day for mercaptopurine when used as monotherapy for those with normal drug metabolism.*
- *In clinical trials of thiopurines for preventing relapse in patients who achieved remission, remission was typically induced with corticosteroids.*
- *The typical dose of methotrexate is 25mg weekly during induction for 16-24 weeks, and 15mg weekly for maintenance. Methotrexate should be accompanied by daily folic acid supplementation.*
- *Routine monitoring of complete blood counts and liver function tests is recommended when using thiopurines and methotrexate.*

COMBINATION THERAPY OF BIOLOGICS AND IMMUNOMODULATORS

9. **In adult outpatients with moderate-to-severely active Crohn's disease who are naïve to thiopurines and starting infliximab, the AGA SUGGESTS using infliximab in combination with thiopurines rather than infliximab monotherapy *[****Conditional recommendation, low certainty of evidence****].***

10. **In adult outpatients with moderate-to-severely active Crohn's disease, the AGA makes NO RECOMMENDATION on using infliximab in combination with methotrexate over infliximab monotherapy [***No recommendation, knowledge gap***].**

11. **In adult outpatients with moderate-to-severely active Crohn's disease, the AGA makes NO RECOMMENDATION on using adalimumab in combination with thiopurines or methotrexate over adalimumab monotherapy [**No recommendation, knowledge gap**].**

12. **In adult outpatients with moderate-to-severely active Crohn's disease, the AGA makes NO RECOMMENDATION in favor of, or against, using non-TNF-targeting biologics (vedolizumab, ustekinumab, risankizumab, mirikizumab,**

guselkumab) in combination with thiopurines or methotrexate or corresponding biologic monotherapy [No recommendation, knowledge gap**]**

Implementation Considerations:

- *The benefit of routinely combining immunomodulators with TNF antagonists in patients who have previously failed immunomodulator monotherapy is uncertain.*
- *There may be benefits of adding immunomodulators when starting TNF antagonists in specific situations where patients may be at a higher risk for immunogenicity. These include patients with prior history of immunogenicity with a TNF antagonist, patients being re-exposed to TNF antagonists after a drug holiday, patients carrying HLA-DQ-A1*05 variants and patients with high drug clearance such as those with more severe disease, high burden of inflammation, low albumin, etc.*

DE-ESCALATION OF THERAPY

13. In adult outpatients with moderate-to-severely active Crohn's disease who are in corticosteroid-free clinical remission for at least 6 months on combination therapy of TNF antagonists and an immunomodulator, the AGA SUGGESTS WITHDRAWING IMMUNOMODULATORS. [Conditional recommendation, low certainty of evidence]

Comment: *Patients, particularly those with difficult-to-treat disease, who place a lower value on the trivial-to-small increase in risk of long-term side effects of continuing immunomodulators (such as risk of malignancy or infection), and a higher value on avoiding a trivial-to-small increase in risk of relapse with withdrawal of immunomodulators, may reasonably choose to continue combination therapy*

Implementation Considerations:

- *There may be benefit in continuing combination therapy with TNF antagonists and immunomodulators in those who are felt to be at higher risk of immunogenicity, such as those with prior immunogenic failure to a biologic therapy (i.e. anti-drug antibody formation), those with lower trough TNF antagonist concentrations despite dose escalation, or those with HLA-DQA1*05 carriage.*

14. In adult outpatients with moderate-to-severely active Crohn's disease who are in corticosteroid-free clinical remission for at least 6 months on combination therapy of TNF antagonists and an immunomodulator, the AGA suggests AGAINST WITHDRAWAL OF TNF ANTAGONISTS. [Conditional recommendation, low certainty of evidence**]**

EARLY ADVANCED THERAPY

15. In adult outpatients with moderate-to-severely active Crohn's disease, the AGA SUGGESTS early advanced therapy compared with step therapy (initial use of corticosteroids and/or immunomodulator monotherapy) [*Conditional recommendation, very low certainty of evidence***]**

Implementation Considerations:

- *All trials that informed the evidence used combination therapy with TNF antagonists with immunomodulators.*

TREATING TO ENDOSCOPIC REMISSION VS CLINICAL REMISSION

16. In adult outpatients with Crohn's disease, the AGA makes no recommendation in favor, or against, treating to a target of endoscopic remission, compared with treating to a target of symptomatic remission [*No recommendation, knowledge gap***]**

Table 2. Key overarching considerations in the management of adult outpatients with moderate-to-severe Crohn's disease

1. Patients should have confirmation of active inflammation based on CD-related symptoms, biomarkers, and/or endoscopic evaluation prior to starting advanced therapies.
2. Patients should have both general and therapy-specific pre-treatment work up prior to initiation of such treatments. These include screening for hepatitis B and tuberculosis exposure prior to any biologic or advanced small molecule treatments, and thiopurine methyl transferase (TPMT) testing prior to initiation of thiopurines. There may be other treatment- and patient-specific tests that should be performed in accordance with the labels from regulatory agencies.
3. It is important to evaluate for factors influencing risk of treatment-related complications including assessment of comorbidities, frailty, and functional status and concomitant medications, and assessment of thromboembolic and cardiovascular risk factors.
4. Vaccination against influenza, pneumococcal pneumonia, and herpes zoster should be considered prior to initiation of immunosuppressive therapies in order to decrease risk of serious infections.
5. Initiation of advanced therapy should be followed by monitoring for both symptomatic response and/or remission and improvement in objective markers of inflammation during follow-up
6. Periodic laboratory monitoring for potential therapy-related toxicity should be performed while receiving immunosuppressive therapies, according to drug label

Table 3. Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessment, Development and Evaluation Framework

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with their values and preferences. Use shared-decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will involve various stakeholders. Performance measures should assess whether decision making is appropriate.

Table 4. Focused questions and corresponding PICOs being addressed in the guidelines. Questions in the "living" mode will be reviewed every 6 months for new evidence. Evidence synthesis will be updated when new phase 3 or phase 4 data of a relevant intervention or new agents become publicly available, there is change in regulatory guidance, or there are large studies suggesting meaningful change in safety of existing therapies or treatment strategies

S#	Focused Question	PICO Question			
		Patients	**Intervention**	**Comparator**	**Critical Outcomes**
1. (Living)	In adult outpatients with moderate-to-severely active CD, what is the efficacy of TNF antagonists (infliximab, adalimumab, certolizumab pegol), vedolizumab, ustekinumab, upadacitinib, and IL-23 antagonists (risankizumab, mirikizumab, guselkumab), for induction and maintenance of remission?	Adult outpatients with moderate-to-severely active CD	• TNF antagonists (infliximab, adalimumab, certolizumab pegol) • Vedolizumab • Ustekinumab • Upadacitinib • IL-23 antagonists (risankizumab, mirikizumab, guselkumab)	Placebo	• Induction of clinical remission • Maintenance of clinical remission
2. (Living)	In adult outpatients with moderate-to-severely active CD who are **naïve to advanced therapies**, what is the comparative efficacy of infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, upadacitinib, risankizumab, mirikizumab and guselkumab, for induction and maintenance of remission?	Adult outpatients with moderate-to-severely active CD who are naïve to advanced therapies	• Infliximab • Adalimumab • Certolizumab pegol • Vedolizumab • Ustekinumab • Upadacitinib • Risankizumab • Mirikizumab • Guselkumab	Placebo or another active comparator	• Induction of clinical remission • Maintenance of clinical remission
3 (Living)	In adult outpatients with moderate-to-severely active CD who **have been exposed to advanced therapies**, what is the comparative efficacy of infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, upadacitinib, risankizumab, mirikizumab and guselkumab for induction and maintenance of remission?	Adult outpatients with moderate-to-severely active CD who have been exposed to advanced therapies	• Infliximab • Adalimumab • Certolizumab pegol • Vedolizumab • Ustekinumab • Upadacitinib • Risankizumab • Mirikizumab • Guselkumab	Placebo or another active comparator	• Induction of clinical remission • Maintenance of clinical remission •
4.	In adult outpatients with moderate-to-severely active CD, what is the efficacy of immunomodulator	Adult outpatients with moderate-to-severely active CD	• Thiopurines (azathioprine, mercaptopurine)	Placebo (or 5-aminosalicylates [5-ASA])	• Achieving remission

	monotherapy (thiopurines, methotrexate) for induction and maintenance of remission?		• Methotrexate (oral or subcutaneous)		• Prevention of relapse (≈maintenance of remission)
5. (Living)	In adult outpatients with moderate-to-severely active CD, is combination therapy of TNF antagonists with an immunomodulator (thiopurines or methotrexate) superior to TNF monotherapy or immunomodulator monotherapy for induction and maintenance of remission?	Adult outpatients with moderate-to-severely active CD	Combination therapy with a TNF antagonist and an immunomodulator (thiopurines or methotrexate)	• TNF antagonist monotherapy • Immunomodulator monotherapy (thiopurines or methotrexate)	• Induction of clinical remission • Maintenance of clinical remission
6. (Living)	In adult outpatients with moderate-to-severely active CD, is combination therapy of a non-TNF biologic with an immunomodulator (thiopurines or methotrexate) superior to TNF monotherapy or immunomodulator monotherapy for induction and maintenance of remission?	Adult outpatients with moderate-to-severely active CD	Combination therapy with a non-TNF antagonist biologic and an immunomodulator (thiopurines or methotrexate)	• Non-TNF antagonist biologic monotherapy • Immunomodulator monotherapy (thiopurines or methotrexate)	• Induction of clinical remission • Maintenance of clinical remission
7. (Living)	In adult outpatients with moderate-to-severely active CD in steroid-free remission on combination therapy of TNF antagonist + immunomodulator, is discontinuation of (a) an immunomodulator or (b) discontinuation of a TNF antagonist, inferior to continuation of combination therapy?	Adult outpatients with moderate-to-severely active CD in steroid-free remission on combination therapy	• Discontinuation of an immunomodulator • Discontinuation of a biologic	Continuation of combination therapy	• Prevention of relapse
8.	In adult outpatients with moderate-to-severely active CD, is early use of advanced therapies superior to step up therapy for decreasing the risk of disease-related complications?	Adult outpatients with moderate-to-severely active CD	Top-down therapy • Upfront use of advanced therapies with or without immunomodulator therapy	Step therapy • Acceleration to advanced therapy only after failure of IMMs	• Disease-related complications • Maintenance of remission

9.	In adult outpatients with moderate-to-severely active CD, is treat-to-target of endoscopic remission (resolution of inflammation on endoscopy) superior to treat-to-target of symptomatic remission, for maintenance of remission and decreasing risk of disease-related complications?	Adult outpatients with moderate-to-severely active CD	Treat-to-target of endoscopic remission • Systematic assessment for symptoms and endoscopic inflammation, followed by treatment escalation in those with evidence of inflammation, regardless of presence or absence of symptoms	Treat-to-target of symptomatic remission • Systematic assessment for symptoms, followed by treatment escalation in those with ongoing symptoms	• Disease-related complications • Maintenance of remission

Table 5. GRADE Evidence Profile comparing TNF antagonists (infliximab, adalimumab and certolizumab pegol) with placebo for induction and maintenance of remission in patients with moderate-to-severely active Crohn's disease

INFLIXIMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with infliximab				
Induction of clinical remission (CRITICAL)	11/54 (20.4%)	**29/52 (55.8%)**	**RR 2.16** (1.24 to 3.77)	174 more per 1,000 (from 36 more to 416 more)	106 (2 RCTs)	⊕⊕⊕◯[1] MODERATE
Maintenance of clinical remission (CRITICAL)	66/258 (25.6%)	**208/381 (54.6%)**	**RR 1.99** (1.58 to 2.49)	218 more per 1,000 (from 128 more to 328 more)	639 (3 RCTs)	⊕⊕⊕⊕ HIGH

ADALIMUMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with adalimumab				
Induction of clinical remission (CRITICAL)	31/366 (8.5%)	**110/370 (29.7%)**	**RR 3.35** (2.31 to 4.86)	353 more per 1,000 (from 197 more to 579 more)	736 (5 RCTs)	⊕⊕⊕◯[2] MODERATE
Maintenance of clinical remission (CRITICAL)	36/275 (14.3%)	**106/276 (40.1%)**	**RR 2.67** (1.94 to 3.68)	367 more per 1,000 (from 207 more to 590 more)	551 (4 RCTs)	⊕⊕⊕◯[2] MODERATE

CERTOLIZUMAB PEGOL COMPARED TO PLACEBO FOR MODERATE TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with infliximab				
Induction of clinical remission (CRITICAL)	119/608 (19.6%)	**161/616 (26.1%)**	**RR 1.32** (1.07 to 1.62)	48 more per 1,000 (from 11 more to 93 more)	1224 (3 RCTs)	⊕⊕⊕◯[3] MODERATE

INFLIXIMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with infliximab				
Maintenance of clinical remission (CRITICAL)	61/210 (29.0%)	**103/215 (47.9%)**	**RR 1.65** (1.28 to 2.12)	143 more per 1,000 (from 62 more to 246 more)	425 (1 RCT)	⊕⊕⊕◯[4] MODERATE

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Lower limit of 95% of absolute effect crosses the clinically meaningful difference of drug over placebo (10%)
[2]Rated down for imprecision since optimal information size not met (<200 events)
[3]Rated down for serious imprecision since magnitude of benefit is below the 100 per 1000 absolute benefit rate of clinically meaningful difference threshold over placebo, identified by the guideline panel.
[4]Lower limit of 95% of absolute effect crosses the clinically meaningful difference of drug over placebo

Table 6. GRADE Evidence Profile comparing vedolizumab with placebo for induction and maintenance of remission in patients with moderate-to-severely active Crohn's disease

VEDOLIZUMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with vedolizumab				
Induction of clinical remission (CRITICAL)	45/433 (10.4%)	**83/508 (16.3%)**	**RR 1.60** (1.13 to 2.25)	90 more per 1,000 (from 19 more to 188 more)	941 (3 RCTs)	⊕⊕⊕◯[1] MODERATE
Maintenance of clinical remission (CRITICAL)	81/299 (18.3%)	**253/595 (45.2%)**	**RR 1.54** (1.25 to 1.89)	119 more per 1,000 (from 55 more to 196 more)	894 (3 RCTs)	⊕⊕⊕◯[2] MODERATE

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Rated down for serious imprecision since magnitude of benefit is below the 100 per 1000 absolute benefit rate of clinically meaningful difference threshold over placebo, identified by the guideline panel.
[2]Lower limit of 95% of absolute effect crosses the clinically meaningful difference of drug over placebo for clinical remission outcome

Table 7. GRADE Evidence Profile comparing interleukin-12/23 antagonist (ustekinumab) and interleukin-23 antagonists (mirikizumab, risankizumab, guselkumab) with placebo for induction and maintenance of remission in patients with moderate-to-severely active CD

USTEKINUMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with ustekinumab				
Induction of clinical remission (CRITICAL)	69/589 (11.7%)	**148/589 (25.1%)**	**RR 2.12** (1.63 to 2.74)	224 more per 1,000 (from 126 more to 348 more)	1178 (2 RCTs)	⊕⊕⊕⊕ HIGH
Maintenance of clinical remission (CRITICAL)	67/204 (18.3%)	**99/200 (45.2%)**	**RR 1.51** (1.19 to 1.91)	128 more per 1,000 (from 47 more to 227 more)	404 (2 RCTs)	⊕⊕⊕◯[1] MODERATE

RISANKIZUMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with mirikizumab				
Induction of clinical remission (CRITICAL)	86/401 (21.4%)	**247/568 (43.5%)**	**RR 1.98** (1.60 to 2.44)	147 more per 1,000 (from 90 more to 216 more)	969 (3 RCTs)	⊕⊕⊕◯[2] MODERATE
Maintenance of clinical remission (CRITICAL)	67/164 (40.8%)	**180mg: 87/157 (55.4%)** **360mg: 74/141 (52.5%)**	**180mg: RR 1.36** (1.08 to 1.71) **360mg: RR 1.28** (1.01 to 1.64)	**180mg**: 79 more per 1,000 (from 18 more to 156 more) **360mg:** 62 more per 1,000 (from 2 more to 141 more)	462 (1 RCT)	**180mg:** ⊕⊕⊕◯[3] MODERATE **360mg:** ⊕⊕⊕◯[3] MODERATE

MIRIKIZUMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with risankizumab				

Induction of clinical remission (CRITICAL)	56/263 (21.3%)	**248/675 (36.7%)**	**RR 1.61** (1.26 to 2.07)	92 more per 1,000 (from 39 more to 160 more)	938 (2 RCTs)	⊕⊕⊕◯[4] MODERATE
Maintenance of clinical remission (CRITICAL)	39/199 (19.6%)	**313/579 (54.1%)**	**RR 2.76** (2.06 to 3.69)	387 more per 1,000 (from 233 more to 592 more)	778 (1 RCT)	⊕⊕⊕⊕ HIGH

GUSELKUMAB COMPARED TO PLACEBO FOR MODERATE TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with guselkumab				
Induction of clinical remission (CRITICAL)	38/209 (18.2%)	**309/643 (48.1%)**	**RR 2.66** (1.97 to 3.58)	249 more per 1,000 (from 146 more to 387 more)	852 (3 RCTs)	⊕⊕⊕⊕ HIGH
Maintenance of clinical remission (CRITICAL)	18/148 (12.2%)	**289/582 (49.7%)**	**RR 4.08** (2.62 to 6.34)	678 more per 1,000 (from 356 more to 1000 more)	730 (2 RCTs)	⊕⊕⊕⊕ HIGH

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Lower limit of 95% of absolute effect crosses the clinically meaningful difference of drug over placebo for clinical remission outcome
[2]Lower limit of 95% of absolute effect crosses the clinically meaningful difference of drug over placebo for induction of clinical remission outcome
[3]Rated down for serious imprecision since magnitude of benefit is below the 100 per 1000 absolute benefit rate of minimal clinically important difference threshold over placebo, identified by the guideline panel.
[4]Rated down for serious imprecision since magnitude of benefit is below the 100 per 1000 absolute benefit rate of minimal clinically important difference threshold over placebo, identified by the guideline panel.

Table 8. GRADE Evidence Profile comparing upadacitinib with placebo for induction and maintenance of remission in patients with moderate-to-severely active Crohn's disease

UPADACITINIB COMPARED TO PLACEBO FOR MODERATE TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with upadacitinib				
Induction of clinical remission (CRITICAL)	93/384 (24.2%)	**313/710 (44.1%)**	**RR 1.79** (1.47 to 2.17)	119 more per 1,000 (from 71 more to 176 more)	1094 (3 RCTs)	⊕⊕⊕◯[1] MODERATE
Maintenance of clinical remission (CRITICAL)	25/165 (15.2%)	**15mg: 63/169 (37.3%)** **30mg: 80/168 (47.6%)**	**15mg: RR 2.46** (1.63 to 3.71) **30mg: RR 3.14** (2.12 to 4.66)	**15mg**: 321 more per 1,000 (from 139 more to 596 more) **30mg:** 471 more per 1,000 (from 246 more to 805 more)	502 (1 RCT)	**15mg:** ⊕⊕⊕◯[2] MODERATE **30mg:** ⊕⊕⊕◯[2] MODERATE

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Lower limit of 95% of absolute effect crosses the clinically meaningful difference of drug over placebo for induction of clinical remission outcome
[2]Rated down for imprecision since optimal information size not met (<200 events)

Table 9: GRADE Evidence-to-decision framework for use of advanced therapies over no intervention for the management of patients with moderate-to-severely active Crohn's disease. Clinically meaningful difference threshold of drug over placebo was set at 10%. Judgements made by guideline panel are in **bold**.

DOMAIN	CRITERIA	JUDGEMENT					
Problem	Is the problem a priority?	No	Probably No	Probably yes	**YES**	Varies	Don't know
Desirable effects	How substantial are the desirable anticipated effects?	**Trivial to Small (<10%) CZP, VDZ**		**Moderate (10-30%) IFX, UST, RIS, MIRI, GUS, UPA**	**Large (>30%) ADA**	Varies	Don't know
Undesirable effects	How substantial are the undesirable anticipated effects?	**Trivial IFX, ADA, CZP, VDZ, UST, RIS, GUS, MIRI, UPA**	Small	Moderate	Large	Varies	Don't know
Certainty of evidence	What is the overall certainty of the evidence of effects	Very low	Low	**Moderate IFX, ADA, CZP, VDZ, RIS, MIRI, UPA**	**High UST, GUS**	No included studies	
Values	Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**	
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	Favors comparison/control	Probably favors comparison	Does not favor either comparison or intervention	**Probably favors intervention CZP, VDZ**	**Favors intervention IFX, ADA, UST, RIS, MIRI, GUS, UPA**	Varies/ don't know
Resource use	Is the incremental cost small relative to the net benefits?	No	**Probably No**	Uncertain	Probably yes	Yes	Uncertain
Equity	What would be the impact on health inequities?	Increased	**Probably increased**	Probably no impact	Probably reduced	Reduced	Varies/Don't know

Acceptability	Is the option acceptable to key stakeholders?	No	Probably No	Probably yes	**Yes**	Varies	Don’t know
Feasibility	Is the option feasible to implement?	No	Probably No	Probably yes	**Yes**	Varies	Don’t know

[Abbreviations: ADA-Adalimumab, CZP-Certolizumab pegol, GUS-Guselkumab, IFX-Infliximab, MIRI-Mirikizumab, RIS-Risankizumab, UPA-Upadacitinib, UST-Ustekinumab, VDZ-Vedolizumab]

Table 10. GRADE Evidence Profile comparing thiopurines vs. no thiopurines for achieving steroid-free remission, and preventing relapse in patients with moderate-to-severely active Crohn's disease

THIOPURINES COMPARED TO PLACEBO FOR MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with thiopurines				
Achieving clinical remission (CRITICAL)	68/183 (37.1%)	95/197 (48.2%)	**RR 1.23 (0.97 to 1.54)**	85 more per 1,000 (from 11 fewer to 201 more)	380 (5 RCTs)	⊕◯◯◯[1,2,3] VERY LOW
Relapse after achieving clinical remission (CRITICAL)	97/172 (56.4%)	127/175 (72.6%)	**RR 1.23 (1.00 to 1.50)**	130 more per 1,000 (from 0 fewer to 282 more)	347 (5 RCT)	⊕⊕◯◯[1,4] LOW

[1] Rated down for risk of bias (due to inadequate blinding and allocation concealment)
[2] Rated down for indirectness (since these trials did not truly assess induction of remission, but rather the ability to achieve corticosteroid-free clinical remission, over a wide range of time, using a variety of disease activity indices with definitions inconsistent with modern definitions of remission)
[3] Rated down for imprecision since 95% CI crosses unity
[4] Rated down for imprecision since 95% CI crosses MID of 10%

Table 11. GRADE Evidence Profile assessing subcutaneous and oral methotrexate for achieving steroid-free remission, and preventing relapse in patients with moderate-to-severely active Crohn's Disease

SUBCUTANEOUS METHOTREXATE COMPARED TO PLACEBO FOR MODERATE TO SEVERE LUMINAL CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with subcutaneous methotrexate				
Achieving clinical remission (CRITICAL)	9/47 (19.1%)	37/94 (39.4%)	**RR 2.06 (1.09 to 3.89)**	203 more per 1,000 (from 17 more to 553 more)	141 (1 RCT)	⊕⊕⊕◯[1] MODERATE
Relapse after achieving clinical remission (CRITICAL)	14/36 (38.9%)	26/40 (65.0%)	**RR 1.67 (1.05 to 2.67)**	261 more per 1,000 (from 19 more to 649 more)	76 (1 RCT)	⊕⊕⊕◯[1] MODERATE

ORAL METHOTREXATE COMPARED TO PLACEBO FOR MODERATE TO SEVERE LUMINAL CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with oral methotrexate				
Achieving clinical remission (CRITICAL)	12/26 (46.2%)	10/26 (38.5%)	**RR 0.83 (0.44 to 1.58)**	78 fewer per 1,000 (from 258 fewer to 268 more)	52 (1 RCT)	⊕◯◯◯[2,3] VERY LOW
Relapse after achieving clinical remission (CRITICAL)	8/12 (66.7%)	9/10 (90.0%)	**RR 1.35 (0.86 to 2.12)**	233 more per 1,000 (from 93 fewer to 747 more)	22 (1 RCT)	⊕◯◯◯[2,3] VERY LOW

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Rated down for imprecision since 95% CI crosses MID of 10% and optimal information size not met (<200 events)
[2] Rated down for indirectness (used low dose oral methotrexate <15mg/week)
[3] Rated down for very serious imprecision due to very wide 95% CI (unable to rule out significant risk of harm with intervention)

Table 12. GRADE Evidence-to-decision framework for use of immunomodulator monotherapy for the management of patients with moderate-to-severely active Crohn's Disease. Clinically meaningful difference threshold of active interventions was set at 10%. Judgements made by guideline panel are in **bold**

DOMAIN	CRITERIA	JUDGEMENT					
Problem	Is the problem a priority?	No	Probably No	Probably yes	YES	Varies	Don't know
Desirable effects	How substantial are the desirable anticipated effects?	**Trivial to Small (<10%)** **TP (Ind)** **PO MTX (Ind)**		**Moderate (10-30%)** **TP (M)** **SQ MTX (Ind + M)** **PO MTX (M)**	Large (>30%)	Varies	Don't know
Undesirable effects	How substantial are the undesirable anticipated effects?	**Trivial to Small** **TP, PO or SQ MTX**		Moderate	Large	Varies	Don't know
Certainty of evidence	What is the overall certainty of the evidence of effects	**Very low** **TP (Ind)** **PO MTX (Ind + M)**	**Low** **TP (M)**	**Moderate** **SQ MTX (Ind + M)**	High	No included studies	
Values	Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**	
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	Favors comparison/control	Probably favors comparison	**Does not favor either comparison or intervention** **TP (Ind)** **PO MTX (Ind)**	**Probably favors intervention** **TP (M)** **SQ MTX (Ind + M)** **PO MTX (M)**	Favors intervention	Varies/ don't know
Resource use	Is the incremental cost small relative to the net benefits?	No	Probably No	Uncertain	**Probably yes**	Yes	Uncertain
Equity	What would be the impact on health inequities?	Increased	Probably increased	Probably no impact	**Probably reduced**	Reduced	Varies/Don't know

Acceptability	Is the option acceptable to key stakeholders?	No	Probably No	Probably yes	**Yes**	Varies	Don't know
Feasibility	Is the option feasible to implement?	No	Probably No	Probably yes	**Yes**	Varies	Don't know

[Abbreviations: Ind-Induction, M-Maintenance, MTX-methotrexate, PO-per os, SQ-subcutaneous, TP-thiopurine]

Table 13. GRADE Evidence Profile comparing TNF antagonists + immunomodulators vs. TNF antagonist monotherapy for achieving remission in patients with moderate-to-severely active CD.

COMBINATION THERAPY WITH TNF ANTAGONISTS + IMMUNOMODULATORS COMPARED TO TNF ANTAGONIST MONOTHERAPY FOR MODERATE- TO- SEVERE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with TNF antagonist monotherapy	Risk with combination therapy				
Induction of clinical remission, W10-16 (CRITICAL)	287/458 (62.7%)	**324/479 (67.6%)**	**RR 1.04 (0.89 to 1.23)**	25 more per 1,000 (from 69 fewer to 144 more)	937 (4 RCTs)	⊕⊕◯◯[1,2] LOW
Maintenance of clinical remission, W26-52 (CRITICAL)	257/458 (56.1%)	**301/479 (62.8%)**	**RR 1.10 (0.97 to 1.25)**	56 more per 1,000 (from 17 fewer to 140 more)	937 (4 RCTs)	⊕⊕◯◯[1,2] LOW

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Rated down for inconsistency (difference in interventions, patients)
[2]Rated down for serious imprecision with wide 95% CI

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Table 14. GRADE Evidence-to-decision framework for use of combination therapy over TNF monotherapy for the management of patients with moderate-to-severe Crohn's disease. Clinically meaningful difference threshold of active interventions was set at 5%. Judgements made by guideline panel are in **bold**

DOMAIN	CRITERIA	JUDGEMENT					
Problem	Is the problem a priority?	No	Probably No	Probably yes	**YES**	Varies	Don't know
Desirable effects	How substantial are the desirable anticipated effects?	**Trivial to Small (<10%)**		Moderate (10-30%)	Large (>30%)	Varies	Don't know
Undesirable effects	How substantial are the undesirable anticipated effects?	**Trivial to Small**		Moderate	Large	Varies	Don't know
Certainty of evidence	What is the overall certainty of the evidence of effects	Very low	**Low**	Moderate	High	No included studies	
Values	Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**	
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	Favors comparison/control	Probably favors comparison	**Does not favor either comparison or intervention**	Probably favors intervention	Favors intervention	Varies/ don't know
Resource use	Is the incremental cost small relative to the net benefits?	No	Probably No	Uncertain	**Probably yes**	Yes	Uncertain
Equity	What would be the impact on health inequities?	Increased	**Probably increased**	Probably no impact	Probably reduced	Reduced	Varies/Don't know

Acceptability	Is the option acceptable to key stakeholders?	No	Probably No	Probably yes	**Yes**	Varies	Don’t know
Feasibility	Is the option feasible to implement?	No	Probably No	Probably yes	**Yes**	Varies	Don’t know

Table 15. GRADE Evidence Profile comparing withdrawal of immunomodulators or withdrawal of biologics compared with continuing combination therapy for risk of relapse in patients with moderate-to-severely active Crohn's disease in steroid-free remission on combination therapy

WITHDRAWAL OF IMMUNOMODULATORS (WHILE CONTINUINING BIOLOGIC THERAPY) COMPARED TO CONTINUING COMBINATION THERAPY IN ADULT OUTPATIENTS WITH MODERATE-TO-SEVERE CROHN'S DISEASE IN STEROID-FREE REMISSION

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with continuing combination therapy	Risk with IMM withdrawal				
Risk of relapse at 12 months (CRITICAL)	30/202 (14.9%)	**34/202 (16.8%)**	**RR 1.15 (0.75 to 1.76)**	22 more per 1,000 (from 37 fewer to 113 more)	404 (5 RCTs)	⊕⊕◯◯[1,2] LOW

WITHDRAWAL OF BIOLOGICS (WHILE CONTINUINING IMMUNOMODULATOR MONOTHERAPY) COMPARED TO CONTINUING COMBINATION THERAPY IN ADULT OUTPATIENTS WITH MODERATE-TO-SEVERE CROHN'S DISEASE IN STEROID-FREE REMISSION

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with continuing combination therapy	Risk with biologic withdrawal				
Risk of relapse at 12 months (CRITICAL)	19/169 (11.2%)	**52/170 (30.6%)**	**RR 2.23 (1.08 to 4.61)**	138 more per 1,000 (from 9 more to 406 more)	396 (4 RCTs)	⊕⊕◯◯[1,3] LOW

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Rated down for serious risk of bias (open-level trials with subjective end points)
[3]Rated down for imprecision since optimal information size not met (<200 events)

Table 16. GRADE Evidence-to-decision framework for use of biologic withdrawal or IMM withdrawal over continuing combination therapy in patients with moderate-to-severely active Crohn's disease in steroid-free remission for >6m. Clinically meaningful difference threshold of active interventions was set at 5%. Judgements made by guideline panel are in **bold**

DOMAIN	CRITERIA	JUDGEMENT					
Problem	Is the problem a priority?	No	Probably No	Probably yes	**YES**	Varies	Don't know
Desirable effects	How substantial are the desirable anticipated effects?	**Trivial (<5%) IMM Withdrawal, TNF antagonist withdrawal**	Small	Moderate (10-30%)	Large (>30%)	Varies	Don't know
Undesirable effects	How substantial are the undesirable anticipated effects?	**Trivial IMM Withdrawal**	Small	**Moderate TNF antagonist withdrawal**	Large	Varies	Don't know
Certainty of evidence	What is the overall certainty of the evidence of effects	Very low	**Low**	Moderate	High	No included studies	
Values	Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**		
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	Favors comparison/control	**Probably favors comparison TNF antagonist withdrawal**	Does not favor either comparison or intervention	**Probably favors intervention IMM Withdrawal**	Favors intervention	Varies/ don't know
Resource use	Is the incremental cost small relative to the net benefits?	No	**Probably No TNF antagonist withdrawal**	Uncertain	**Probably yes IMM Withdrawal**	Yes	Uncertain
Equity	What would be the impact on health inequities?	Increased	**Probably increased**	**Probably no impact IMM Withdrawal**	Probably reduced	Reduced	Varies/Don't know

			TNF antagonist withdrawal				
Acceptability	Is the option acceptable to key stakeholders?	No	Probably No	Probably yes	**Yes**	Varies	Don’t know
Feasibility	Is the option feasible to implement?	No	Probably No	Probably yes	**Yes**	Varies	Don’t know

Table 17. GRADE Evidence Profile comparing early combined immunosuppression with step therapy in adults with moderate-to-severely active Crohn's Disease.

EARLY COMBINED IMMUNOSUPPRESSION COMPARED WITH STEP THERAPY IN ADULTS WITH ACTIVE CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with step therapy	Risk with ECI				
Clinical Remission at 12 months (CRITICAL)	700/1155 (60.6%)	**891/1342 (66.4%)**	**RR 1.18 (0.96 to 1.46)**	109 more per 1,000 (from 24 fewer to 279 more)	2497 (3 RCTs)	⊕◯◯◯[1,2,3] VERY LOW
Disease complications at 12 months (CRITICAL)	204/1155 (17.7%)	**198/1342 (14.8%)**	**RR 0.62 (0.29 to 1.34)**	67 fewer per 1,000 (from 125 fewer to 60 more)	2497 (3 RCTs)	⊕⊕◯◯[1,2,4] LOW

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Rated down for serious risk of bias (open-level trials)
[2]Rated down for imprecision due to wide confidence intervals
[3]Rated down for inconsistency in effect size across trials
[4]While the trials were open label, the endpoint of disease complications was relatively objective, and open-label nature is unlikely to impact this. Hence, we opted not rate down for risk of bias

Table 18. GRADE Evidence-to-decision framework for use of combination therapy over TNF monotherapy for the management of patients with moderate-to-severely active Crohn's disease. Clinically meaningful difference threshold of active interventions was set at 5%. Judgements made by guideline panel are in **bold**

DOMAIN	CRITERIA	JUDGEMENT					
Problem	Is the problem a priority?	No	Probably No	Probably yes	**YES**	Varies	Don't know
Desirable effects	How substantial are the desirable anticipated effects?	Trivial to Small (<10%)		**Moderate (10-30%)**	Large (>30%)	Varies	Don't know
Undesirable effects	How substantial are the undesirable anticipated effects?	**Trivial to Small**		Moderate	Large	Varies	Don't know
Certainty of evidence	What is the overall certainty of the evidence of effects	**Very low (Clinical remission)**		**Low (Disease complications)**	Moderate	High	No included studies
Values	Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability		Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**	
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	Favors comparison/control	Probably favors comparison	Does not favor either comparison or intervention	**Probably favors intervention**	Favors intervention	Varies/ don't know
Resource use	Is the incremental cost small relative to the net benefits?	No	**Probably No**	Uncertain	Probably yes	Yes	Uncertain
Equity	What would be the impact on health inequities?	Increased	**Probably increased**	Probably no impact	Probably reduced	Reduced	Varies/Don't know

Acceptability	Is the option acceptable to key stakeholders?	No	Probably No	Probably yes	Yes	**Varies**	Don't know
Feasibility	Is the option feasible to implement?	No	Probably No	**Probably yes**	Yes	Varies	Don't know

Table 19. GRADE Evidence Profile comparing treating to a target of endoscopic remission in comparison to a target of clinical remission in adults with moderate-to-severely active Crohn's disease.

TREAT-TO-TARGET OF ENDOSCOPIC REMISSION COMPARED WITH TREAT-TO-TARGET OF CLINICAL REMISSION IN ADULTS WITH CROHN'S DISEASE

Outcomes	Study event rates (95% CI)		Relative effect (95% CI)	Absolute effect*	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with TTT Clinical Remission	Risk with TTT Endoscopic Remission				
Clinical Remission at 12 months (CRITICAL)	453/790 (57.3%)	**469/742 (63.2%)**	**RR 1.04 (0.78 to 1.39)**	23 more per 1,000 (from 126 fewer to 224 more)	1532 (2 RCTs)	⨁◯◯◯[1,2,3] VERY LOW

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Rated down for serious risk of bias (open-level trials)
[2]Rated down for imprecision due to wide confidence intervals
[3]Rated down for inconsistency in effect size across trials (I^2=90%)