Targeted Immune Modulators for Crohn Disease and Ulcerative Colitis

Updated Systematic Review

Washington P&T Committee Meeting

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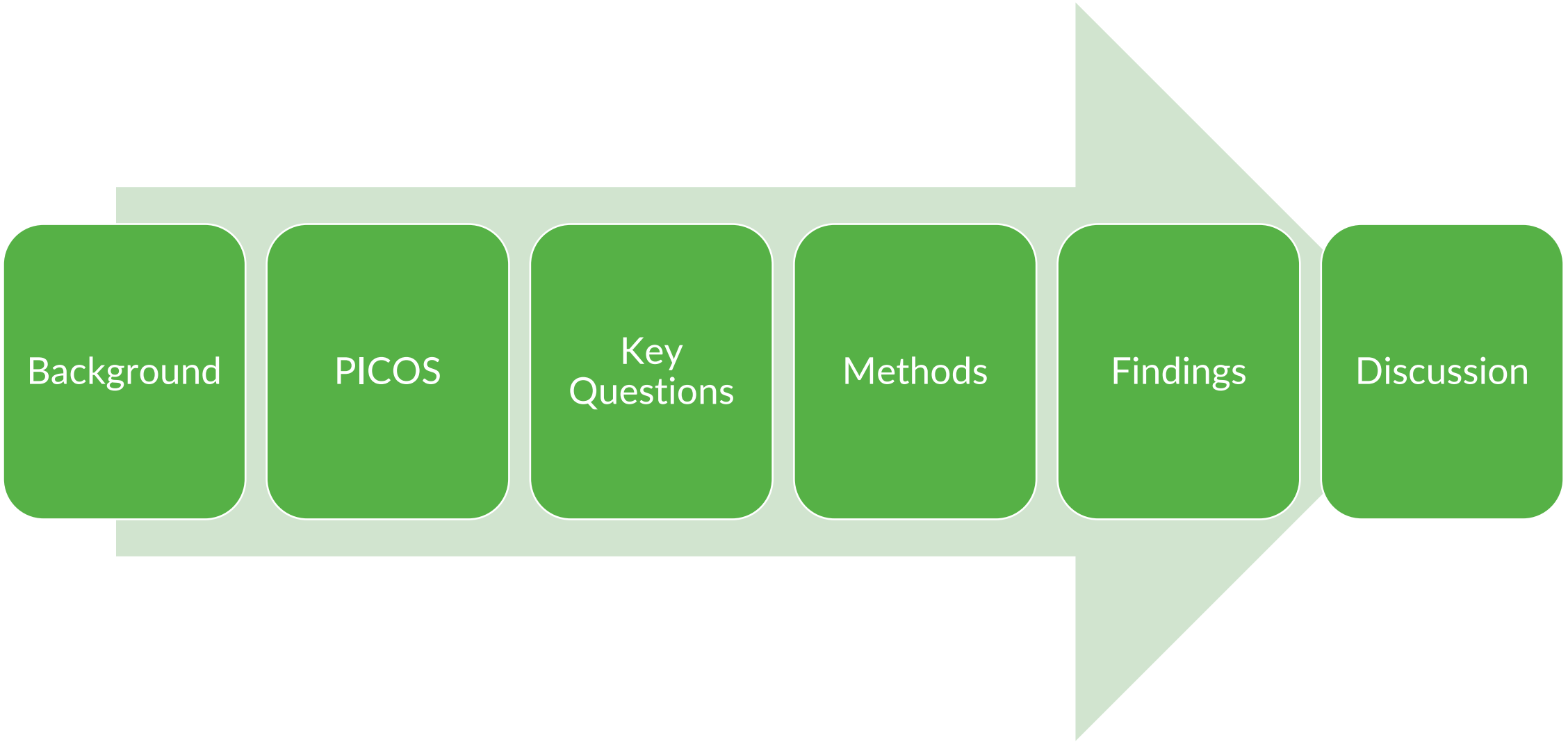
OHSU

Overview


Background
PICOS
Key Questions
Methods
Findings
Discussion

Abbreviations Used

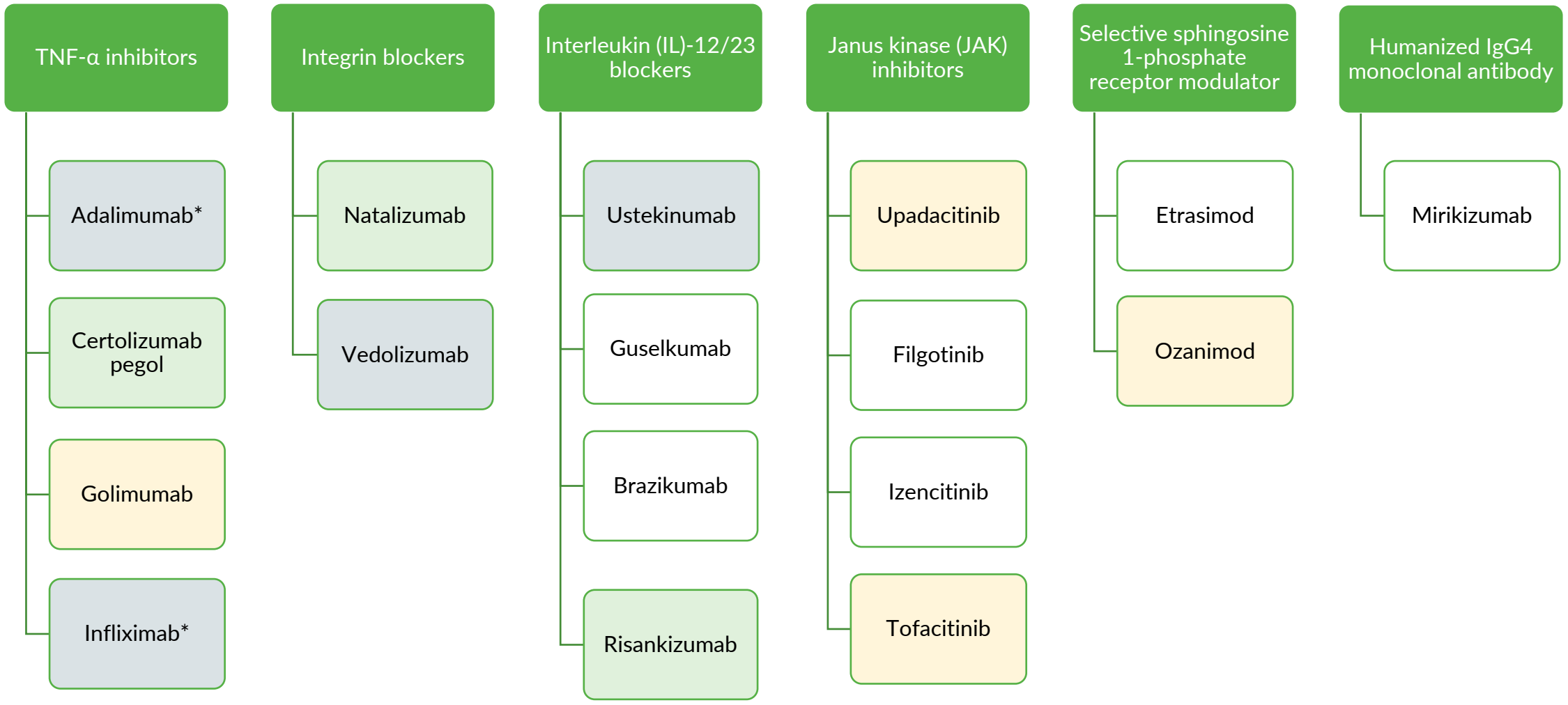
- AE: adverse event
- aHR: adjusted hazard ratio
- ARD: absolute risk difference
- CDAI: Crohn Disease Activity Index
- CI: confidence interval
- CoE: certainty of evidence
- DERP: Drug Effectiveness Review Project
- EuroQoL EQ-5D: European Quality of Life 5-Dimension Questionnaire
- FDA: US Food and Drug Administration
- GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
- HR: hazard ratio
- IBDQ: Inflammatory Bowel Disease Questionnaire
- IRR: incident rate ratio
- MCS: Mayo Clinic Score
- MID: minimal important difference
- PRO-2: patient-reported outcome
- PY: patient-year
- RCT: randomized controlled trial
- RoB: risk of bias
- RR: relative risk
- SAE: serious adverse event
- TIM: targeted immune modulator
- TNF-α: tumor necrosis factor alpha

Background

Background

- Crohn disease and ulcerative colitis are chronic inflammatory diseases of the gastrointestinal tract, diagnosed by colonoscopy.
  - Crohn disease is characterized by inflammation involving the full thickness of the bowel wall at any point from mouth to anus.
  - Ulcerative colitis is characterized by mucosal ulceration limited to the colon and rectum.
- TIMs are a group of biologic drugs used to treat Crohn disease and ulcerative colitis by selectively blocking mechanisms involved in the inflammatory and immune responses.
  - FDA approved the first TIM (infliximab) for Crohn disease in 1998; additional agents, including biosimilars, have since been approved for both conditions.

TIM Agents for Crohn Disease and Ulcerative Colitis



PICOS (for the Updated Review)

- Population: Adults with Crohn disease or ulcerative colitis
- Interventions: FDA-approved TIMs or pipeline drugs
- Comparators:
  - FDA-approved drugs: another listed intervention (head-to-head comparison)
  - Pipeline drugs: any listed TIM, standard of care, or placebo
- Outcomes: Measures of clinical improvement and disease remission, quality of life, AEs, SAEs, and other health outcomes
- Study Designs:
  - RCTs > 12-week study duration
  - Cohort studies > 12-week study duration and > 1,000 participants (harms only)

Key Questions

1. Comparative effectiveness of TIMs to treat Crohn disease and ulcerative colitis
2. Comparative harms of TIMs to treat Crohn disease and ulcerative colitis
3. Characteristics of ongoing studies

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Changes Compared with Previous Report

- Excluded peficitinib and PF-04236921
- Excluded three previously included studies: 2 cohort studies (did not report on the comparative risks among the drugs of interest) and 1 RCT (focused on PF-04236921)
- Included 3 new pipeline drugs: guselkumab, brazikumab, and izencitinib
- Added section on mixed populations and split some comparisons

Methods

Methods

- Ovid MEDLINE, Embase, Cochrane Library
  January 1, 2019, through July 14, 2022
- Individual study RoB assessment
- OpenEpi for ARD, IRR, RR, and CI calculations
- GRADE approach for overall certainty of evidence
- ClinicalTrials.gov, ScanMedicine, and ISRCTN searches for ongoing studies

DERP Risk of Bias

Low	• Clear reporting of methods and mitigation of potential biases and conflicts of interest
Moderate	• Incomplete information about methods that might mask important limitations or a meaningful conflict of interest
High	• Clear flaws that might introduce serious bias

GRADE Certainty of Evidence

Outcomes rated — **Disease remission, clinical improvement, AEs, SAEs, withdrawals due to AEs, and infections**

High	• Very confident that the estimate of effect of intervention on outcome lies close to the true effect.
Moderate	• Moderately confident in estimate of effect of intervention on outcome. True effect is likely close to estimate, but possibly different.
Low	• Little confidence in estimate of effect of intervention on outcome. True effect may be substantially different from estimate.
Very low	• No confidence in estimate of effect of intervention on outcome. True effect is likely substantially different from estimate.

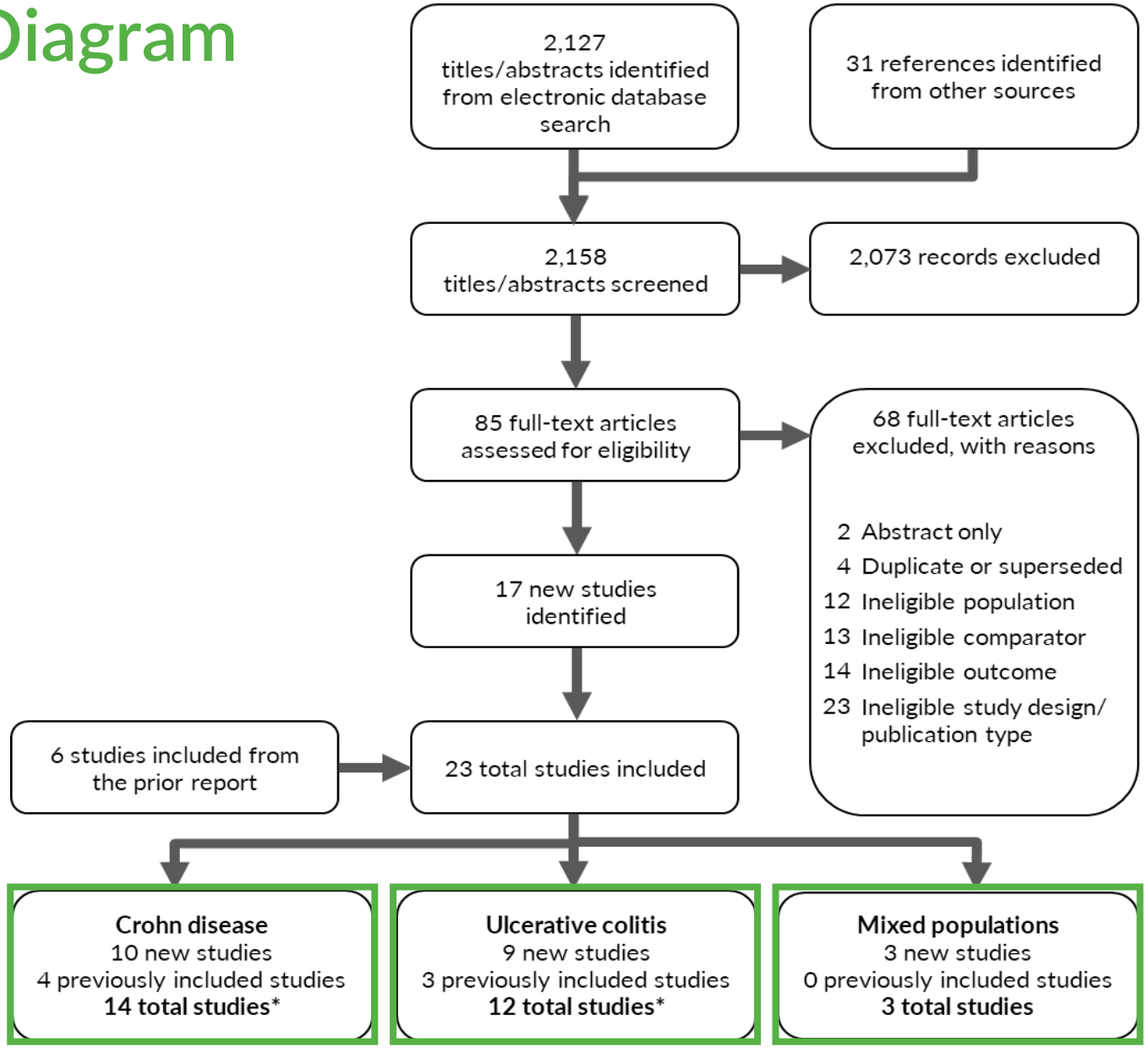
RCTs

Cohort

Findings

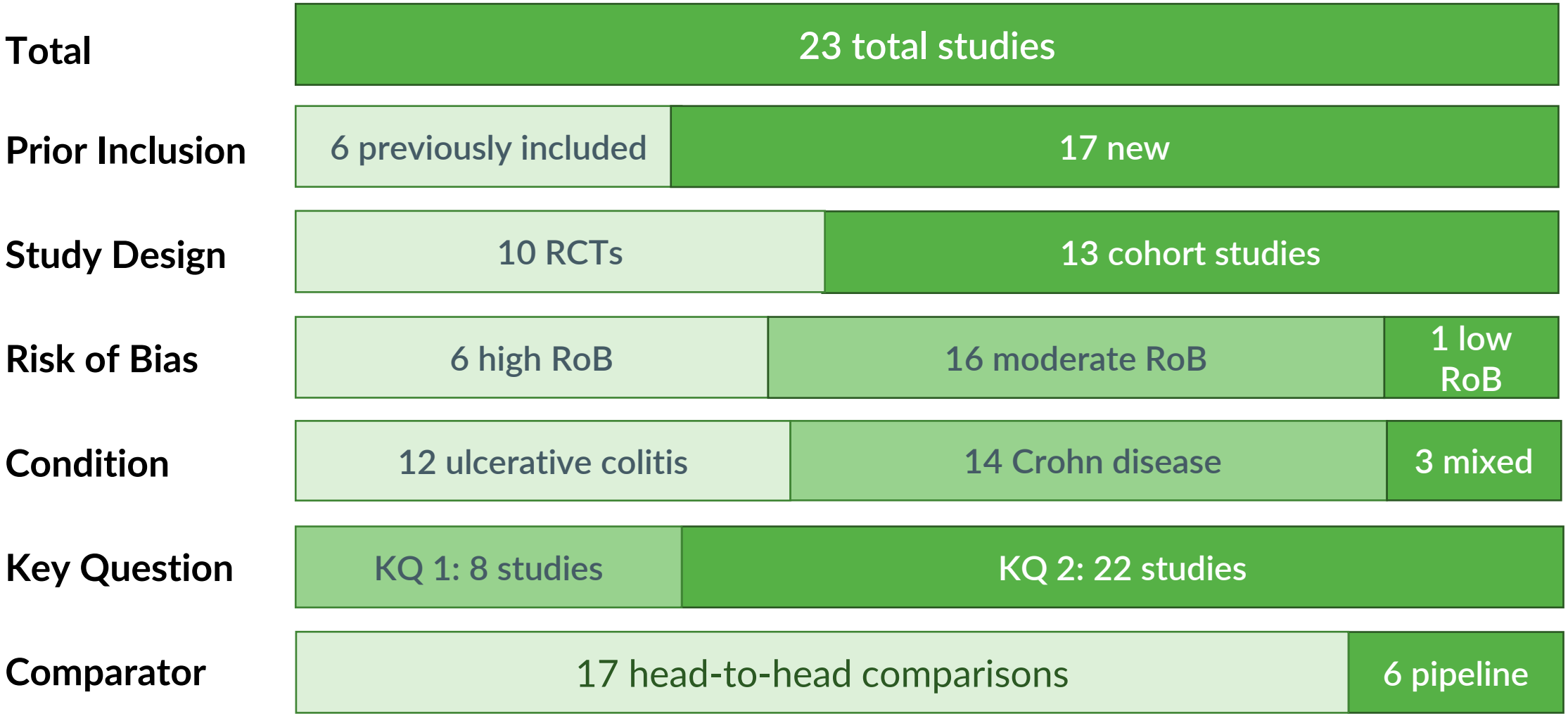
Published Studies

Literature Flow Diagram



* 6 studies reported results for both Crohn disease and ulcerative colitis and are counted twice.

Study Characteristics



Structure of Findings

- **Crohn disease**

✓Benefits from RCTs on TIMs

✓Harms from RCTs and cohort studies on TIMs

✓Benefits and harms on pipeline drugs

- **Ulcerative colitis**

✓Benefits from RCTs on TIMs

✓Harms from RCTs and cohort studies on TIMs

✓Benefits and harms on pipeline drugs

- **Mixed population (Crohn disease and ulcerative colitis)**

✓Harms from cohort studies on TIMs

- New evidence from this update

Commonly Used Instruments to Assess Outcomes

- IBDQ
  - 32 questions on four domains (bowel symptoms, systemic symptoms, emotional functioning, social functioning)
  - Score 0 to 224 (higher is better)
  - MID: 16 points
- CDAI
  - 8 weighted clinical factors (number of liquid stools, abdominal pain, general well-being, others)
  - Score from 0 to 600 (lower is better; < 150 = minimal disease; > 450 = severe disease)
  - MID: decrease from baseline of at least 100 points (FDA recommendation)
- Additional material in slide set (and Appendix D in report) summarizes other instruments

Findings

Crohn Disease

Crohn Disease: Efficacy and/or Harms

3 RCTs and 8 cohort studies including 5 head-to-head comparisons

	Adalimumab	Certolizumab pegol	Golimumab	Infliximab	Natalizumab	Ozanimob	Risankizumab	Tofacitinib	TNF-α inhibitors	Upadacitinib	Ustekinumab	Vedolizumab
Adalimumab				1 RCT 1 RCT 2 cohorts								
Certolizumab pegol	1 cohort			1 cohort								
Golimumab												
Infliximab												
Natalizumab												
Ozanimod												
Risankizumab												
Tofacitinib												
TNF-α inhibitors												
Upadacitinib												
Ustekinumab	1 RCT											
Vedolizumab									1 cohort 4 cohorts 1 cohort			

High-RoB Study

Moderate-RoB Study

Low-RoB Study

New Studies

KQ1: Comparative Effectiveness in Crohn Disease

Evidence

- Adalimumab vs. infliximab (1 moderate-RoB RCT, 1 high-RoB RCT)
- Ustekinumab vs. adalimumab (1 moderate-RoB RCT)

Findings – Adalimumab vs. Infliximab

- **Clinical improvement (1 RCT; N = 20); GRADE: Very Low**
  - No difference in clinical, endoscopic, or histological recurrence at 12 months
- **Quality of life (1 RCT; N = 73); GRADE: Very Low**
  - No difference in median IBDQ measures throughout study (193 vs. 188) at 54 weeks

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KQ1: Comparative Effectiveness in Crohn Disease

Findings – Ustekinumab vs. Adalimumab

- **Clinical response (1 RCT; N = 386);** GRADE: Moderate
  - No difference in clinical response (72% vs. 66%) at 52 weeks
- **Clinical remission (1 RCT; N = 386);** GRADE: Moderate
  - No difference in clinical remission (65% vs. 61%) at 52 weeks
- **Corticosteroid-free remission (1 RCT; N = 386);** GRADE: Moderate
  - No difference in corticosteroid-free remission (61% vs. 57%) at 52 weeks
- **PRO-2 remission (1 RCT; N = 386);** GRADE: Moderate
  - No difference in PRO-2 remission (57% vs. 55%) at 52 weeks

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Blue header field indicates new study.

KQ2: Comparative Harms in Crohn Disease

Evidence

- Adalimumab vs. infliximab (1 moderate-RoB RCT; 2 moderate-RoB cohort studies)
- Certolizumab pegol vs. adalimumab (1 moderate-RoB cohort study)
- Infliximab vs. certolizumab pegol (1 moderate-RoB cohort study)
- Upadacitinib vs. adalimumab (1 moderate-RoB RCT)
- Vedolizumab vs. TNF-α inhibitors (1 high- and 5 moderate-RoB cohort studies)

KQ2: Comparative Harms in Crohn Disease

Findings – Adalimumab vs. Infliximab

- **Overall AEs (1 RCT; N = 73); GRADE: Very Low**
  - No difference between groups (RR, 1.14; 95% CI, 0.89 to 1.46) at 54 weeks
- **Withdrawals due to AE (1 RCT; N = 73); GRADE: Very Low**
  - No difference between groups (RR 6.17; 95% CI, 0.78 to 48.71) at 54 weeks
- **SAEs (1 RCT; N = 73); GRADE: Very Low**
  - No difference between groups (RR, 9.95; 95% CI, 0.57 to 174.1) at 54 weeks
- **Serious infections (2 cohort studies; N = 2,525); GRADE: Very Low**
  - No difference between groups (aHR, 1.14; 95% CI, 0.61 to 2.08)

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KQ2: Comparative Harms in Crohn Disease

Findings – Certolizumab pegol vs. Adalimumab

- **Serious infections (1 cohort study; N = 1,046); GRADE: Very Low**
  - No difference between groups (aHR, 2.1; 95% CI, 0.98 to 4.4)

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Findings – Certolizumab pegol vs. Infliximab

- **Serious infections (1 cohort study; N = 1,046); GRADE: Very Low**
  - No difference between groups (aHR, 0.47; 95% CI, 0.08 to 2.75)

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KQ2: Comparative Harms in Crohn Disease

Findings – Ustekinumab vs. Adalimumab

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- **Overall AEs (1 RCT; N = 386); GRADE: High**
  - No difference between groups (80% vs. 78%) at 52 weeks
- **SAEs (1 RCT; N = 386); GRADE: Moderate**
  - No difference between groups (13% vs. 16%) at 52 weeks
- **Withdrawals due to AEs (1 RCT; N = 386); GRADE: Low**
  - No difference between groups (6% vs. 11%) at 52 weeks
- **Injection-site reactions (1 RCT; N = 386); GRADE: Low**
  - Lower incidence with ustekinumab (6% vs. 11%) at 52 weeks
- **Serious infections (1 RCT; N = 386); GRADE: Very Low**
  - No difference between groups (2% vs. 3%) at 52 weeks
- **Opportunistic infections (1 RCT; N = 386); GRADE: Very Low**
  - No difference between groups (1% vs. 1%) at 52 weeks

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KQ2: Comparative Harms in Crohn Disease

Findings – Vedolizumab vs. TNF-α inhibitors

- **Serious infections (5 cohort studies; N = 22,928);** GRADE: Very Low
  - No difference between groups (HR, 1.10; 95% CI, 0.87 to 1.38)
- **Opportunistic infections (1 cohort study; N = 5,987);** GRADE: Very Low
  - No difference between groups (HR, 1.40; 95% CI, 0.90 to 2.09)

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Efficacy and Harms of TIM Agents for Crohn Disease

	Clinical Response	Clinical Remission	Cortico-Steroid-Free Remission	PRO-2 Remission	Quality of Life	Clinical Improve-ment	Functional Capacity	Overall AEs	With-drawal due to AEs	SAEs	Injection-Site Reaction	Serious Infections	Oppor-tunistic Infections
Adalimumab vs. Infliximab					●○○○	●●○○		●○○○	●○○○	●○○○	●○○○	●○○○	
Certolizumab pegol vs. Adalimumab												●○○○	
Infliximab vs. Certolizumab pegol												●○○○	
Ustekinumab vs. Adalimumab	●●●○	●●●○	●●●○	●●●○				●●●●	●●○○	●●●○	●●○○	●○○○	●○○○
Vedolizumab vs. TNF-α inhibitors												●○○○	●○○○

Color Key: ***favors first TIM***; ***favors second TIM***; ***no significant differences***.

GRADE Certainty of Evidence: no evidence *(blank)*; very low ●○○○; low ●●○○; moderate ●●●○; high ●●●●

Pipeline TIMs in Crohn Disease

Evidence

- Brazikumab (MEDI2070) vs. placebo (1 moderate-RoB RCT)
- Guselkumab vs. placebo (1 high-RoB RCT)
- Guselkumab vs. ustekinumab (1 high-RoB RCT)
- Mirikizumab vs. placebo (1 moderate-RoB RCT)

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Pipeline TIMs in Crohn Disease

Findings – Brazikumab (MEDI2070) vs. Placebo

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- **Clinical response (1 RCT; N = 121);** GRADE: Low
  - No difference between groups (37% vs. 28%) at 12 weeks
- **Clinical remission (1 RCT; N = 121);** GRADE: Low
  - No difference between groups (20% vs. 13%) at 12 weeks
- **Overall AEs (1 RCT; N = 121);** GRADE: Moderate
  - No difference between groups (68% vs. 68%) at 12 weeks
- **SAEs (1 RCT; N = 121);** GRADE: Low
  - No difference between groups (9% vs. 8%) at 12 weeks
- **Withdrawals due to AEs (1 RCT; N = 121);** GRADE: Low
  - No difference between groups (9% vs. 10%) at 12 weeks
- **Serious infections (1 RCT; N = 121);** GRADE: Low
  - No difference between groups (7% vs. 12%) at 12 weeks

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Pipeline TIMs in Crohn Disease

Findings – Guselkumab vs. Placebo

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- **Clinical response (1 RCT; N = 246); GRADE: Low**
  - Higher incidence with guselkumab (200 mg: 71%; 600 mg: 67%; 1,200 mg: 61%) compared to placebo (25%) at 12 weeks
- **Clinical remission (1 RCT; N = 246); GRADE: Low**
  - Higher incidence with guselkumab (200 mg: 57%; 600 mg: 56%; 1,200 mg: 46%) compared to placebo (16%) at 12 weeks
- **PRO-2 remission (1 RCT; N = 246); GRADE: Low**
  - Higher incidence with guselkumab (200 mg: 44%; 600 mg: 51%; 1,200 mg: 33%) compared to placebo (16%) at 12 weeks
- **Quality of life (1 RCT; IBDQ score > 170; N = 246); GRADE: Low**
  - Larger improvement with guselkumab (200 mg: 56%; 600 mg: 51%; 1,200 mg: 46%) compared to placebo (23%) at 12 weeks

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Pipeline TIMs in Crohn Disease

Findings – Guselkumab vs. Placebo

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- **Overall AEs (1 RCT; N = 246); GRADE: Low**
  - Lower incidence with guselkumab 1,200-mg dosage (42.5%) compared to placebo (60.0%); no difference with guselkumab 200 (43.8%) and 1,000-mg dosage (50.7%) at 12 weeks
- **SAEs (1 RCT; N = 246); GRADE: Very Low**
  - No differences between groups (guselkumab 200 mg: 4.1%; 600 mg: 5.5%; 1,200 mg: 1.4% vs. placebo: 5.7%) at 12 weeks
- **Withdrawals due to AEs (1 RCT; N = 246); GRADE: Very Low**
  - No differences between groups (guselkumab 200 mg: 1.4%; 600 mg: 0.0%; 1,200 mg: 1.4% vs. placebo: 2.9%) at 12 weeks
- **Serious infections (1 RCT; N = 246); GRADE: Very Low**
  - No differences between groups (guselkumab 200 mg: 1.4%; 600 mg: 2.7%; 1,200 mg: 0.0% vs. placebo: 0.0%) at 12 weeks
- **Opportunistic infections (1 RCT; N = 246); GRADE: Very Low**
  - No differences between groups (200 mg: 0.0%; 600 mg: 0.0%; 1,200 mg: 0.0% vs. placebo: 0.0%) at 12 weeks

Blue header field indicates new study.

Pipeline TIMs in Crohn Disease

Findings – Guselkumab vs. Ustekinumab

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- **Clinical response (1 RCT; N = 248); GRADE: Low**
  - No difference between groups (guselkumab 200 mg: 71%; 600 mg: 67%; 1,200 mg: 61% vs. ustekinumab: 67%) at 12 weeks
- **Clinical remission (1 RCT; N = 248); GRADE: Low**
  - No difference between groups (guselkumab 200 mg: 57%; 600 mg: 56%; 1,200 mg: 46% vs. ustekinumab: 46%) at 12 weeks
- **PRO-2 remission (1 RCT; N = 248); GRADE: Low**
  - No difference between groups (guselkumab 200 mg: 44%; 600 mg: 51%; 1,200 mg: 33% vs. ustekinumab: 40%) at 12 weeks
- **Quality of life (1 RCT; IBDQ score > 170; N = 248); GRADE: Low**
  - No difference between groups (guselkumab 200 mg: 56%; 600 mg: 51%; 1,200 mg: 46% vs. ustekinumab: 51%) at 12 weeks

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Pipeline TIMs in Crohn Disease

Findings – Guselkumab vs. Ustekinumab

- **Overall AEs (1 RCT; N = 248); GRADE: Low**
  - No difference between groups (guselkumab 200 mg: 43.8%; 600 mg: 50.7%; 1,200 mg: 42.5% vs. ustekinumab: 50.7%) at 12 weeks
- **SAEs (1 RCT; N = 248); GRADE: Very Low**
  - No difference between groups (guselkumab 200 mg: 4.1%; 600 mg: 5.5%; 1,200 mg: 1.4% vs. ustekinumab: 5.6%) at 12 weeks
- **Withdrawals due to AEs (1 RCT; N = 248); GRADE: Very Low**
  - No difference between groups (guselkumab 200 mg: 1.4%; 600 mg: 0.0%; 1,200 mg: 1.4% vs. ustekinumab: 0.0%) at 12 weeks
- **Serious infections (1 RCT; N = 248); GRADE: Very Low**
  - No difference between groups (guselkumab 200 mg: 1.4%; 600 mg: 2.7%; 1,200 mg: 0.0% vs. ustekinumab: 1.4%) at 12 weeks
- **Opportunistic infections (1 RCT; N = 248); GRADE: Very Low**
  - No differences between groups (guselkumab 200 mg: 0.0%; 600 mg: 0.0%; 1,200 mg: 0.0% vs. placebo: 0.0%) at 12 weeks

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Blue header field indicates new study.

Pipeline TIMs in Crohn Disease

Findings – Mirikizumab vs. Placebo

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- **Clinical response (1 RCT; N = 191);** GRADE: Low
  - Higher incidence with mirikizumab (200 mg: 48.4%; 600 mg: 56.3%; 1,000 mg: 42.2%) compared to placebo (34.5%) at 12 weeks
- **PRO-2 response (1 RCT; N = 191);** GRADE: Low
  - Higher incidence with mirikizumab (200 mg: 61.3%; 600 mg: 68.8%; 1,000 mg: 60.9%) compared to placebo (35.9%) at 12 weeks
- **Clinical remission (1 RCT; N = 191);** GRADE: Low
  - Higher incidence for mirikizumab 600 mg (40.6%) and 1,000 mg dosage (26.6%), but not for 200 mg dosage (16.1%), compared to placebo (9.4%) at 12 weeks
- **PRO-2 remission (1 RCT; N = 191);** GRADE: Low
  - Higher incidence for mirikizumab 600 mg (28.1%) but not for 200 mg (12.9%) or 1,000 mg dosage (21.9%), compared to placebo (6.3%) at 12 weeks
- **Quality of life (1 RCT; IBDQ score change from baseline; N = 191);** GRADE: Low
  - Larger improvement with all dosages mirikizumab compared to placebo (values NR) at 12 weeks

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Pipeline TIMs in Crohn Disease

Findings – Mirikizumab vs. Placebo

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- **Overall AEs (1 RCT; N = 191); GRADE: Low**
  - No differences between groups (mirikizumab 200 mg: 58.1%; 600 mg: 65.6%; 1,200 mg: 65.6% vs. placebo: 70.3%) at 12 weeks
- **SAEs (1 RCT; N = 191); GRADE: Low**
  - No differences between groups (mirikizumab 200 mg: 0.0%; 600 mg: 9.4%; 1,200 mg: 3.1% vs. placebo: 10.9%) at 12 weeks
- **Withdrawals due to AEs (1 RCT; N = 191); GRADE: Very Low**
  - No differences between groups (mirikizumab 200 mg: 3.2%; 600 mg: 9.4%; 1,200 mg: 0.0% vs. placebo: 6.3%) at 12 weeks

Blue header field indicates new study.

Findings

Ulcerative Colitis

Ulcerative Colitis: Efficacy and/or Harms

4 RCTs and 8 cohort studies including 4 head-to-head comparisons

	Adalimumab	Certolizumab pegol	Golimumab	Infliximab	Natalizumab	Ozanimob	Risankizumab	Tofacitinib	TNF-α inhibitors	Upadacitinib	Ustekinumab	Vedolizumab
Adalimumab				2 cohorts								
Certolizumab pegol												
Golimumab												
Infliximab												
Natalizumab												
Ozanimob												
Risankizumab												
Tofacitinib									1 cohort			
TNF-α inhibitors												
Upadacitinib												
Ustekinumab												
Vedolizumab	1 RCT								1 cohort 2 cohorts 1 cohort			

High-RoB Study

Moderate-RoB Study

Low-RoB Study

New Studies

KQ1: Comparative Effectiveness in Ulcerative Colitis

Evidence

- 1 moderate-RoB RCT comparing vedolizumab to adalimumab

Findings – Vedolizumab vs. Adalimumab

- **Clinical remission (1 RCT; N = 769); GRADE: Moderate**
  - Higher incidence with vedolizumab (ARD, 8.8%; 95% CI, 2.5% to 15.0%) at 52 weeks
- **Corticosteroid-free remission (1 RCT; N = 769); GRADE: Low**
  - No difference between groups (ARD, -9.3%; 95% CI, -18.9% to 0.4%) at 52 weeks
- **Quality of life (1 RCT; N = 769); GRADE: Moderate**
  - Larger improvement with vedolizumab (ARD, 9.6%; 95% CI, 2.8% to 16.5%) at 52 weeks

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KQ2: Comparative Harms in Ulcerative Colitis

Evidence

- Infliximab vs. adalimumab (2 moderate-RoB cohort studies)
- Tofacitinib vs. TNF-α inhibitors (1 high-RoB cohort study)
- Vedolizumab vs. adalimumab (1 high-RoB RCT)
- Vedolizumab vs. TNF-α inhibitors (1 high-, 2 moderate-, and 1 low-RoB cohort studies)

Findings – Infliximab vs. Adalimumab

- **Serious infections (1 RCT; N = 1,960); GRADE: Very Low**
  - No difference between groups (aHR, 0.62; 95% CI, 0.29 to 1.34)

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KQ2: Comparative Harms in Ulcerative Colitis

Findings – Tofacitinib vs. TNF-α inhibitors

- **Serious infections (1 cohort study; N = 5,577);** GRADE: Very Low
  - Lower incidence with tofacitinib (IR, 1.75 vs. 3.33)
- **Opportunistic infections (1 cohort study; N = 5,577);** GRADE: Very Low
  - Lower incidence with tofacitinib (IR, 0.16 vs. 1.45)

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Blue header field indicates new study.

KQ2: Comparative Harms in Ulcerative Colitis

Findings – Vedolizumab vs. Adalimumab

- **Overall AEs (1 RCT; N = 769); GRADE: Moderate**
  - No difference between groups (RR, 0.91; 95% CI, 0.82 to 1.003)
- **SAEs (1 RCT; N = 769); GRADE: Low**
  - No difference between groups (RR, 0.80; 95% CI, 0.55 to 1.17)
- **Withdrawals due to AE (1 RCT; N = 769); GRADE: Low**
  - No difference between groups (RR, 0.69; 95% CI, 0.38 to 1.25)
- **Infections (1 RCT; N = 769); GRADE: Low**
  - No difference between groups (34.6/100 PY vs. 23.4/100 PY)

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KQ2: Comparative Harms in Ulcerative Colitis

Findings – Vedolizumab vs. TNF-α inhibitors

- **SAEs (1 cohort study; N = 604); GRADE: Very Low**
  - Lower incidence with vedolizumab (HR, 0.37; 95% CI, 0.21 to 0.63)
- **Serious infections (4 cohort studies; N = 21,786); GRADE: Very Low**
  - Lower incidence with vedolizumab (HR, 0.68; 95% CI, 0.50 to 0.93)
- **Opportunistic infections requiring hospitalization (1 cohort study; N = 2,621); GRADE: Very Low**
  - No difference between groups (IRR, 0.48; 95% CI, 0.09 to 1.63)

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Efficacy and Harms of TIM Agents for Ulcerative Colitis

	Clinical Response	Clinical Remission	Cortico-steroid-Free Remission	PRO-2 Remission	Quality of Life	Clinical Improvement	Functional Capacity	Overall AEs	SAEs	Withdrawal due to AEs	Injection-Site Reaction	Serious Infections	Oppor-tunistic Infections
Infliximab vs. Adalimumab											●○○○	●○○○	
Tofacitinib vs. TNF-α inhibitors												●○○○	●○○○
Vedolizumab vs. Adalimumab		●●●○	●●○○		●●●○			●●●○	●●○○	●●○○		●○○○	
Vedolizumab vs. TNF-α inhibitors									●○○○			●○○○	●○○○

Color Key: ***favors first TIM***; ***favors second TIM***; ***no significant differences***.

GRADE Certainty of Evidence: no evidence *(blank)*; very low ●○○○; low ●●○○; moderate ●●●○; high ●●●●

Pipeline TIMs in Ulcerative Colitis

Evidence

- Etrasimod vs. placebo (1 moderate-RoB RCT)
- Filgotinib vs. placebo (1 high-RoB RCT)
- Mirikizumab vs. placebo (1 moderate-RoB RCT)

Pipeline TIMs in Ulcerative Colitis

Findings – Etrasimod vs. Placebo

- **Clinical response (1 RCT; N = 156);** GRADE: Low
  - Higher incidence with etrasimod 2 mg (50.6%) but not with etrasimod 1 mg (43.7%), compared to placebo (32.5%) at 12 weeks
- **Clinical remission (1 RCT; N = 156);** GRADE: Low
  - Higher incidence with etrasimod 2 mg (33%) but not with etrasimod 1 mg (16%), compared to placebo (8.1%) at 12 weeks
- **Improvement in the total MCS (1 RCT; N = 156);** GRADE: Low
  - Higher improvement with etrasimod 2 mg (3.35) but not with etrasimod 1 mg (2.69), compared to placebo (2.08) at 12 weeks

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Blue header field indicates new study.

Pipeline TIMs in Ulcerative Colitis

Findings – Etrasimod vs. Placebo

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- **Overall AEs (1 RCT; N = 156);** GRADE: Low
  - No difference between groups (etrasimod 1 mg: 59.6%; 2 mg: 56% vs. placebo: 50%) at 12 weeks
- **SAEs (1 RCT; N = 156);** GRADE: Very Low
  - No difference between groups (etrasimod 1 mg: 5.8%; 2 mg: 0% vs. placebo: 11.1%) at 12 weeks
- **Withdrawals due to AEs (1 RCT; N = 156);** GRADE: Very Low
  - No difference between groups (etrasimod 1 mg: 5.8%; 2 mg: 8% vs. placebo: 0%) at 12 weeks
- **Serious infections (1 RCT; N = 156);** GRADE: Very Low
  - No difference between groups (etrasimod 1 mg: 1.9%; 2 mg: 0% vs. placebo: 0%) at 12 weeks

Blue header field indicates new study.

Pipeline TIMs in Ulcerative Colitis

Findings – Filgotinib vs. Placebo

Report Pages 38, 39

- **Clinical response (1 RCT; N = 571); GRADE: Very Low**
  - Higher incidence with filgotinib 100 mg (23.8% vs. 13.5%) and with filgotinib 200 mg (37.2% vs. 11.2%) compared to placebo at 58 weeks
- **Corticosteroid-free clinical remission (1 RCT; N = 571); GRADE: Very Low**
  - Higher incidence with filgotinib 200 mg (27.2% vs. 6.4%) but not with filgotinib 100 mg (13.6% vs. 5.4%), compared to placebo at 58 weeks
- **Quality of life (1 RCT; EuroQoL EQ-5D; N = 571); GRADE: Low**
  - Larger improvement with filgotinib 200 mg (3 vs. -3) but not with filgotinib 100 mg (-1 vs. -2), compared to placebo at 58 weeks

Blue header field indicates new study.

Pipeline TIMs in Ulcerative Colitis

Findings – Filgotinib vs. Placebo

Report Pages 38, 39

- **Overall AEs (1 RCT; N = 571); GRADE: Low**
  - No difference between groups (filgotinib 100 mg: 60.3% vs. placebo: 65.9%; filgotinib 200 mg: 66.8% vs. placebo: 59.6%) at 58 weeks
- **SAEs (1 RCT; N = 571); GRADE: Very Low**
  - No difference between groups (filgotinib 100 mg: 4.5% vs. placebo: 7.7%; filgotinib 200 mg: 4.5% vs. placebo: 0%) at 58 weeks
- **Withdrawals due to AEs (1 RCT; N = 571); GRADE: Very Low**
  - No difference between groups (filgotinib 100 mg: 5.6% vs. placebo: 4.4%; filgotinib 200 mg: 3.5% vs. placebo: 2.0%) at 58 weeks
- **Serious infections (1 RCT; N = 571); GRADE: Very Low**
  - No difference between groups (filgotinib 100 mg: 1.7% vs. placebo: 2.2%; filgotinib 200 mg: 1.0% vs. placebo: 0%) at 58 weeks
- **Opportunistic infections (1 RCT; N = 571); GRADE: Very Low**
  - No difference between groups (filgotinib 100 mg: 0% vs. placebo: 0%; filgotinib 200 mg: 0% vs. placebo: 0%) at 58 weeks

Blue header field indicates new study.

Pipeline TIMs in Ulcerative Colitis

Findings – Mirikizumab vs. Placebo

Report Page 39

- **Clinical response (1 RCT; N = 249);** GRADE: Low
  - Higher incidence with mirikizumab (50 mg: 41.3%; 200 mg: 59.7%; 600 mg: 49.2%), compared to placebo (20.6%) at 12 weeks
- **Clinical remission (1 RCT; N = 249);** GRADE: Low
  - Higher incidence with mirikizumab 200 mg (22.6%) but not for other dosages (50 mg: 15.9%; 600 mg: 11.5%), compared to placebo (4.8%) at 12 weeks
- **Symptomatic remission (1 RCT; N = 249);** GRADE: Low
  - Higher incidence with mirikizumab 200 mg (58.1%) and 600 mg dosage (45.9%) but not 50 mg dosage (36.5%), compared to placebo (20.6%) at 12 weeks
- **Quality of life (1 RCT; IBDQ score; N = 249);** GRADE: Low
  - Larger improvement with mirikizumab 200 mg (38.1) and 600 mg dosage (43.8) but not 50 mg dosage (31.3), compared to placebo (19.9) at 12 weeks

Blue header field indicates new study.

Pipeline TIMs in Ulcerative Colitis

Findings – Mirikizumab vs. Placebo

- **Overall AEs (1 RCT; N = 249); GRADE: Low**
  - No difference between groups (mirikizumab 50 mg: 57.1%; 200 mg: 51.6%; 600 mg: 53.3% vs. placebo: 50.8%) at 12 weeks
- **SAEs (1 RCT; N = 249); GRADE: Very Low**
  - No difference between groups (mirikizumab 50 mg: 0%; 200 mg: 3.2%; 600 mg: 5.0% vs. placebo: 3.2%) at 12 weeks
- **Withdrawals due to AEs (1 RCT; N = 249); GRADE: Very Low**
  - No difference between groups (mirikizumab 50 mg: 0%; 200 mg: 1.6%; 600 mg: 3.3% vs. placebo: 4.8%) at 12 weeks

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Blue header field indicates new study.

Findings

Mixed Population (Crohn Disease or Ulcerative Colitis)

OHSU

Mixed Population: Efficacy and/or harms

3 cohort studies including 10 head-to-head comparisons

	Adalimumab	Certolizumab pegol	Golimumab	Infliximab	Natalizumab	Ozanimod	Risankizumab	Tofacitinib	TNF-α inhibitors	Upadacitinib	Ustekinumab	Vedolizumab
Adalimumab				1 cohort								
Certolizumab pegol												
Golimumab												
Infliximab												
Natalizumab												
Ozanimod												
Risankizumab												
Tofacitinib									1 cohort			
TNF-α inhibitors												
Upadacitinib												
Ustekinumab	1 cohort			1 cohort				1 cohort	2 cohorts			
Vedolizumab	1 cohort			1 cohort					1 cohort		1 cohort	

High-RoB Study

Moderate-RoB Study

Low-RoB Study

New Studies

KQ1: Comparative Effectiveness in Mixed Population

Evidence

- No evidence

KQ2: Comparative Harms in Mixed Population

Evidence

- Adalimumab vs. infliximab (1 moderate-RoB cohort study)
- Tofacitinib vs. TNF-α inhibitors (1 moderate-RoB cohort study)
- Ustekinumab vs. adalimumab (1 moderate-RoB cohort study)
- Ustekinumab vs. infliximab (1 moderate-RoB cohort study)
- Ustekinumab vs. TNF-α inhibitors (2 moderate-RoB cohort studies)
- Ustekinumab vs. tofacitinib (1 moderate-RoB cohort study)
- Vedolizumab vs. adalimumab (1 moderate-RoB cohort study)
- Vedolizumab vs. infliximab (1 moderate-RoB cohort study)
- Vedolizumab vs. ustekinumab (1 moderate-RoB cohort study)
- Vedolizumab vs. TNF-α inhibitors (1 high-, 2 moderate-, and 1 low-RoB cohort studies)

KQ2: Comparative Harms in Mixed Population

Findings – Adalimumab vs. Infliximab

- **Serious infections (1 cohort study; N = 1,575); GRADE: Very Low**
  - No difference between groups (HR, 1.06; 95% CI, 0.77 to 1.46)

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Findings – Tofacitinib vs. TNF-α inhibitors

- **Serious infections (1 cohort study; N = 1,575); GRADE: Very Low**
  - No difference between groups (HR, 0.59; 95% CI, 0.27 to 1.05)

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Findings – Ustekinumab vs. Adalimumab

- **Serious infections (1 cohort study; N = 1,575); GRADE: Very Low**
  - No difference between groups (HR, 1.31; 95% CI, 0.65 to 2.66)

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Blue header field indicates new study.

KQ2: Comparative Harms in Mixed Population

Findings – Ustekinumab vs. Infliximab

- **Serious infections (1 cohort study; N = 1,575); GRADE: Very Low**
  - No difference between groups (HR, 1.39; 95% CI, 0.69 to 2.81)

Report Page 44

Findings – Ustekinumab vs. TNF-α inhibitors

- **Serious infections (1 cohort study; N = 23,091); GRADE: Very Low**
  - No difference between groups (HR, 0.84; 95% CI, 0.66 to 1.03)

Report Page 44

Findings – Ustekinumab vs. Tofacitinib

- **Serious infections (1 cohort study; N = 21,516); GRADE: Very Low**
  - No difference between groups (4.3% vs. 5.6%)

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Blue header field indicates new study.

KQ2: Comparative Harms in Mixed Population

Findings – Vedolizumab vs. Adalimumab

- **Serious infections (1 cohort study; N = 1,575); GRADE: Very Low**
  - No difference between groups (HR, 1.52; 95% CI, 0.99 to 2.33)

Report Page 44

Findings – Vedolizumab vs. Infliximab

- **Serious infections (1 cohort study; N = 1,575); GRADE: Very Low**
  - Lower incidence of serious infections with vedolizumab (HR, 1.61; 95% CI, 1.06 to 2.45)

Report Page 44

Findings – Vedolizumab vs. Ustekinumab

- **Serious infections (1 cohort study; N = 1,575); GRADE: Very Low**
  - No difference between groups (HR, 1.16; 95% CI, 0.58 to 2.33)

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Blue header field indicates new study.

KQ2: Comparative Harms in Mixed Population

Findings – Vedolizumab vs. TNF-α inhibitors

- **Serious infections (1 cohort study; N = 1,575); GRADE: Very Low**
  - No difference between groups (HR, 1.36; 95% CI, 0.69 to 2.71)

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Blue header field indicates new study.

Pipeline TIMs in Mixed Population

Evidence

- No evidence

Efficacy and Harms of TIM Agents for Mixed Population

	Clinical Response	Clinical Remission	Cortico-steroid-Free Remission	PRO-2 Remission	Quality of Life	Clinical Improve-ment	Functional Capacity	Overall AEs	SAEs	With-drawal due to AEs	Injection-Site Reaction	Serious Infections	Oppor-tunistic Infections
Adalimumab vs. Infliximab												●○○○	
Tofacitinib vs. TNF-α inhibitors												●○○○	
Ustekinumab vs. Adalimumab												●○○○	
Ustekinumab vs. Infliximab												●○○○	
Ustekinumab vs. TNF-α inhibitors												●○○○	
Ustekinumab vs. Tofacitinib												●○○○	
Vedolizumab vs. Adalimumab												●○○○	
Vedolizumab vs. Infliximab												●○○○	
Vedolizumab vs. Ustekinumab												●○○○	
Vedolizumab vs. TNF-α inhibitors												●○○○	

Color Key: favors first TIM; favors second TIM; no significant differences.

GRADE Certainty of Evidence: no evidence *(blank)*; very low ●○○○; low ●●○○; moderate ●●●○; high ●●●●

Indirect Evidence (KQ1 and KQ2)

Report Pages 56, 57

- 1 recent network meta-analyses for TIM agents for Crohn disease
- 2 recent network meta-analysis for TIM agents for ulcerative colitis
- Details can be found in the full report

Ongoing Studies

KQ 3: Ongoing Studies Summary

Report Pages 48-55

- 29 studies (28 new for this update)
  - 25 RCTs
  - 4 cohort studies
- Crohn disease
  - 7 RCTs
- Ulcerative colitis
  - 18 RCTs
  - 1 cohort study
- Crohn disease and ulcerative colitis
  - 3 cohort study
- Earliest completion date at the end of 2023 (1 study); 6 previously included studies were completed but not published yet

Discussion

Limitations

- Limited number of studies
- RCTs not powered for harm outcomes; cohort studies have methodological limitations
- Drug manufacturers sponsored all the eligible RCTs
- Most cohort studies used administrative or claims data
- This review did not include:
  - RCTs shorter than 12 weeks
  - Cohort studies with fewer than 1,000 participants
  - Data from conference abstracts or press releases
  - Studies published in languages other than English

Conclusions

- For Crohn disease, evidence is limited to 3 RCTs and 8 cohort studies:
  - Evidence addresses 5 comparisons (out of 21 possible comparisons)
  - No differences in efficacy and harms between ustekinumab and adalimumab
  - Exception: higher risk for injection-site reactions for adalimumab
  - Very low CoE for all other comparisons

Conclusions

- For ulcerative colitis, evidence is limited to 4 RCTs and 6 cohort studies:
  - Evidence addresses 4 comparisons (out of 28 possible comparisons)
  - Greater effectiveness with no differences in harms for vedolizumab than adalimumab
  - Very low CoE for all other comparisons

Conclusions

- 29 ongoing studies: 25 RCTs and 4 cohort studies

✓ 7 RCTs on Crohn disease

✓ 18 RCTs and 1 cohort study on ulcerative colitis

✓ 3 cohort studies on either Crohn disease or ulcerative colitis

Questions?

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Instruments Used to Measure Outcomes in Trials of TIMs for Crohn Disease and Ulcerative Colitis

Abbreviation	Name	Condition(s) Used In	General Description	Range and Direction
CDAI	Crohn Disease Activity Index	CD	Eight clinical factors, each summed after adjustment with a weighting factor. These include: • Number of liquid or soft stools each day for 7 days x 2 • Abdominal pain (graded from 0-3 on severity) each day for 7 days x 5 • General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days x 7 • Presence of complications x 20 • Taking Lomotil or opiates for diarrhea x 30 • Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite) x 10 • Absolute deviation of hematocrit from 47% in men and 42% in women x 6 • Percentage deviation from standard weight x 1	Lower numbers are better; values of 150 and less equal minimal disease; values above 150 equal active disease, and values above 450 equal extremely severe disease; CDAI 70 represents a decrease of 70 points or more.
CDEIS	Crohn Disease Endoscopy Index of Severity	CD	Segment score averaged over segments on which data were available, ulcerated stenosis in any segment, and nonulcerated stenosis in any segment.	0-44, lower is better
EQ-5D	EuroQoL 5-Dimension Assessment Instrument	All	Descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can take 1 of 3 responses. The responses record 3 levels of severity (no problems/some or moderate problems/extreme problems) within a particular EQ-5D dimension.	0-1, higher is better
IBDQ	Inflammatory Bowel Disease Questionnaire	CD and UC	32 questions grouped into 4 domains: bowel symptoms, systemic symptoms, emotional functioning, and social functioning	0-7, higher is better

Instruments Used to Measure Outcomes in Trials of TIMs for Crohn Disease and Ulcerative Colitis

Abbreviation	Name	Condition(s) Used In	General Description	Range and Direction
MCS	Mayo Clinic scores	UC	This score comprises 4 subscores each scored either 0, 1, 2, or 3. The subscores include rectal bleeding (RB), stool frequency (SF), physician's global assessment (PGA), and endoscopy (ENDO) subscore.	0-12, higher is more severe
PRO-2	Patient-Reported Outcome 2	CD and UC	Includes an evaluation of stool frequency (SF) and rectal bleeding (RB) subscores during 3 consecutive days a week before colonoscopy.	For the SF subscore: 0 (normal level of stools), 1 (1-2 stools more than normal), 2 (3-4 stools more than normal, and 3 (5 or more stools more than normal). For the RB subscore: 0 (no seen blood), 1 (streaks of blood with the stool less than half the time), 2 (obvious blood with the stool most of the time) and 3 (blood alone passed). Overall 0-6, higher is more severe.
SES-CD score	Simple Endoscopic Score for Crohn Disease	CD	A score assessing the following subgroups: size of mucosal ulcers, the ulcerated surface, the endoscopic extension and the presence of stenosis.	0-3 for each subgroup. Overall: 0-2 (remission), 3-6 (mild endoscopic activity), 7-15 (moderate endoscopic activity), >15 (severe endoscopic activity).
SF-36	Short-Form 36	CD and UC	A patient-reported survey of patient health including the following subgroups: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health or emotional wellbeing.	Subgroups are measured on a scale of 0-100, each carrying equal weight. A score of 0 is maximum disability whereas a score of 100 is equivalent to no disability.

GRADE: Quality of Evidence Summary

Comparative Effectiveness and Harms – Crohn Disease

Outcome	Certainty of Evidence	Relationship	Rationale
Adalimumab vs. Infliximab			
Clinical improvement (1 RCT) at 52 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Quality of life (1 RCT) at 54 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 2 levels for very serious imprecision
Overall AEs (1 RCT) at 54 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 2 levels for very serious imprecision
Withdrawal due to AEs (1 RCT) at 54 weeks	Very low ●○○○	No difference between groups	
SAEs (1 RCT) at 54 weeks	Very low ●○○○	No difference between groups	
Injection-site reactions (1 RCT) at 54 weeks	Very low ●○○○	Higher incidence with adalimumab	Downgraded 1 level for indirectness and 3 levels for extremely serious imprecision
Serious infections (2 cohort studies)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 2 levels for very serious imprecision
Certolizumab pegol vs. Adalimumab			
Serious infections (1 cohort study) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 2 levels for very serious imprecision
Infliximab vs. Certolizumab pegol			
Serious infections (1 cohort study) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 2 levels for very serious imprecision

GRADE: Quality of Evidence Summary

Comparative Effectiveness and Harms – Crohn Disease

Ustekinumab vs. Adalimumab			
Clinical response (1 RCT) at 52 weeks	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Clinical remission (1 RCT) at 52 weeks	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Corticosteroid-free remission (1 RCT) at 52 weeks	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
PRO-2 remission (1 RCT) at 52 weeks	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Overall AEs (1 RCT) at 52 weeks	High ●●●●	No difference between groups	Not downgraded
SAEs (1 RCT) at 52 weeks	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
Withdrawal due to adverse events (1 RCT) at 52 weeks	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Injection site reactions (1 RCT) at 52 weeks	Low ●●○○	Lower incidence with ustekinumab	Downgraded 2 levels for very serious imprecision
Serious infections (1 RCT) at 52 weeks	Very low ●○○○	No difference between groups	Downgraded 3 levels for extremely serious imprecision
Opportunistic infections (1 RCT) at 52 weeks	Very low ●○○○	No difference between groups	Downgraded 3 levels for extremely serious imprecision
Vedolizumab vs. TNF-α inhibitors			
Serious infections (5 cohort studies)	Very low ●○○○	No difference between groups	Downgraded 1 level for inconsistency
Opportunistic infections (1 cohort study)	Very low ●○○○	No difference between groups	Downgraded 1 level for imprecision

GRADE: Quality of Evidence Summary

Pipeline Agent Effectiveness and Harms – Crohn Disease

Outcome	Certainty of Evidence	Relationship	Rationale
Brazikumab (MEDI2070) vs. Placebo			
Clinical response (1 RCT[17]) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Clinical remission (1 RCT[17]) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Overall AEs (1 RCT[17]) at 12 weeks	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs (1 RCT[17]) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Withdrawals due to AE (1 RCT[17]) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Serious infections (1 RCT[17]) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Guselkumab vs. Placebo			
Clinical response (1 RCT[16]) at 12 weeks	Low ●●○○	Higher incidence with guselkumab (all dosages)	Downgraded 1 level for study limitations and 1 level for imprecision
Clinical remission (1 RCT[16]) at 12 weeks	Low ●●○○	Higher incidence with guselkumab (all dosages)	Downgraded 1 level for study limitations and 1 level for imprecision
PRO-2 remission (1 RCT[16]) at 12 weeks	Low ●●○○	Higher incidence with guselkumab (all dosages)	Downgraded 1 level for study limitations and 1 level for imprecision
Quality of life (1 RCT[16]) at 12 weeks	Low ●●○○	Higher incidence with guselkumab (all dosages)	Downgraded 1 level for study limitations and 1 level for imprecision
Overall AEs (1 RCT[16]) at 12 weeks	Low ●●○○	Higher incidence with guselkumab 1,200 mg; no difference for other dosages	Downgraded 1 level for study limitations and 1 level for imprecision
SAEs (1 RCT[16]) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Withdrawal due to AEs (1 RCT[16]) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 3 levels for extremely serious imprecision
Serious infections (1 RCT[16]) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 3 levels for extremely serious imprecision
Opportunistic infections (1 RCT[16]) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 3 levels for extremely serious imprecision

GRADE: Quality of Evidence Summary

Pipeline Agent Effectiveness and Harms – Crohn Disease

Guselkumab vs. Ustekinumab			
Clinical response (1 RCT) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
Clinical remission (1 RCT) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
PRO-2 remission (1 RCT) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
Quality of life (1 RCT) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
Overall AEs (1 RCT) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for imprecision
SAEs (1 RCT) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Withdrawal due to AEs (1 RCT) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 3 levels for extremely serious imprecision
Serious infections (1 RCT) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 3 levels for extremely serious imprecision
Opportunistic infections (1 RCT) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and 3 levels for extremely serious imprecision
Mirikizumab vs. Placebo			
Clinical response (1 RCT) at 12 weeks	Low ●●○○	Higher incidence with mirikizumab (all dosages)	Downgraded 2 levels for very serious imprecision
PRO-2 response (1 RCT) at 12 weeks	Low ●●○○	Higher incidence with mirikizumab (all dosages)	Downgraded 2 levels for very serious imprecision
Clinical remission (1 RCT) at 12 weeks	Low ●●○○	Higher incidence with mirikizumab 600 mg and 1,000 mg; no difference for mirikizumab 200 mg	Downgraded 2 levels for very serious imprecision
PRO-2 remission (1 RCT) at 12 weeks	Low ●●○○	Higher incidence with mirikizumab 600 mg; no difference for other dosages	Downgraded 2 levels for very serious imprecision
Quality of life (1 RCT) at 12 weeks	Low ●●○○	Higher incidence with mirikizumab (all dosages)	Downgraded 2 levels for very serious imprecision
Overall AEs (1 RCT) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
SAEs (1 RCT) at 12 weeks	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Withdrawal due to AEs (1 RCT) at 12 weeks	Very low ●○○○	No difference between groups	Downgraded 3 levels for extremely serious imprecision

GRADE: Quality of Evidence Summary

Comparative Effectiveness and Harms – Ulcerative Colitis

Outcome	Certainty of Evidence	Relationship	Rationale
Infliximab vs. Adalimumab			
Injection site reaction (1 cohort)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Serious infections (2 cohort studies)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Tofacitinib vs. TNF-α inhibitors			
Serious infection (1 cohort study)	Very low ●○○○	Lower incidence rate with tofacitinib	Downgraded 1 level for study limitations and 1 level for imprecision
Opportunistic infections (1 cohort study)	Very low ●○○○	Lower incidence rate with tofacitinib	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Vedolizumab vs. Adalimumab			
Clinical remission at 52 weeks (1 RCT)	Moderate ●●●○	Higher incidence with vedolizumab	Downgraded 1 level for imprecision
Corticosteroid-free remission[a] at 52 weeks (1 RCT)	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Quality of life at 52 weeks (1 RCT)	Moderate ●●●○	Larger improvement with vedolizumab	Downgraded 1 level for imprecision
Overall AEs at 52 weeks (1 RCT)	Moderate ●●●○	No difference between groups	Downgraded 1 level for imprecision
SAEs at 52 weeks (1 RCT)	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Withdrawals due to AEs at 52 weeks (1 RCT)	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
Serious infections at 52 weeks (1 RCT)	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision

GRADE: Quality of Evidence Summary
Comparative Effectiveness and Harms – Ulcerative Colitis

Outcome	Certainty of Evidence	Relationship	Rationale
Vedolizumab vs. TNF-α inhibitors			
SAEs (1 cohort study)	Very low ●○○○	Lower incidence with vedolizumab	Downgraded 1 level for study limitations and 2 levels for very serious imprecision
Serious infections (4 cohort studies)	Very low ●○○○	Lower incidence with vedolizumab	Downgraded 1 level for inconsistency
Opportunistic infections (1 cohort study)	Very low ●○○○	No difference between groups	Downgraded 2 levels for very serious imprecision

GRADE: Quality of Evidence Summary

Pipeline Agent Effectiveness and Harms – Ulcerative Colitis

Outcome	Certainty of Evidence	Relationship	Rationale
Etrasimod vs. Placebo			
Clinical response at 12 weeks (1 RCT)	Low ●●○○	Higher incidence with etrasimod 2 mg but not with etrasimod 1 mg	Downgraded 2 levels for very serious imprecision
Clinical remission at 12 weeks (1 RCT)	Low ●●○○	Higher incidence with etrasimod 2 mg but not with etrasimod 1 mg	Downgraded 2 levels for very serious imprecision
Improvement in the total MCS at 12 weeks (1 RCT)	Low ●●○○	Higher incidence with etrasimod 2 mg but not with etrasimod 1 mg	Downgraded 2 levels for very serious imprecision
Overall AEs at 12 weeks (1 RCT)	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
SAEs at 12 weeks (1 RCT)	Very low ●○○○	No difference between groups	Downgraded 3 levels for extremely serious imprecision
Withdrawals due to AEs at 12 weeks (1 RCT)	Very low ●○○○	No difference between groups	Downgraded 3 levels for extremely serious imprecision
Serious infections at 12 weeks (1 RCT)	Very low ●○○○	No difference between groups	Downgraded 3 levels for extremely serious imprecision
Filgotinib vs. Placebo			
Clinical remission at 58 weeks (1 RCT)	Very low ●○○○	Higher incidence with filgotinib (all dosages)	Downgraded 1 level for study limitations, 1 level for indirectness and 2 levels for very serious imprecision
Corticosteroid-free remission at 26 weeks (1 RCT)	Very low ●○○○	Higher incidence with filgotinib 200 mg but not with filgotinib 100 mg	Downgraded 1 level for study limitations, 1 level for indirectness and 2 levels for very serious imprecision
Quality of life (SF-36 physical and mental component summary, WPAI work productivity loss, European Quality of Life 5-Dimension questionnaire visual analogue scale, IBDQ score) at 58 weeks (1 RCT)	Low ●●○○	Higher incidence with filgotinib 200 mg, but not with filgotinib 100 mg	Downgraded 1 level for study limitations and 1 level for indirectness
Overall AEs at 58 weeks (1 RCT)	Low ●●○○	No difference between groups	Downgraded 1 level for study limitations and 1 level for indirectness
SAEs at 58 weeks (1 RCT)	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations and indirectness and 2 levels for very serious imprecision
Withdrawals due to AEs at 58 weeks (1 RCT)	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations, 1 level for indirectness and 2 levels for very serious imprecision
Serious infection at 58 weeks (1 RCT)	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations, 1 level for indirectness and 3 levels for extremely serious imprecision
Opportunistic infection at 58 weeks (1 RCT)	Very low ●○○○	No difference between groups	Downgraded 1 level for study limitations, 1 level for indirectness and 3 levels for extremely serious imprecision

GRADE: Quality of Evidence Summary

Pipeline Agent Effectiveness and Harms – Ulcerative Colitis

Outcome	Certainty of Evidence	Relationship	Rationale
Mirikizumab vs. Placebo			
Clinical response at 12 weeks (1 RCT)	Low ●●○○	Higher incidence with mirikizumab (all dosages)	Downgraded 2 levels for very serious imprecision
Clinical remission at 12 weeks (1 RCT)	Low ●●○○	Higher incidence with mirikizumab 200 mg, but not for other dosages	Downgraded 2 levels for very serious imprecision
Symptomatic remission at 12 weeks (1 RCT)	Low ●●○○	Higher incidence with mirikizumab 200 mg and 600 mg dosage, but not 50 mg dosage	Downgraded 2 levels for very serious imprecision
Quality of life (IBDQ score) at 12 weeks (1 RCT)	Low ●●○○	Higher incidence with mirikizumab 200 mg and 600 mg but not 50 mg dosage	Downgraded 2 levels for very serious imprecision
Overall AEs at 12 weeks (1 RCT)	Low ●●○○	No difference between groups	Downgraded 2 levels for very serious imprecision
SAEs at 12 weeks (1 RCT)	Very low ●○○○	No difference between groups	Downgraded 3 levels for extremely serious imprecision
Withdrawals due to AEs at 12 weeks (1 RCT)	Very low ●○○○	No difference between groups	Downgraded 3 levels for extremely serious imprecision

GRADE: Quality of Evidence Summary

Comparative Effectiveness and Harms – Mixed Population

Outcome	Certainty of Evidence	Relationship	Rationale
Adalimumab vs. Infliximab			
Serious infections (1 cohort study)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Tofacitinib vs. TNF-α inhibitors			
Serious infections (1 cohort study)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Ustekinumab vs. Adalimumab			
Serious infections (1 cohort study)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Ustekinumab vs. Infliximab			
Serious infections (1 cohort study)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Ustekinumab vs. TNF-α inhibitors			
Serious infections (2 cohort studies)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for inconsistency
Ustekinumab vs. Tofacitinib			
Serious infections (1 cohort study)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Vedolizumab vs. Adalimumab			
Serious infections (1 cohort study)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Vedolizumab vs. Infliximab			
Serious infections (1 cohort study)	Very low ●○○○	Lower incidence with vedolizumab	Downgraded 1 level for indirectness and 1 level for imprecision
Vedolizumab vs. Ustekinumab			
Serious infections (1 cohort study)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for imprecision
Vedolizumab vs. TNF-α inhibitors			
Serious infections (1 cohort study)	Very low ●○○○	No difference between groups	Downgraded 1 level for indirectness and 1 level for imprecision


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