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DERP VI Surveillance: Targeted Immune Modulators for Crohn's Disease and Ulcerative Colitis

February 2021

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Objectives

The purpose of this Drug Effectiveness Review Project (DERP) surveillance report is to preview the volume and nature of new research and relevant clinical information that has emerged since the last systematic review on targeted immune modulators (TIMs) for the treatment of Crohn's disease and ulcerative colitis. The literature search for this report focuses on new randomized controlled trials (RCTs), retrospective and prospective cohort studies of harms, and actions taken by the US Food and Drug Administration (FDA) since the last report, including approval of new drugs, formulations, or indications and identification of serious harms. Comprehensive searches, risk of bias assessment, and synthesis of evidence would follow only if DERP participants commission an update review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

Topic History and Context

This report is the first surveillance document on this topic since the completion of the seventh systematic review update of targeted immune modulators for the treatment of Crohn's disease and ulcerative colitis (February 2020). The search strategy for that systematic review was through August 2019.

Table 1. Topic History and Search Dates

Document Type	Date Presented	Search Dates
Systematic Review - Update 7	February 2020	January 2017 through August 2019
Systematic Review - Update 6	June 2018	January 2016 through November 2017
Systematic Review - Update 5	April 2016	November 2013 through January 2016
Systematic Review - Update 4	June 2014	October 2011 through November 2013
Systematic Review - Update 3	March 2012	January 2009 through October 2011
Systematic Review - Update 2	November 2009	August 2006 through April 2009
Systematic Review - Update 1	January 2007	March 2005 through August 2006
Original Systematic Review	December 2005	January 1980 through March 2005

PICOS

Population

- Adults with Crohn's disease
- Adults with ulcerative colitis

Interventions

Table 2. Included Drugs and Biosimilars

Generic Name	Brand Name	Mechanism	Route	Approved Population[a]	Date of FDA Approval
Adalimumab	Humira	TNF-α Inhibitor	SC	Crohn's disease Ulcerative colitis	12/31/2002
Adalimumab-atto	Amjevita	TNF-α Inhibitor	SC	Crohn's disease Ulcerative colitis	12/23/2016
Adalimumab-adaz	Hyrimoz	TNF-α Inhibitor	SC	Crohn's disease	10/30/2018
Adalimumab-adbm	Cyltezo	TNF-α Inhibitor	SC	Ulcerative colitis	08/25/2017

Generic Name	Brand Name	Mechanism	Route	Approved Population[a]	Date of FDA Approval
Certolizumab pegol	Cimzia	TNF-α Inhibitor	SC	Crohn's disease	04/22/2008
Golimumab	Simponi	TNF-α Inhibitor	SC	Ulcerative colitis	04/24/2009
Infliximab	Remicade	TNF-α Inhibitor	IV	Crohn's disease Ulcerative colitis	08/24/1998
Infliximab-abda	Renflexis	TNF-α Inhibitor	IV	Crohn's disease Ulcerative colitis	04/21/2017
Infliximab-dyyb	Inflectra	TNF-α Inhibitor	IV	Crohn's disease Ulcerative colitis	04/05/2016
Infliximab-qbtx	Ixifi	TNF-α Inhibitor	IV	Crohn's disease Ulcerative colitis	12/13/2017
Natalizumab	Tysabri	α4 integrin inhibitor	IV	Crohn's Disease	11/11/2004
Risankizumab-rzaa	Skyrizi	IL-23 Inhibitor	SC	Plaque psoriasis[b]	04/23/2019
Tofacitinib	Xeljanz	JAK inhibitor	PO	Ulcerative colitis	11/16/2012
Upadacitinib	Rinvoq	JAK inhibitor	PO	Rheumatoid arthritis[c]	08/16/2019
Ustekinumab	Stelara	IL-12/23 p40 Inhibitor	Initial dose IV then SC	Crohn's disease Ulcerative colitis	09/23/2016
Vedolizumab	Entyvio	α4β7 integrin Inhibitor	IV	Crohn's disease Ulcerative colitis	05/20/2014
Pipeline Drugs					
Peficitinib	Smyraf	JAK inhibitor	PO	Under investigation (pipeline)	NA[d]
PF-04236921	NA	IL-6 Inhibitor	SC	Under investigation (pipeline)	NA

Notes. [a] Details of approved indications for each drug can be found in the full prescribing information. Some agents are approved for indications other than inflammatory bowel disease; [b] Risankizumab is approved for moderate-to-severe plaque psoriasis and is currently being evaluated for use in Crohn's disease and ulcerative colitis; [c] Upadacitinib is approved for moderate-to-severe rheumatoid arthritis and is currently being evaluated for use in Crohn's disease and ulcerative colitis; [d]Pefictinib is currently only approved in Japan. Abbreviations. IL: interleukin; IV: intravenous; JAK: Janus kinase; NA: not applicable; PO: per os (orally); SC: subcutaneous; TNF-α: tumor necrosis factor alpha.

Comparators

- For FDA approved drugs: another listed TIM intervention (head-to-head comparison)
- For pipeline drugs: any listed TIM, standard of care, placebo

Outcomes

- Health outcomes
  - Quality of life
  - Functional capacity
  - Productivity, ability to sustain employment

- Clinical improvement
- Disease remission
- Pain
- Reduction in disease-related hospitalizations
- Reduction in disease-specific mortality
- Rebound/flare
- Steroid withdrawal

- Harms
  - Overall adverse events (AEs)
  - Withdrawals due to AE
  - Overall serious adverse events (SAEs)
  - Specific AEs and SAEs (e.g., lymphoma, all malignancies, serious infectious diseases, herpes zoster, opportunistic infections, congestive heart failure)
  - Mortality

Study Designs

- RCTs with ≥ 12-week study duration
- Retrospective and prospective cohort studies comparing an intervention type to another for harms outcomes
  - ≥ 12-week study duration
  - Minimum total sample size of 1,000

Key Questions

KQ1. What is the comparative effectiveness of TIMs to treat Crohn's disease and ulcerative colitis?
KQ2. What are the comparative harms of TIMs to treat Crohn's disease and ulcerative colitis?
KQ3. Do the included drugs differ in their effectiveness or harms in the following subgroups: age and racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease?

Methods

Using the PICOS outlined above, researchers at the Center for Evidence-based Policy (Center) searched for eligible RCTs and retrospective or prospective cohort studies of harms in ClinicalTrials.gov, the ISRCTN Registry, and the FDA website. Using relevant clinical trial numbers and other identifiers, we then searched Epub Ahead of Print, Ovid MEDLINE, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from August 2019 to January 8, 2020. We used the Google search engine to identify studies published since the implementation of the search strategy in the most recent systematic review of targeted immune modulators for the treatment of Crohn's disease and ulcerative colitis (February 2020). We used limits for English language and human participants. We also searched the FDA website to identify newly approved drugs, formulations, indications, and new serious harms (e.g., boxed warnings) or warnings for included interventions. We also searched IPD Analytics to identify new FDA actions.

Findings

New Drugs or Formulations

During this surveillance period, the FDA approved 4 new biosimilars of existing TNF-α inhibitors for the treatment of Crohn's disease and ulcerative colitis (Table 3). Infliximab-axxq (Avsola) is the fourth biosimilar of infliximab. Adalimumab-bwwd (Hadlima), Adalimumab-afzb (Abrilada), and Adalimumab-fkjp (Hulio) are the fourth, fifth, and sixth biosimilars of adalimumab, respectively.

Table 3. Newly Approved Therapies for the Treatment of Crohn's Disease and Ulcerative Colitis

Generic Name	Brand Name	Mechanism	Route	Approved Population[a]	Date of FDA Approval
Infliximab-axxq[1]	Avsola	TNF-α Inhibitor	SC	Crohn's disease[b] Ulcerative colitis[b]	12/06/2019
Adalimumab-bwwd[2]	Hadlima	TNF-α Inhibitor	SC	Crohn's disease[c] Ulcerative colitis[c]	07/23/2019
Adalimumab-afzb[3]	Abrilada	TNF-α Inhibitor	SC	Crohn's disease[c] Ulcerative colitis[c]	11/18/2019
Adalimumab-fkjp[4]	Hulio	TNF-α Inhibitor	SC	Crohn's disease[c] Ulcerative colitis[c]	07/06/2020

Notes. [a] Details of approved indications for each drug can be found in the full prescribing information. Some agents are approved for indications other than inflammatory bowel disease. [b] Approved for ages 6 years and older. [c] Approved for ages 18 years and older. Abbreviations. SC: subcutaneous; TNF-α: tumor necrosis factor alpha.

New Indications

The scope of this TIMs report focuses on adults with Crohn's disease or ulcerative colitis. However, we identified recent FDA actions that expands the drug labels for TIMs agents.

- Infliximab biosimilars: During this surveillance period, the FDA added children 6 years of age and older diagnosed with ulcerative colitis to the list of approved indications for 3 biosimilars of infliximab:
  - Infliximab-abda (Renflexis)[5]
  - Infliximab-dyyb (Inflectra)[6]
  - Infliximab-qbtx (Ixifi)[7]

- Tofacitinib (Xeljanz): In December 2019, the FDA approved the extended-release formulation of tofacitinib (Xeljanz XR)[8] for the once daily treatment of adults with moderately to severely active UC. Patients treated with Xeljanz 5 mg twice daily may switch to the once daily treatment of Xeljanz XR 11 mg and patients treated with Xeljanz 10 mg twice daily may switch to the once daily treatment of Xeljanz XR 22 mg.[8]

New Serious Harms or Warnings

- Natalizumab (Tysabri): In June 2020, the FDA updated a black box warning of increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, with natalizumab. The update specified risk factors for PML in patients taking natalizumab including the presence of anti-JCV

antibodies, duration of therapy (i.e., longer than 2 years), and prior use of immunosuppressants.[9]

- Infliximab (Remicade) and biosimilars: An RCT observed higher rates of mortality and hospitalizations in individuals with heart failure who received a 10 mg/kg dose of infliximab, and higher rates of cardiovascular adverse events in patients who received a 5 mg/kg dose compared with placebo.[10] In response, the FDA issued a label amendment in May 2020 for infliximab and all biosimilars with a contraindication for doses > 5 mg/kg in patients with moderate to severe heart failure.[11]
- Vedolizumab (Entyvio): In March 2020, the FDA issued new warnings for increased risk of infusion-related and hypersensitivity reactions, including anaphylaxis and PML, potentially resulting from treatment with vedolizumab.[12]
- Ustekinumab (Stelara): In December 2020, the FDA issued a warning to monitor all patients treated with ustekinumab for signs and symptoms of posterior reversible encephalopathy syndrome (PRES) after 2 cases were reported in clinical trials. If PRES occurs, discontinuation of treatment with ustekinumab is recommended.[13]

Randomized Controlled Trials

No new RCTs were identified since the searches in the last systematic review.

Ongoing Studies

We identified 14 ongoing studies[14-27] of eligible interventions conducted among adults with Crohn's disease or ulcerative colitis, 2 of which were newly identified during this surveillance period (1 RCT[22] and 1 prospective cohort[23]). Table 4 displays the registry number for the trial (NCT), included conditions, treatment groups, eligible outcomes, estimated enrollment, study duration, and estimated primary completion date of these ongoing studies.

Out of the 14 ongoing studies, 8 studies assessed TIMs in adults with Crohn's disease, 5 studies evaluated adults with ulcerative colitis, and 1 study included adults with either Crohn's disease or ulcerative colitis. The majority of studies evaluated therapies not yet approved by the FDA for the treatment of adults with Crohn's disease or ulcerative colitis. Five studies[16-19,22] assessed risankizumab, which is currently only approved for the treatment of plaque psoriasis, and 4 studies[24-27] assessed upadactinib, which is currently approved for the treatment of rheumatoid arthritis. Estimated sample sizes range from 107 to 5,302 participants. Primary completion dates range from 2020 to 2030.

Table 4. Ongoing Comparative Studies of TIMs for Crohn's Disease and Ulcerative Colitis

NCT Number Trial Name (if available)	Condition	Treatment Groups	Eligible Outcomes	N Enrolled Study Duration	Primary Completion Date
Adalimumab vs. Ustekinumab					
NCT03464136[14] SEAVUE	Crohn's disease	• Adalimumab (40 mg) • Ustekinumab (6 mg/kg loading dose then 90 mg) • Placebo	• Remission • Clinical response • Adverse events • Serious adverse events • Infections	N = 386 (actual) 52 weeks	December 2020 (actual)

NCT Number Trial Name (if available)	Condition	Treatment Groups	Eligible Outcomes	N Enrolled Study Duration	Primary Completion Date
Guselkumab vs. Ustekinumab					
NCT03466411[15] GALAXI	Crohn's disease	• Guselkumab (5 doses) • Ustekinumab • Placebo	• Disease activity • Clinical response • Remission	N = 2,000 (estimated) 12 weeks	June 2022 (estimated)
Risankizumab vs. Placebo					
NCT03105102[16]	Crohn's disease	• Risankizumab (SC and IV) • Placebo	• Endoscopic response • Remission • Disease activity • Adverse Events • Hospitalizations	N = 1250 (estimated) 52 weeks	June 2026 (estimated)
NCT03104413[17] Study M15-991	Crohn's disease	• Risankizumab (SC and IV) • Placebo	• Endoscopic response • Remission • Disease activity • Adverse Events • Hospitalizations	N = 579 (actual) 12 weeks	February 2021 (estimated)
NCT03398135[18]	Ulcerative colitis	• Risankizumab (SC and IV) • Placebo	• Endoscopic response • Remission • Disease activity • Health-related quality of life • Adverse Events • Hospitalizations	N = 760 (estimated) 52 weeks	December 2023 (estimated)
NCT03398148[19]	Ulcerative colitis	• Risankizumab (SC and IV) • Placebo	• Endoscopic response • Remission • Disease activity • Health-related quality of life • Adverse Events • Hospitalizations	N = 720 (estimated) 12 weeks	September 2022 (estimated)
Upadacitinib vs. Placebo					
NCT03345836[24]	Crohn's disease	• Upadacitinib • Placebo	• Remission • Endoscopic response • Health-related quality of life • Hospitalizations	N = 645 (estimated) 12 weeks	June 2021 (estimated)
NCT03345849[25]	Crohn's disease	• Upadacitinib • Placebo	• Remission • Endoscopic response • Health-related quality of life • Hospitalizations	N = 501 (estimated) 12 weeks	September 2021 (estimated)

NCT Number Trial Name (if available)	Condition	Treatment Groups	Eligible Outcomes	N Enrolled Study Duration	Primary Completion Date
NCT03006068[26]	Ulcerative colitis	• Upadacitinib (multiple doses) • Placebo	• Adverse events	N = 950 (estimated) 288 weeks	August 2024 (estimated)
NCT02819635[27]	Ulcerative colitis	• Upadacitinib (multiple doses) • Placebo	• Remission • Endoscopic response • Health-related quality of life • Hospitalizations	N = 1,267 (actual) 52 weeks	February 2022 (estimated
Ustekinumab vs. Risankizumab					
NCT04524611[22]	Crohn's disease	• Ustekinumab (SC and IV) • Risankizumab (SC and IV)	• Clinical and endoscopic remission • Endoscopic response	N = 517 (estimated) 48 weeks	June 2023 (estimated)
Ustekinumab vs. Other biologic agents					
NCT04372108[23]	Crohn's disease	• Ustekinumab • Other biologic agents (i.e., infliximab, adalimumab, or vedolizumab)	• Incidence of malignancies • Opportunistic infections • Serious infections	N = 1,536 (estimated) 12 years	August 2030 (estimated)
Vedolizumab vs. Other biologic agents					
NCT02674308[20] Entyvio PASS	Crohn's disease, ulcerative colitis	• Vedolizumab • Other biologic agents (i.e., adalimumab, certolizumab pegol, golimumab, infliximab)	• Adverse events • Serious adverse events • Specific adverse events (e.g., infections, malignancies)	N = 5,302 (actual) 7 years	July 2021 (estimated)
Vedolizumab vs. Infliximab					
NCT03679546[21] EFFICACI	Ulcerative colitis	• Vedolizumab (300 mg) • Infliximab (5 mg/kg)	• Remission • Endoscopic response • Hospitalizations • Adverse events	N = 150 (estimated) 14 weeks	January 2023 (estimated)

Abbreviations. IV: intravenous; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; SC: subcutaneous; TIM: targeted immune modulator.

Summary

Since the completion of the DERP systematic review of TIMs for Crohn's disease and ulcerative colitis (February 2020), we identified:

- 4 new drugs
  - Infliximab-axxq (Avsola): approved in December 2019 for the treatment of Crohn's disease and ulcerative colitis

  - Adalimumab-bwwd (Hadlima): approved in July 2019 for the treatment of Crohn's disease and ulcerative colitis.
  - Adalimumab-afzb (Abrilada): approved in November 2019 for the treatment Crohn's disease and ulcerative colitis.
  - Adalimumab-fkjp (Hulio): approved in July 2020 for the treatment of Crohn's disease and ulcerative colitis.

- 4 new indications
  - Infliximab-abda for ulcerative colitis in children aged 6 years and older
  - Infliximab-dyyd for ulcerative colitis in children aged 6 years and older
  - Infliximab-qbtx for ulcerative colitis in children aged 6 years and older
  - Extended release tofactinib (Xeljanz XR) for ulcerative colitis in adults aged 18 years and older

- No new formulations

- 4 new warnings or serious harms
  - Black box warning for progressive multifocal leukoencephalopathy (PML) with natalizumab (Crohn's disease)
  - Contraindication for infliximab and all infliximab biosimilars at doses > 5 mg/kg in patients with moderate to severe heart failure (Crohn's disease and ulcerative colitis)
  - Posterior reversible encephalopathy syndrome (PRES) with ustekinumab (Crohn's disease and ulcerative colitis)
  - Increased risk of infusion-related and hypersensitivity reactions and PML with vedolizumab (Crohn's disease and ulcerative colitis)

- No new RCTs

- 14 ongoing studies
  - 6 head-to-head studies of FDA approved interventions for the treatment of adults with Crohn's disease or ulcerative colitis
  - 8 placebo-controlled studies of TIMs not yet approved by the FDA for the treatment of adults with Crohn's disease or ulcerative colitis

Using the *Is There a There There Scale* (ITS) (Table 4), we rated this topic as *Maybe* (see Appendix A for ratings and definitions).

Table 4. Summary and ITS Rating

Clinical Evidence	Yes How many?	No
New Comparative Trial		☒
New Placebo-controlled Trial		☒
New Meaningful[a] Study		☒
Ongoing Study Likely to be Published in the Next Year	☑ • Adalimumab vs. ustekinumab: 1 • Risankizumab vs. placebo: 1	

Clinical Evidence	Yes How many?	No
	• Upadacitinib vs. placebo: 1 • Vedolizumab vs. other TIMs: 1	
FDA Actions	**Yes** **Description**	**No**
New Drug or Formulation	☑ • Infliximab-axxq (Avsola) • Adalimumab-bwwd (Hadlima) • Adalimumab-afzb (Abrilada) • Adalimumab-fkjp (Hulio)	
New Indication	☑ • Infliximab-abda: pediatric ulcerative colitis • infliximab-dyyb: pediatric ulcerative colitis • Infliximab-qbtx: pediatric ulcerative colitis • Extended-release tofacitinib: ulcerative colitis	
New Serious Harm or Warning	☑ • Natalizumab: Added specific risk factors to existing black box warning for PML • Infliximab: contraindicated at doses > 5 mg/kg for individuals with moderate to severe heart failure • Ustekinumab: risk of PRES • Vedolizumab: risk of PML and infusion/hypersensitivity reactions	
ITS Rating: Maybe		

Abbreviations. ITS: Is There a There There Scale; PML: progressive multifocal leukoencephalopathy; PRES: posterior reversible encephalopathy syndrome. Note. [a] *Large studies (≥ 100 participants), studies that have long-term follow-up (≥ 12 months), studies that compare one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies that include an intervention or outcome that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.*

References

1. U.S. Food and Drug Administration. Avsola (infliximab-axxq) for injection, for intravenous use. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761086s000lbl.pdf. Accessed January 7, 2021.

2. U.S. Food and Drug Administration. Hadlima (adalimumab-bwwd) injection, for subcutaneous use. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761059s000lbl.pdf. Accessed January 12, 2021.

3. U.S. Food and Drug Administration. Abrilada (adalimumab-afzb) injection, for subcutaneous use. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761118s000lbl.pdf. Accessed January 12, 2021.

4. U.S. Food and Drug Administration. Hulio (adalimumab-fkjp) injection, for subcutaneous use. 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761154s000lbl.pdf. Accessed January 12, 2021.

5. U.S. Food and Drug Administration. Renflexis (infliximab-abda) for injection, for intravenous use. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761054s009lbl.pdf. Accessed January 7, 2021.

6. U.S. Food and Drug Administration. Inflectra (infliximab-dyyb) lyophilized concentrate for injection, for intravenous use. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125544s009lbl.pdf. Accessed January 7, 2021.

7. U.S. Food and Drug Administration. Ixifi (infliximab-qbtx) lyophilized concentrate for injection, for intravenous use 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761072s006lbl.pdf. Accessed January 7, 2021.

8. U.S. Food and Drug Administration. Xeljanz XR (tofacitinib) extended-release tablets, for oral use. 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213082s000lbl.pdf. Accessed January 7, 2021.

9. U.S. Food and Drug Administration. Tysabri (natalizumab) injection, for intravenous use. 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125104s968s969lbl.pdf. Accessed January 7, 2021.

10. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor in patients with moderate-to-severe heart failure. *Circulation.* 2003;107(25):3133-3140. doi: doi:10.1161/01.CIR.0000077913.60364.D2.

11. U.S. Food and Drug Administration. Remicaide (infliximab) for injection, for intravenous use. 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103772s5389s5391s5394lbl.pdf. Accessed January 7, 2021.

12. U.S. Food and Drug Administration. Entyvio (vedolizumab) for injection, for intravenous use. 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125476s025s030lbl.pdf. Accessed January 7, 2021.

13. U.S. Food and Drug Administration. Stelara (ustekinumab) injection, for subcutaneous or intravenous use. 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761044s008lbl.pdf. Accessed January 7, 2021.

14. ClinicalTrials.gov. Safety and efficacy of adalimumab versus ustekinumab for one year (SEAVUE). 2020; https://clinicaltrials.gov/ct2/show/NCT03464136. Accessed January 8, 2021.

15. ClinicalTrials.gov. A study of the efficacy and safety of guselkumab in participants with moderately to severely active Crohn's disease (GALAXI). 2020; https://clinicaltrials.gov/ct2/show/NCT03466411. Accessed January 8, 2021.

16. ClinicalTrials.gov. A study of the efficacy and safety of risankizumab in participants with Crohn's disease. 2020; https://clinicaltrials.gov/ct2/show/NCT03105102. Accessed January 8, 2021.

17. ClinicalTrials.gov. A study to assess the efficacy and safety of risankizumab in participants with moderately to severely active Crohn's disease who failed prior biologic treatment. 2021; https://clinicaltrials.gov/ct2/show/NCT03104413. Accessed January 8, 2021.

18. ClinicalTrials.gov. A study to assess the efficacy and safety of risankizumab in participants with ulcerative colitis. 2020; https://clinicaltrials.gov/ct2/show/NCT03398135. Accessed January 8, 2021.

19. ClinicalTrials.gov. A multicenter, randomized, double-blind, placebo controlled induction study to evaluate the efficacy and safety of risankizumab in participants with moderately to severely active ulcerative colitis. 2020; https://clinicaltrials.gov/ct2/show/NCT03398148. Accessed January 8, 2021.

20. ClinicalTrials.gov. Entyvio (vedolizumab) long term safety study (Entyvio PASS). 2020; https://clinicaltrials.gov/ct2/show/NCT02674308. Accessed January 8, 2021.

21. ClinicalTrials.gov. Efficacy of intravenous infliximab versus vedolizumab after failure of subcutaneous anti-tnf in patients with ulcerative colitis (EFFICACI). 2021; https://clinicaltrials.gov/ct2/show/NCT03679546. Accessed January 8, 2021.

22. ClinicalTrials.gov. Study comparing intravenous/subcutaneous risankizumab to IV/SC ustekinumab to assess change in Crohn's disease activity index in adult participants with moderate to severe Crohn's disease. 2020; https://clinicaltrials.gov/ct2/show/NCT04524611. Accessed January 8, 2021.

23. ClinicalTrials.gov. A study to assess the long-term safety of ustekinumab versus other biologics in patients with Crohn's disease. 2020; https://clinicaltrials.gov/ct2/show/NCT04372108. Accessed January 8, 2021.

24. ClinicalTrials.gov. A study of the efficacy and safety of upadacitinib (ABT-494) in participants with moderately to severely active Crohn's disease who have inadequately responded to or are intolerant to biologic therapy. 2020; https://clinicaltrials.gov/ct2/show/NCT03345836. Accessed January 8, 2021.

25. ClinicalTrials.gov. A study of the efficacy and safety of upadacitnib (ABT-494) in participants with moderately to severely active Crohn's disease who have inadequately responded to or are intolerant to conventional and/or biologic therapies. 2021; https://clinicaltrials.gov/ct2/show/NCT03345849. Accessed January 8, 2021.

26. ClinicalTrials.gov. A study to evaluate the long-term safety and efficacy of upadacitinib (ABT-494) in participants with ulcerative colitis (UC). 2021; https://clinicaltrials.gov/ct2/show/NCT03006068. Accessed January 8, 2021.

27. ClinicalTrials.gov. A study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in participants with moderately to severely active ulcerative colitis (UC). 2021; https://clinicaltrials.gov/ct2/show/NCT02819635. Accessed January 8, 2021.

Appendix A. ITS Ratings and Definitions

The *Is There a There There Scale* (ITS) consists of 3 ratings: *no*, *maybe*, and *yes*. The definitions of these ratings and methods for selection are described below. Center for Evidence-based Policy (Center) researchers will use these definitions to rate each surveillance topic. The assigned rating is offered as guidance and does not require DERP participants to follow this recommendation. Each rating is strictly based on the identified new research and clinical information and is not comprehensive to all aspects of policy decision making, such as competing priorities, budget, contracting, or internal and external state agency needs.

No

- We did not find clinical evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of No is typically given when there are few new studies and/or no new meaningful studies, and no new serious harms.

Maybe

- We found some clinical evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of Maybe is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

Yes

- We found clinical evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of Yes is typically given when there are multiple new comparative trials and meaningful studies and/or new serious harms, drugs, formulations, or indications.