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Drug Class Update: Targeted Immune Modulators

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Date of Last Review: August 2024
Literature Search: 01/01/2023–06/25/2025

Current Status of PDL Class:
See **Appendix 1**.

Purpose: To evaluate recently published evidence for the safety and efficacy of Targeted Immune Modulators (TIMs) in managing various autoimmune conditions including rheumatoid arthritis (RA), ankylosing spondylitis (AS), plaque psoriasis (PsO), psoriatic arthritis (PsA), Crohn's disease (CD) and ulcerative colitis (UC).

Plain Language Summary:

- Targeted immune modulators are medicines that prevent the body's immune system from attacking the body's own healthy tissues. These medicines are used to treat autoimmune conditions including ankylosing spondylitis, rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis. In these conditions, the immune system attacks the cells in the body which causes inflammation and pain, decreases quality of life, and limits the ability to complete daily activities.
- Rheumatoid arthritis primarily affects the joints, causing pain, swelling and stiffness. Ankylosing spondylitis is a type of arthritis that primarily affects the joints in the spine, causing back pain and stiffness. Plaque psoriasis is a skin condition with raised, irritated, and scaly patches of skin that may be itchy and painful. Psoriatic arthritis is a condition that causes pain and swelling in the joints of some people with psoriasis. Crohn's disease and ulcerative colitis are painful conditions that impact the large intestine and cause diarrhea, abdominal discomfort, and bloody bowel movements.
- This review identified 12 new clinical guidelines that help providers decide the best medicine to treat different autoimmune conditions with targeted immune modulators. The guidelines are in line with current Oregon Health Plan policies. The targeted immune modulators can increase the risk of infections, headache, and feeling tired, so the benefit of the medicine should be considered as well as the possible side effects.
- For all targeted immune modulators, the provider must explain to the Oregon Health Authority why their patient needs the medicine. This process is called prior authorization.

Conclusions:

- Since the previous Pharmacy and Therapeutics (P & T) Committee review 7 systematic reviews[1-7] and 12 guidelines have been issued or updated to guide the use of TIMs in AS,[8-10] RA,[11] PsA,[12,13] PsO,[14] UC,[15-18] and generalized pustular psoriasis (GPP).[19,20] Guidance for the use of TIMs in rare conditions including hidradenitis suppurativa (HS),[21,22] systemic sclerosis,[23] and in interleukin-1 (IL-1) mediated autoinflammatory diseases[24] has also recently been published. Finally, recommendations for prevention of chronic and opportunistic infections prior to initiating therapy with TIMs are now available.[25]

Biosimilars vs. Reference Products

- A 2023 systematic review and meta-analysis evaluated the therapeutic equivalence of biosimilars of adalimumab, etanercept, and infliximab with their reference biologic drugs for management of RA.[1] Moderate-quality evidence suggests that biosimilars are not associated with differences in efficacy in

people with RA compared to their reference biologic agent using American College of Rheumatology (ACR) criteria to assess improvement in RA symptoms (see **Appendix 2** for description of ACR criteria**)**.[1] Moderate-quality evidence shows that biosimilars result in little to no difference for most safety outcomes (serious adverse events, drug discontinuation, hypersensitivity) compared to reference products.[1] Low-quality evidence shows there is little difference between biosimilars and reference products for treatment-emergent adverse events (TEAEs), injection site reactions, and development of antidrug antibodies.[1]

Ankylosing Spondylitis

- For the management of 2 types of AS, radiographic axial spondyloarthritis (r-axSpA) and non-radiographic axSpA (nr-axSpA), tumor necrosis factor inhibitors (TNFi) (golimumab, certolizumab pegol) and IL-17 inhibitors (IL17i:secukinumab, ixekizumab) improved symptoms of AS compared to placebo in 5 high-quality RCTs.[2] Many RCTs evaluated symptoms using ASAS40 response (see **Appendix 2** for details). When compared to placebo, the IL-23i and IL-12/23i (risankizumab, ustekinumab) failed to show efficacy in treating r-axSpA (4 RCTs; high-quality evidence).[2] No new safety risks were identified with TNFi use in observational studies, there was no new data for IL-17i.[2] In 3 observational studies comparing TNFi to IL-17i, secukinumab and etanercept were associated with an increased risk of uveitis, a frequent co-morbidity observed in patients with AS.[2]
- Four high-quality, placebo-controlled RCTs showed Janus kinase inhibitors (JAKi) filgotinib, tofacitinib, and upadacitinib are efficacious in treating patients with r-axSpA (based on ASAS20 and ASAS40 responses) with an acceptable short term safety profile.[3] The most frequently reported adverse events with JAKi were infections. One placebo-controlled RCT at low risk of bias (RoB) showed apremilast was not effective in reducing symptoms of r-axSpA.[3]
- The ASA-EULAR 2022 recommendations for management of AS are presented in **Table 2** and include the following statements:
    - Patients suffering from pain and stiffness should use a nonsteroidal anti-inflammatory drug (NSAID) as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs, continuous use is preferred if needed to control symptoms (Strong Recommendation; High-Quality Evidence).[8]
    - Patients with purely axial disease should normally not be treated with conventional synthetic DMARDs (csDMARDs: leflunomide, sulfasalazine, methotrexate [MTX]), due to lack of efficacy; however, sulfasalazine may be considered in patients with peripheral arthritis (Strong Recommendation; High-Quality Evidence).[8]
    - TNFi, IL-17i or JAKi should be considered in patients with persistently high disease activity (Ankylosing Spondylitis Disease Activity Score [ASDAS] $\geq$ 2.1) despite conventional treatments; current practice is to start with a TNFi or IL-17i (Strong Recommendation; High-Quality Evidence).[8]
    - If there is a history of recurrent uveitis or active inflammatory bowel disease (IBD), preference should be given to a TNFi (Strong Recommendation; High-Quality Evidence). In patients with significant psoriasis, an IL-17i may be preferred (Strong Recommendation; Moderate-Quality Evidence).[8]
- National Institute for Care and Excellence (NICE) recommendations for treating AS with tofacitinib and bimekizumab were issued in October 2023.[9,10]
    - Tofacitinib or bimekizumab are recommended as an option for treating active AS that is not controlled well enough with conventional therapy in adults, only if TNFi are not suitable or do not control the condition well enough.[9,10]
    - Assess response to therapy after 16 weeks of treatment. Continue treatment only if there is clear evidence of response, defined as:
        - a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units (see **Appendix 2**) and
        - a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.[9,10]

Rheumatoid Arthritis

- High-quality RCTs for JAKi (baricitinib, upadacitinib, filgotinib) combined with MTX or csDMARDs showed JAKi improved RA symptoms compared to placebo based upon American College of Rheumatology (ACR) response (see **Appendix 2**).[4] Monotherapy with filgotinib was not more effective than MTX in achieving ACR20 response at week 24 (one low RoB RCT).[4] In a head-to-head comparison, upadacitinib combined with MTX was more effective than adalimumab with MTX in achieving ACR50 response at week 12 (low RoB RCT).[4] Upadacitinib combined with csDMARDs was superior to abatacept combined

with csDMARDs in reducing the severity of RA symptoms as assessed by the Disease Activity Score-28 C-Reactive Protein (DAS28-CRP) at week 12 (one low RoB RCT).[4] Filgotinib 200 mg once daily plus MTX was noninferior to adalimumab 40 mg every 2 weeks plus MTX in achieving DAS28-CRP ≤3.2 at 12 weeks (one low RoB RCT).[4]

- The risk of malignancies and major adverse cardiovascular events (MACE) is similar, or even decreased, with bDMARDs compared with csDMARDs.[5] However, these adverse outcomes occurred more frequently with tofacitinib than with TNFi in patients who had certain cardiovascular risk factors.[5] The risk of serious infections is increased with bDMARDs compared with csDMARDs and is similar across bDMARDs and the JAKi, tofacitinib.[5] Of note, herpes zoster is more common with JAKi than with csDMARDs or bDMARDs, with the possible exception of filgotinib.[5] Lower intestinal perforations are rare but occur more often with tocilizumab than with other bDMARDs.[5]
- The 2022 EULAR Task Force recommendations for pharmacologic management of RA are presented in **Table 3** and include the following:
    - Therapy with csDMARDs (MTX) should be started as soon as the diagnosis of RA is made (Strong Recommendation; High-Quality Evidence).[11]
    - If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAKi may be considered, but risk factors for cardiovascular events and malignancies must be considered (Efficacy: Strong Recommendation; High-Quality Evidence and Safety: Strong Recommendation; Moderate-Quality Evidence).[11]

Psoriatic Arthritis

- For PsA management, bDMARDs (golimumab, secukinumab, ustekinumab, guselkumab, risankizumab, tildrakizumab, bimekizumab) improve PsA symptoms compared to placebo in RCTs (high-quality evidence).[6] In head-to-head, low RoB RCTs of the IL17i (secukinumab and ixekizumab) compared with TNFi (adalimumab), there were comparable ACR response rates, but better skin responses in patients who received IL-17i.[6] High-quality evidence from RCTs that evaluated the tsDMARDs, deucravacitinib (a tyrosine kinase-2 inhibitor [TYK2]) and the JAKi, upadacitinib, showed significantly higher ACR20 response rates compared with placebo treatment.[6] Upadacitinib 30 mg (but not 15 mg) once daily improved ACR 20 response compared with adalimumab 40 mg every 2 weeks in one low RoB RCT, at the expense of more adverse events with upadacitinib.[6] In 2 observational studies, patients treated with IL-17i had higher rates of hospitalized infections compared with TNFi, while another study did not show an increased risk.[6] Fungal infections occurred more frequently in patients receiving IL-17i compared with placebo and TNFi treatment.[6] Very few cases of fungal infections were observed in patients treated with an IL23i.[6] Higher event rates of serious infections, opportunistic infections, and herpes zoster rates were observed with upadacitinib treatment compared with adalimumab, while rates of MACE and venous thromboembolisms (VTEs) were similar.[6]
- In June 2024, Canada's Drug Agency (CDA) published a reimbursement review for the use of bimekizumab.[13] Bimekizumab is recommended as monotherapy or in combination with MTX to treat adults with active PsA.[13] Bimekizumab is not recommended in patients with PsA and comorbid IBD, severe uveitis, or active infection.[13]
- NICE recommends bimekizumab alone or with MTX as an option for treating active PsA in adults who cannot tolerate or have not responded well enough to DMARDs.[12] Bimekizumab is recommended only for adults who have had 2 csDMARDs and at least 1 bDMARD (golimumab, ustekinumab, guselkumab, ixekizumab, risankizumab, certolizumab pegol, secukinumab) or if TNFi (etanercept, infliximab, adalimumab) are contraindicated but would otherwise be considered.[12]

Plaque Psoriasis

- In adults with moderate-to-severe PsO, the IL-17i are associated with an increased risk of *Candida* infections compared with placebo.[7] Secukinumab, but not ixekizumab or brodalumab, significantly increased the risk of *Candida* infection.[7] Compared to placebo, the incidence of *Candida* infection was 0.83%–5.08% for secukinumab, 0.99% for brodalumab, and 0.88%–1.47% for ixekizumab.[7] There was no difference in *Candida* infection risk between IL-17i and TNFi (95% confidence interval [CI], 0.92 to 3.07, P=0.09).[7] There was no evidence that the TIMs increased the risk of serious infections in adults with PsO (95% CI, 0.93 to 2.06; P=0.11) or that the TIMs differed in the risk of serious infections.[7] Most outcomes had low or very low strength of evidence.[7] The strength of

evidence was graded as high quality for secukinumab versus placebo, moderate quality for IL-17i versus IL-12/23i for *Candida* infection, and moderate quality for guselkumab versus placebo for serious infections.[7]

- The CDA does not recommend the use of deucravacitinib for the treatment of adults with moderate-to-severe PsO who are candidates for systemic therapy or phototherapy.[14] The evidence from 2 clinical trials was insufficient to determine that deucravacitinib offered treatment benefits over the currently available treatments in Canada for the moderate-to-severe plaque PsO in adults.[14]

Ulcerative Colitis

- In December 2024, the American Gastroenterological Association (AGA) published updated guidance for the management of UC:[18]
    - In adult outpatients with moderate-to-severe UC, the use of infliximab, golimumab, vedolizumab, tofacitinib, upadacitinib, ustekinumab, ozanimod, etrasimod, risankizumab and guselkumab are recommended over no treatment (strong recommendation, moderate to high certainty of evidence).[18]
    - In adult outpatients with moderate-to-severe UC, the use of adalimumab, filgotinib or mirikizumab is suggested over no treatment (conditional recommendation, moderate certainty of evidence).[18]
    - In adult outpatients with moderate-to-severe UC who are *naïve to advanced therapies*, using a HIGHER efficacy medication (infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib, risankizumab, guselkumab) OR an INTERMEDIATE efficacy medication (golimumab, ustekinumab, tofacitinib, filgotinib, mirikizumab), is suggested rather than a LOWER efficacy medication (adalimumab) (conditional recommendation, low certainty of evidence).[18]
    - In adult outpatients with moderate-to-severe UC who have previously been exposed to 1 or more advanced therapies (particularly a TNFi), using a HIGHER efficacy medication (tofacitinib, upadacitinib, ustekinumab) OR an INTERMEDIATE efficacy medication (filgotinib, mirikizumab, risankizumab, guselkumab), is suggested rather than a LOWER efficacy medication (adalimumab, vedolizumab, ozanimod, etrasimod) (conditional recommendation, low certainty of evidence).[18]
- NICE recommends etrasimod and risankizumab as options in UC patients.[15,16] Etrasimod is recommended as an option for moderately to severely active UC in people aged 16 years and over when conventional or biological treatments cannot be tolerated or the condition has not responded well enough, or lost response to treatment.[15] Risankizumab is recommended for a similar population, only if a TNFi has not worked, or cannot be tolerated or is not suitable.[16]
- The August 2024 CDA reimbursement review recommends etrasimod for treatment of adults with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or advanced treatment (i.e., biologics, S1P receptor modulators, JAKi).[17]

Generalized Pustular Psoriasis

- The 2025 CDA guidance recommends spesolimab for acute treatment of GPP flares and for the prevention of GPP flares in patients aged 12 years and older and weighing at least 40 kg.[20] For continued renewal of spesolimab for the prevention of flares, the severity of GPP as measured by the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score at initiation should be maintained (not worsen), patients should experience fewer flares compared to baseline, and the reduction in the number of flares should be sustained.[20] A description of the GPPGA scoring is included in **Appendix 2.**
- NICE recommendations (2025) include additional suggestions regarding the use of GPPGA assessment and recommend spesolimab as an option for treating GPP flares in adults, only if it is used to treat: [19]
    1. Initial moderate to severe flares when:
        - the GPPGA total score is 3 or more, and
        - there are fresh pustules (new appearance or worsening of existing pustules), and
        - the GPPGA pustulation subscore is at least 2, and
        - at least 5% of the body's surface area is covered with erythema (abnormal redness of the skin or mucous membranes) and has pustules.[19]

2. Spesolimab is recommended to treat subsequent flares with a GPPGA pustulation subscore of 2 or more, if the last flare was treated with spesolimab and resolved to a GPPGA pustulation subscore of 0 or 1 (clear or almost clear skin).[19] A second dose of spesolimab can be used after 8 days if a flare has not resolved to a GPPGA pustulation subscore of 0 or 1.[19]

Hidradenitis Suppurativa

- The CDA recommends secukinumab for adults with moderate-to-severe HS who have responded inadequately to conventional systemic HS therapy (i.e., oral antibiotics).[22] For renewal after initial authorization, physician must provide proof of beneficial clinical effect defined as at least a 50% reduction in abscess and inflammatory nodule count with no increased in abscess or draining fistula count.[22]
- NICE recommends secukinumab as an option for treating active moderate-to-severe HS in adults when HS has not responded well enough to conventional systemic treatment, only if adalimumab is not suitable, did not work or has stopped working.[21] Assess response to secukinumab after the first 16 weeks of treatment, and only continue if there is clear evidence of a response, defined as: a reduction of 25% or more in the total abscess and inflammatory nodule count, and no increase in abscesses and draining fistulas.[21]

Systemic Sclerosis

- In 2023, the EULAR Task Force updated recommendations for rituximab and tocilizumab for key fibrotic manifestations of systemic sclerosis.[23] Recommendations that discuss csDMARDs or TIMs are summarized below using the EULAR standard operating procedures for level of evidence (LoE) and strength of recommendation (SoR) presented in **Table 1**.
    - Methotrexate (1B), mycophenolate mofetil (1B) and/or rituximab (1A) should be considered for systemic sclerosis skin fibrosis (LoE: 1a-b; SoR: A/B).[23]
    - Tocilizumab may be considered for skin fibrosis in patients with early, inflammatory diffuse cutaneous systemic sclerosis (LoE: 1b; SoR: C).[23]
    - Mycophenolate mofetil (1A), cyclophosphamide (1A) or rituximab (1A) should be considered for systemic sclerosis-interstitial lung disease (LoE: 1a; SoR: A).[23]
    - Tocilizumab should be considered for the treatment of systemic sclerosis-interstitial lung disease (LoE:1b; SoR: B).[23]

Interleukin-1 Autoinflammatory Diseases

- In 2021, a EULAR Task Force developed evidence-based recommendations for treat of IL-1 mediated systemic autoinflammatory diseases, including the cryopyrin-associated periodic syndromes (CAPS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD) and deficiency of the IL-1 receptor antagonist (DIRA).[24] Efficacy and safety have been demonstrated for the use of 3 IL-1 blockers (anakinra, rilonacept and canakinumab) in these conditions although direct comparative studies are lacking.[24] EULAR recommendations for treatment of CAPS, TRAPS, MKD, and DIRA are summarized in **Table 4.**

Screening and Prophylaxis of Infections in Adults with Autoimmune Conditions

- In 2022, a EULAR Task Force issued guidance for screening and prophylaxis of infections in adults with autoimmune conditions.[25] Eight recommendations were developed (see **Table 5**) based upon EULAR standard operating procedures (see **Table 1**)**.**[25]

New Formulations

- Eight new intravenous and subcutaneous biosimilar products for the reference product of STELARA (ustekinumab) received Food and Drug Administration (FDA) approval in 2024 and 2025.[26] All the ustekinumab biosimilar products are indicated for treatment of adults with moderate to severe PsO, Crohn's disease (CD), UC, or active PsA and pediatric patients 6 years and older with moderate to severe PsO or active PsA.[27]
- In 2025 a biosimilar for tocilizumab, AVTOZMA (tocilizumab-anoh) received FDA approval for treatment of adults with RA, giant cell arteritis, or coronavirus disease and pediatric patients 2 years of age and older with juvenile idiopathic arthritis (JIA).[28]

- An autoinjector device for OMVOH (mirikizumab) was approved 3/25.[29] The device is available in 100 mg/mL and 200 mg/2 mL prefilled pens as dosing varies according to the UC or CD indications.[29]

Expanded Food and Drug Administration Indications Since the Last P&T Review

- OTZELA (apremilast) for pediatric patients 6 years of age and older and weighing at least 20 kg with active PsA.[30]
- YUFLYMA (adalimumab-aaty) for adults with uveitis.[31]
- TREMFYA (guselkumab) for adults with moderately to severely active UC and CD.[32]
- CIMZIA (certolizumab pegol) for polyarticular JIA (pJIA) in patients aged 2 years and older.[33]
- BIMZELX (bimekizumab) for adults with active PsA, active AS and nr-axSpA, and patients with HS.[34]
- OMVOH (mirikizumab) for adults with moderately to severely active CD.[29]

Recommendations:

- Modify TIMs prior authorization (PA) criteria to include expanded indications for recent FDA approvals outlined in the conclusions.
- Update TIMs PA criteria with recent recommendations from published guidelines.
- Review drug costs in executive session.

Summary of Prior Reviews and Current Policy

- The TIMs used in autoimmune conditions were last reviewed by the P & T Committee at the August 2024 meeting. All TIMs require PA to evaluate disease severity and to implement step therapy for common diagnoses. At the August 2024 meeting, the following preferred drug list (PDL) recommendations were implemented for TIMs and biosimilar products:
    - Current preferred products Humira and Enbrel will be designated as preferred, Tier 1.
    - Infliximab-axxq (AVSOLA), Simlandi (branded only), AMJEVITA (100 mg/mL aka “high-concentration” only), and non-branded adalimumab-fkjp (50 mg/mL aka “low-concentration” only) were designated as preferred, Tier 1.
    - Ixekizumab (TALTZ), apremilast (OTEZLA), tofacitinib citrate (XELJANZ) were designated as preferred, Tier 2.
    - Secukinumab (COSENTYX) was designated as non-preferred.
    - All other TIMs and their biosimilar products were designated as non-preferred.
- The Food and Drug Administration (FDA)-approved (TIMs) for selected autoimmune conditions are summarized in **Appendix 1.** Frequently used assessment outcomes for assessing disease improvement in AS, RA, PsO, PsA, CD, and UC are presented in **Appendix 2**.
- The PA criteria for Targeted Immune Modulators (TIMs) approved for use in autoimmune conditions are presented in **Appendix 7.** A summary of the PDL status for the TIMs drug class is provided in **Appendix 3**.

OHP FFS Utilization:

- In the second quarter of 2025 (April 1 to June 30), there were about 103 pharmacy claims for TIMs in the fee-for-service (FFS) population. Fifty percent of the claims were for preferred formulations of adalimumab, tofacitinib, and ixekizumab. For the non-preferred agents, 50% of claims were for upadacitinib, adalimumab biosimilar (HADLIMA), secukinumab, and risankizumab. In the first quarter of 2025 (January 1 to March 30), the most frequently utilized physician-administered TIMs included abatacept, canakinumab, golimumab, infliximab, risankizumab, rituximab, tocilizumab, and vedolizumab.

Background:
Targeted immune modulators include bDMARDs and tsDMARDs. Biologic DMARDs are large, complex, proteins that must be administered parentally. The biologic DMARDs include TNFi, integrin inhibitors, IL-antagonists, and lymphocyte antagonists. The FDA has approved biosimilars for some bDMARDs including adalimumab, etanercept, infliximab, natalizumab, rituximab, and ustekinumab.[26] Targeted synthetic DMARDs are small chemical molecules that can be taken orally. The JAKi, sphingosine 1-phosphate (S1P) receptor modulators, PDE-4i, and TYK2 inhibitor are classified as tsDMARDs. **Appendix 1** summarizes the TIMs indicated for management of selected auto-immune conditions discussed in this class update.

Ankylosing Spondylitis
Ankylosing spondylitis is a chronic rheumatic disorder that primarily affects the sacroiliac joints and spine.[35] Diagnosis is based on radiologic confirmation of sacroiliitis and the presence of at least one clinical symptom: low back pain for at least 3 months, limited lumbar spine motion, or decreased chest expansion.[36] The goals of treatment for patients with AS are to reduce symptoms, maintain spinal flexibility, reduce functional limitations, maintain work ability, and decrease disease complications.[37] Nonsteroidal anti-inflammatory drugs and exercise are recommended as first-line therapies to alleviate pain and stiffness.[38,39] Tumor necrosis factor inhibitors, IL-17i and JAKi are recommended for patients with persistent disease activity despite conventional treatment.[38,39] All FDA-approved TIMs reduce disease activity as assessed by ASAS scores, which is a composite score of 4-6 domains.[40] Percentage of responders in each improvement criteria were reported as ASAS20 (20% improvement), ASAS40 (40% improvement) ASAS5/6 (20% improvement in five of six domains) and ASAS-PR (partial remission).[40] Outcomes used to assess the efficacy of TIMs to manage AS disease activity in clinical trials are summarized in **Appendix 2**.

Rheumatoid Arthritis
The hallmarks of RA are inflammation of the synovial tissues with progressive erosion of bone leading to malalignment of the joint and, in most cases, disability.[41] Tumor necrosis factor plays a central role in the pathophysiology of RA.[41] The 2022 EULAR recommendations suggest RA treatment begin with a csDMARD such as MTX as soon as diagnosis of RA is established.[11] Other csDMARDs recommended to treat RA include sulfasalazine and leflunomide.[11] Biologic DMARDs or JAKi are recommended for patients with a suboptimal response or intolerance to csDMARDs.[11] Primary endpoints used in RA clinical trials are ACR response, the Health Assessment Questionnaire Disability Index (HAQ-DI), and the Disease Activity Score-28 (DAS-28). The ACR response is considered a measure of efficacy and evaluates tender joint count, swollen joint count, patient's assessment of pain, patient's and physician's global assessments of disease activity, patient's assessment of physical function, and laboratory evaluation of an acute-phase reactant (erythrocyte sedimentation rate [ESR] or CRP level).[42] The HAQ-DI is a self-reported measure of functional capacity (total score 0 to 3).[43] Scores of 0 to 1 are generally considered mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[43] A decrease of 0.22 to 0.25 is generally considered the minimum clinically important difference for this scale.[44] The DAS-28 is another index of disease activity (similar to the ACR response) which assesses 28 joints in swelling, tenderness, ESR or CRP levels, and patient global assessment of health. A DAS-28 score greater than 5.1 corresponds to high disease activity and less than 3.2 corresponds to low disease activity.[43] A DAS-28 score of 2.6 corresponds with remission.[43] Outcomes used to assess RA in clinical trials are summarized in **Appendix 2**.

Plaque Psoriasis, Generalized Pustular Psoriasis, and Psoriatic Arthritis
Plaque psoriasis is a chronic, immune-mediated inflammatory disorder of the skin, scalp and joints that affects about 2 to 3% of the population.[45] The development of the disease is driven by multiple pathways of immune mediators, including TNF, IL-23 and IL-17 cytokines. Plaque psoriasis is characterized by itchy, red, scaly, raised lesions on the skin, especially on the scalp, elbows, knees, and trunk. Typically, PsO is classified as mild, moderate or severe. Mild disease involves less than 5% of the body surface area and has little to no impact on quality of life or function. Per 2017 NICE guidance, first-line agents for PsO include topical medications such as: corticosteroids, vitamin D analogs (e.g., calcipotriene), retinoids (e.g., tazarotene) or calcineurin inhibitors (e.g., tacrolimus or pimecrolimus).[46] Phototherapy is an option for patients with moderate-to-severe PsO who have not responded to topical therapy.[46] Systemic csDMARDs are

recommended for patients with moderate-to-severe PsO unresponsive to topical treatments or phototherapy and include MTX, cyclosporine, or acitretin.[46] Biologics including TNFi, IL-12/22i, IL-23i, or IL-17 may be added for patients with moderate-to-severe PsO not controlled by other therapies.[46] Targeted synthetic DMARDs approved to manage PsO include the PDE-4 inhibitor, apremilast and the recently approved TYK2 inhibitor, deucravacitinib.

Other subtypes of psoriasis include guttae, erythrodermic, and pustular psoriasis.[47] Generalized pustular psoriasis is an uncommon subtype that manifests as widespread pustular skin eruptions or erythematous plaques.[47] In GPP, small pustules may join into larger pustules to form pus-filled blisters on the skin, feet, and hands. The blisters can crack, which causes painful breaks in the skin and makes it difficult to walk or complete daily activities using the hands. Other symptoms of this condition include skin redness, irritation, burning, itching, fatigue, achy joints, headache and fever. Common Laboratory abnormalities can include leukocytosis, an elevated ESR, hypocalcemia, other electrolyte abnormalities, hypoalbuminemia, and elevated liver enzymes.[47] In addition, serious complications, including sepsis and hepatic, respiratory, or renal dysfunction, can occur with acute onset of GPP.[48,47] Generalized pustular psoriasis can be triggered by rapid tapering of systemic and potent topical corticosteroids, exposure to sunlight, hypocalcemia, pregnancy, and infection.[47] It is epidemiologically distinct from chronic PsO and more common in women than in men.[47] Spesolimab is the only medication FDA-approved for acute treatment of GPP flares and for the prevention of GPP flares for patients with a history of flares.[20] The severity of GPP is generally assessed using the GPPGA score which is a clinician-scored tool that assesses the extent of erythema, pustules, and lesion scaling on a 5-point scale.[20] A description of the GPPGA scoring is included in **Appendix 2.**

Psoriatic arthritis is a disease with heterogeneous manifestations in patients who have manifest or latent psoriasis.[49] It comprises both musculoskeletal as well as non-musculoskeletal manifestations; the latter particularly include the skin and the nails, but also potentially the gut (inflammatory bowel disease) or the eyes (uveitis).[49] Active chronic PsA is associated with cardiovascular, psychological and metabolic comorbidities, which, together with the musculoskeletal manifestations, impose a significant impact on quality of life and increased risk of mortality.[49] First-line treatment for PsA includes NSAIDs, although in most cases csDMARDs (MTX, sulfasalazine or leflunomide) are necessary.[49]

Several tools have been developed to evaluate symptom improvement and quality of life in patients with PsO. In clinical trials, symptom improvement is often evaluated using the Psoriasis Area and Severity Index (PASI), the static Physician's Global Assessment scale (sPGA), or the Psoriasis Symptom Inventory (PSI). There is no consensus on the most reliable scale, but the PASI is used most often in clinical trials and is considered the most validated scale.[50] The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. Because the PASI only evaluates skin involvement on the trunk, head, arms and legs, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[50,51] It does not consider symptoms affecting hands, feet, face or genitals. Because the PASI scale is not linear, small changes in BSA involvement can result in a significant improvement of the overall score without change in other symptoms.[50] In addition, though the PASI evaluates symptoms on a range of 0 to 72 points, in clinical practice, patients often do not have scores greater than 40.[51] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, an improvement of 100%, indicating complete disease clearance, is considered more clinically significant.[51] Additional outcomes used to assess PsO and PsA in clinical trials are summarized in **Appendix 2.**

<u>Hidradenitis Suppurativa</u>

Hidradenitis suppurativa is a chronic inflammatory skin disease which has a prevalence of 1-4% worldwide and is 3 times more common in women than men.[52,53] The mean age of onset is 22 years.[52] It is characterized by inflamed nodules which occur most frequently in the axillary, inguinal, and anogenital regions of the body.[52,53] These nodules are painful, recurrent, and can result in abscesses, chronic draining sinus tracts, scarring, disfigurement, and disability.[52] Genetic predisposition, hormonal factors, immune factors, medications such as lithium and medroxyprogesterone acetate, obesity, and smoking all are potential contributors to the etiology.[52]

The Hurley clinical staging system describes disease severity by 3 stages: stage 1 indicates abscess formation, single or multiple, without sinus tracts and cicatrization (scar formation); stage 2 indicates recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions; and stage 3 indicates diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.[54] About 69% of patients have stage 1 disease, while approximately 28% and 4% of patients have more severe stage 2 and 3 disease.[54] The minimum clinically significant change in Hurley staging is unclear.[55]

Nonpharmacological treatments for HS include local hygiene and cleansing, reducing heat, humidity, and friction in the area, weight loss to ideal weight, and smoking cessation.[52] Surgical treatment may also be an option for Hurley stage 2 and 3 patients.[52] Pharmacological treatments for HS include antibiotics, retinoids, corticosteroids, and TNFi.[52,54] However, the most commonly used treatments are topical and oral antibiotics.[56] The most commonly used oral antibiotic treatments are tetracyclines.[56]

Crohn's Disease and Ulcerative Colitis

Crohn's disease and UC are classified as inflammatory bowel diseases (IBDs). Crohn's disease is characterized by inflammation involving the full thickness of the bowel wall at any point from mouth to anus, whereas UC is characterized by mucosal ulceration limited to the colon and rectum. Symptoms of both conditions include blood and/or mucus in the stool, urgency, tenesmus, incontinence, increased frequency of bowel movements, and abdominal discomfort. Systemic symptoms include fatigue, weight loss, loss of appetite, anemia, inflammatory eye disease, sclerosing cholangitis, and arthritis. Clinical diagnosis of both conditions is most accurately made with colonoscopy.

Two scoring tools are used to assess disease activity in CD and UC. The Crohn's Disease Activity Score (CDAI) is an evaluation of 8 clinical factors involved in CD assessment, including number of soft stools per day, abdominal pain, general well-being, use of medications for diarrhea, presence of abdominal mass, hematocrit, and percentage deviation from standard weight. A total score of 450 or greater indicates extremely severe disease, a score of 150 or greater indicates active disease, and a score less than 150 indicates minimal disease.[57] The Mayo Clinic Score is used to evaluate UC symptoms.[58] Four subscores evaluate rectal bleeding, stool frequency, patient-reported outcomes, and endoscopy results. Each domain is scored from 0 to 3 points, with a higher score indicating more severe disease.[58] The total score can range from 0-12 with higher scores indicating worse severity. A critical component of this score is the endoscopic findings. Patients with lower scores but with an endoscopic score of 2 or greater are considered more severe regardless of the final score.[58] The domains for the CDAI and Mayo Clinic Score are presented in more depth in **Appendix 2**.

Practice guidelines for CD recommend considering the disease location, severity, complications, and extra intestinal manifestations when choosing a treatment strategy.[57] Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission).[57] NICE guidance recommends TNFi for induction, but only after failure of conventional therapy with corticosteroids, aminosalicylates (i.e., sulfasalazine, mesalamine), azathioprine or mercaptopurine, and should only be used for maintenance if there is clear evidence of active disease.[59] The American College of Gastroenterology (ACG) strongly recommends induction with a TNFi to maintain remission in patients who have moderate-to-severe CD despite treatment with conventional therapy.[57] Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used to treat CD due to insufficient evidence demonstrating efficacy.[57]

The choice of therapy for UC considers the level of disease activity (mild, moderate, or severe), the extent of the disease (proctitis, left-sided disease, extensive disease, or pancolitis), and patient preferences.[60] The 2019 ACG[61] and the NICE[62] guidelines recommend the use of TIMs for treating moderately to severely

active UC in adults whose disease has responded inadequately to conventional therapy including aminosalicylates, corticosteroids, azathioprine or mercaptopurine. Continuation of these agents is only recommended if there is clear evidence of response.[61,62]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 4** with abstracts presented in **Appendix 5**. The Medline search strategy used for this literature scan is available in **Appendix 6**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Therapeutic Equivalence of Biosimilar and Reference Biologic Drugs in Rheumatoid Arthritis
A 2023 systematic review and meta-analysis evaluated the therapeutic equivalence of biosimilars of adalimumab, etanercept, and infliximab with their reference biologic drugs for management of RA.[1] Literature was searched through September 7, 2021 for head-to-head RCTs.[1] Twenty-five RCTs (n=19,642) met inclusion critiera.[1] Fourteen trials (56%) had a low RoB for random sequence generation, 16 trials (64%) had a low RoB for allocation concealment, 12 trials (48%) had a low RoB for blinding of patients and investigators, 10 trials (40%) had a low RoB for blinding of outcome assessors, 22 trials (88%) had a low RoB for outcomes measures, and 8 trials (32%) had a low RoB for incomplete outcome data.[1] Most of the RCTs were industry-sponsored.[1]

All trials included patients with moderate-to-severe RA and experience with MTX.[1] The median baseline age of the participants was 53 years, and the median proportion of females was 81%.[1] Eleven RCTs investigated biosimilars of adalimumab, and 7 trials each investigated etanercept and infliximab.[1] Equivalence was tested using prespecified margins for the ACR criteria (see **Appendix 1**), with at least 20% improvement in the core set measures (ACR20) (i.e., relative risk [RR], 0.94 to 1.06), and for the Health Assessment Questionnaire–Disability Index (HAQ-DI) (i.e., standard mean difference [SMD], −0.22 to 0.22) at 6 months for each outcome.[1] Biosimilars met equivalence with reference biologics in terms of ACR20 response (24 RCTs; n=10,259; RR, 1.01; 95% credible interval [CrI], 0.98 to 1.04) and change of HAQ-DI scores (14 RCTs; n=5,579; SMD, −0.04; 95% CrI, −0.11 to 0.02) considering prespecified margins of equivalence.[1]

Safety outcomes included TEAEs, serious adverse events, drug discontinuation, injection site reactions, hypersensitivity, and positive antidrug antibody formation rates.[1] Overall, biosimilar drugs were associated with similar rates of serious adverse events, discontinuation, and hypersensitivity reactions.[1] However, the risks of TEAEs, injection site reactions, and the formation of antidrug antibodies were lower in patients who received biosimilar drugs than those treated with reference biologic drugs.[1] Overall, 35.9% of patients using biosimilars and 39.6% of patients using reference drugs experienced TEAEs, and 6.2% of patients using biosimilars and 19.9% of patients using reference drugs experienced injection site reactions. Regarding the immunogenicity profile, 30% of patients receiving biosimilars and 33.5% receiving reference biologics had test results positive for antidrug antibodies.[1] There was moderate certainty of evidence that biosimilars likely resulted in little to no difference for safety outcomes assessed, except for TEAEs, injection site reactions, and antidrug antibodies. For these outcomes, the evidence was rated as low certainty.[1]

In summary, moderate-quality evidence suggests that biosimilars were not associated with differences in ACR20 response or HAQ-DI and have a similar safety profile, compared to their reference biologic agent in people with RA.[1]

Efficacy And Safety of Biological Disease Modifying Anti-Rheumatic Drugs for Management of Axial Spondyloarthritis

A 2022 systematic literature review informed the 2022 update of the ASAS-EULAR guideline for the management of r-axSpA and nr-axSpA.[2] This review focused on the evidence for efficacy and safety of bDMARDs.[2] Eligible interventions were any bDMARD therapy (bio-originator or biosimilar), including TNFi, IL-17i, IL-23i, and IL-12/23i, in any formulation and duration.[2] Comparators were defined as the same bDMARD in a different dose/regimen, another bDMARD, any non-bDMARD drug treatment, combination of bDMARD with non-bDMARD treatment, placebo or none (for safety only, if population-based incidence rates were reported).[2] Literature was searched through December 31, 2021 and 148 publications met inclusion criteria.[2] Thirty-six RCTs were published after the previous 2016 systematic review of which 16 RCTs (44%) assessed TNFi (10 originator, 6 biosimilar; including 3 trials on discontinuation and 2 on tapering), 15 RCTs (42%) assessed IL-17i (including 1 trial on discontinuation), 4 RCTs (11%) assessed IL-12/23i and 1 RCT assessed any bDMARD.[2] From these, 18 trials included patients with r-axSpA (50%), while 7 (19%) included patients with nr-axSpA, and 11 (31%) included patients with both nr-axSpA and r-axSpA.[2] In addition, 27 observational studies were included; 16 on safety and 9 on extra-musculoskeletal manifestations (psoriasis, uveitis, IBD); and 2 studies on both outcomes.[2]

For efficacy, ASAS response criteria (ASAS20 and ASAS40) and Spondyloarthritis Research Consortium of Canada (SPARCC) scores for sacroiliac joints and spine were used to evaluate disease improvement (see **Appendix 1**).[2] For safety, the following outcomes were assessed: serious adverse events, withdrawals due to adverse events, deaths, infections, malignancies, congestive heart failure, cardiovascular disease, infusion/injection-site reactions, lipid levels, renal function, hepatic effects, hematological abnormalities, gastrointestinal effects and demyelinating disease.[2]

- *Efficacy of Tumor Necrosis Factor Inhibitors*

Four RCTs of originator TNFi (golimumab, certolizumab, adalimumab, etanercept) met inclusion criteria. Two placebo-controlled studies with low RoB confirmed the efficacy of golimumab in r-axSpA and certolizumab in nr-axSpA (ASAS40 at 16 weeks in golimumab RCT: risk ratio [RR] 5.4; 95% CI 2.8 to 10.5; number needed to treat [NNT] 3 and ASAS40 at 52 week for certolizumab RCT: RR 3.6; 95% CI 2.4 to 5.3; NNT 3).[2] One placebo-controlled RCT with an unclear RoB studied adalimumab in patients axSpA focused on imaging outcomes and partially met its primary outcome (whole-body MRI smallest detectable change of ≥2.3 units met (44% vs. 13%); SPARCC spine improvement of ≥5 units not met (36% vs. 17%) after 6 weeks) and met several secondary outcomes (ASAS40 at 6 weeks: RR 3.1; 95% CI 1.2 to 8.2; NNT 3).[2] Finally, one RCT with unclear RoB compared etanercept to placebo in patients with suspected axSpA (no objective signs of inflammation required) and found no treatment difference (ASAS40 at 16 weeks: RR 1.0; 95% CI 0.2 to 4.6).[2]

- *Efficacy of Interleukin-17 Inhibitors*

Fourteen RCTs assessed the efficacy of IL-17i (secukinumab, ixekizumab, bimekizumab, brodalumab).[2] Patients with r-axSpA who received secukinumab showed greater improvement compared to placebo in 2 phase 3 RCTs (ASAS20 at weeks 12-16: 58.1–60.5% vs. 36.6–36.8%; low/unclear RoB).[2] The efficacy of secukinumab compared to placebo was shown in nr-axSpA, both with loading dose (LD) (ASAS40 41.5% vs. 29.2%) and without LD (39.8% vs. 19.9%).[2] In both r-axSpA and nr-axSpA, response to secukinumab was higher compared to placebo in patients who were TNFi-naïve and in patients with prior inadequate response to TNFi, with higher rates in the TNF-naïve cohort (ASAS40 38.8–43.9% vs. 28.1–36.8%).[2]

Three phase 3 RCTs with low RoB assessed the efficacy of ixekizumab.[2] In 2 of these studies in patients with r-axSpA, one including TNFi-naïve and the other TNFi-insufficient responder (IR) patients, ixekizumab was superior to placebo after 16 weeks (ASAS40 48–52% vs. 18% for TNFi-naïve; 25–31% vs. 13% for TNFi-

IR).[2] Similar results were seen in a trial of patients with nr-axSpA who were TNFi-naïve (ASAS40 35–40% for ixekizumab vs. 19% for placebo).[2] Evidence on several newer IL-17i has also recently emerged.[2] In a phase 3 trial with low RoB, brodalumab was superior to placebo in axSpA after 16 weeks (ASAS40 43.8% vs. 24.1%).[2] A phase 2 dose-ranging study of bimekizumab, which neutralizes both IL-17A and IL-17F, found response rates higher than with placebo in r-axSpA (ASAS40 29.5–45.9% vs. 13.3%, low RoB).[2]

- *Efficacy of Interluekin-23 and Interluekin-12/23 Inhibitors*

Four RCTs investigated the efficacy and safety of IL-23i (risankizumab) and IL-12/23i (ustekinumab), all with negative results.[2] Risankizumab was not superior to placebo in r-axSpA in a phase 2 study with low RoB (ASAS40 15.0–25.0% for various risankizumab doses vs. 17.5% for placebo).[2] Ustekinumab failed in TNFi-naïve patients with r-axSpA in a phase 3 study with low RoB (ASAS40 28.1–31.0% for ustekinumab vs. 28.4% for placebo).[2] These findings led to discontinuation of this study, as well as premature discontinuation of two ongoing phase 3 trials of ustekinumab.[2]

- *Effect of Biologic Disease Modifying Anti-Rheumatic Drugs on Uveitis, Inflammatory Bowel Disease, and Psoriasis*

The frequency of extra-musculoskeletal manifestations including uveitis, IBD and psoriasis observed in RCTs and open label extension trials of patients treated with TNFi and IL-17i was overall low and comparable to the placebo arms.[2] One observational study at low RoB conducted in a large Swedish registry (Swedish Rheumatology Quality Register) found an increased risk of uveitis with etanercept compared to adalimumab (hazard ratio [HR] 3.89; 95% CI 1.85 to 8.06) and infliximab (HR 1.99; 95% CI 1.23 to 3.22).[2] These findings were confirmed in another observational study within the same registry.[2] Other observational studies that evaluate development of uveitis with TNFi did not highlight any differences between TNFi or were at high RoB.[2] In one study, the risk of uveitis was higher with secukinumab compared to adalimumab, conducted in the same Swedish registry mentioned above (HR 2.32; 95% CI 1.16 to 4.63; low RoB).[2] In this study, the incidence of any uveitis episode, first or recurrent, was also higher with secukinumab compared with adalimumab or infliximab.[2] Observational studies of TNFi and the risk of IBD or psoriasis were all at unknown or high RoB with conflicting results.[2] No observational studies were available on the risk of IBD or psoriasis in IL-17i users.[2]

- *Safety Outcomes of Biologic Disease Modifying Anti-Rheumatic Drugs*

The frequency of serious infections, malignancies and cardiovascular events in RCTs of patients treated with TNFi and IL-17i was low.[2] The risk of infections was similar across different TNFi, in 2 observational studies at high RoB.[2] For malignancies, the risk in TNFi users was not increased compared to non-users in 2 large Scandinavian registries (incidence rate ratio (IRR) for any malignancy 0.8; 95% CI 0.6 to 1.1) and in one US cohort.[2] Incidence of neuroinflammatory events was higher in TNFi-experienced patients compared to naïve patients (incidence rate 78–88/100 000 person-years vs. 13–50/100 000 person-years).[2] Incidence of multiple sclerosis in TNFi users compared to the general population was increased (IRR 3.9; 95% CI 1.5 to 10.4), although it was unclear whether this was a drug or disease effect.[2] No observational studies on safety of IL-17i were available.[2]

- *Summary*

The efficacy of 2 TNFis, golimumab and certolizumab, compared to placebo in both r-axSpA and nr-axSpA patients was confirmed based upon ASAS response criteria (ASAS20 and ASAS40).[2] Data on the efficacy of IL-17i (secukinumab, ixekizumab) demonstrated clinically relevant effects in ASAS40 response for both r-axSpA and nr-axSpA compared to placebo.[2] IL-23 and IL-12/23 inhibitors (risankizumab, ustekinumab) failed to show relevant benefits in axSpA when compared to placebo.[2] No new safety risks were identified with TNFi use in observational studies, however, data was lacking for IL-17i.[2] Compared to TNFI, secukinumab (n=1 RCT) and etanercept (n=2 RCTs) were associated with increased risk of uveitis in observational studies.[2]

Efficacy And Safety of Targeted Synthetic Disease Modifying Anti-Rheumatic Drugs for Management of Axial Spondyloarthritis

A second systematic literature review informed the 2022 update of the ASAS-EULAR recommendations for the management of r-axSpA and nr-axSpA.[3] This review evaluated non-biologic and non-pharmacologic treatments for r-axSpA.[3] Literature was searched through January 1, 2022 for eligible RCTs evaluating efficacy and observational trials focused on safety.[3] For the purposes of this literature scan, evidence for the safety and efficacy of tsDMARDs in managing r-axSpA will be highlighted.

Efficacy of 4 tsDMARDs (apremilast, filgotinib, tofacitinib, and upadacitinib) was assessed in patients with r-axSpA in 5 RCTs, all at low RoB.[3] In one Phase 2 RCT, filgotinib was superior to placebo for the primary endpoint (ASAS20 at week 12: RR 1.91; 95% CI 1.35 to 2.71; NNT 3).[3] Two studies of tofacitinib 5 mg twice daily showed improvement in ASAS20 compared with placebo (Phase 2 RCT ASA20 at week 12: RR 2.35; 95% CI 1.25 to 4.41; NNT 5 and Phase 3 RCT ASAS20 at week 16: RR 3.10; 95% CI 1.90 to 5.07; NNT 4).[3] Compared to placebo in patients with r-axSpA, more patients treated with upadacitinib achieved the primary endpoint ASAS40 at week 14 (RR 2.02; 95% CI 1.36 to 3.01; NNT 4).[3] The large majority of the included patients were bDMARD-naïve, with the exception of the filgotinib RCT, which included 9.5% of bDMARD-experienced patients, and of the phase 3 RCT of tofacitinib, in which 23% of patients had previously used bDMARDs.[3] More patients reached ASAS20 and 40 in the TNFi-experienced group with tofacitinib compared with placebo (39% vs. 16% and 25% vs. 6%); while these figures were somewhat higher in the TNFi-naïve group (ASAS 20: 62% vs. 33%; ASAS40: 45% vs. 14%).[3] The efficacy of the 3 JAKi (filgotinib, tofacitinib, upadacitinib) was seen across all disease domains, including disease activity, function, mobility, quality of life and MRI inflammation (bone marrow edema).[3] In one placebo-controlled Phase 3 RCT, the PDE-4 inhibitor, apremilast was not effective in managing axSpA.[3]

In the placebo-controlled RCTs, upadacitinib and tofacitinib were associated with a higher risk of infections than placebo, mostly non-severe infections, in particular herpes zoster, during the first 12 months of treatment.[3] No major cardiovascular or venous thromboembolism events occurred up to 12 months of observation in phase 3 RCTs of upadacitinib and tofacitinib.[3] Liver enzyme elevation and creatine phosphokinase elevation occurred with upadacitinib and tofacitinib, but were infrequent.[3]

In summary, 3 JAKi filgotinib, tofacitinib, and upadacitinib have shown efficacy in r-axSpA when compared to placebo with an acceptable short-term safety profile.[3] The PDE-4 inhibitor, apremilast is not effective in managing r-axSpA.[3]

Efficacy Of Targeted Synthetic and Biologic Disease Modifying Anti-Rheumatic Drugs for Management of Rheumatoid Arthritis

A 2022 systematic literature review informed the 2022 update of EULAR guidance for the management of RA.[4] Literature was searched through January 14, 2022 to identify articles investigating the efficacy of pharmacologic management of RA.[4] Forty-seven articles investigated different medications including: csDMARDs (MTX, leflunomide, sulfasalazine, hydroxychloroquine), bDMARDs (abatacept, adalimumab, certolizumab pegol, denosumab, etanercept, infliximab, rituximab, sarilumab, tocilizumab) and tsDMARDs (baricitinib, filgotinib, tofacitinib, upadacitinib).[4] The RoB assessment resulted in 17/38 (44.7%) trials rated with a low RoB and 17 of 38 trials (44.7%) rated with a high RoB, primarily due to open-label or single-blinded trial designs.[4] For the purposes of this review, new evidence for bDMARDs and tsDMARDs in treating RA will be highlighted.

- *Efficacy Of Biologic Disease Modifying Anti-Rheumatic Drugs*

Most of the new evidence identified for bDMARDs was for investigational agents (olokizumab, opineracept, levilimab, denosumab) which are not FDA-approved for use in RA. One low RoB RCT evaluated rituximab combined with leflunomide versus placebo in combination with leflunomide, but the primary endpoint was not met (ACR50 response at week 24: 27% vs. 15%; p=0.081).[4] Two high RoB, open-label RCTs compared bDMARDs head-to-head.[4] In a study comparing

rituximab with tocilizumab, the primary endpoint was not met (Clinical Disease Activity Index [CDAI] 50% change at week 16: 45% vs. 56%; p=0.31).[4] The other study compared certolizumab with abatacept or tocilizumab, and after 24 weeks, no clinical meaningful differences between treatments were observed.[4]

- *Efficacy Of Targeted Synthetic Disease Modifying Anti-Rheumatic Drugs*

Five RCTs (4 low RoB, one unclear RoB) investigated the efficacy of JAKi in RA.[4] One study with unclear RoB compared combination baricitinib/MTX versus MTX alone and showed baricitinib was more effective in reducing signs and symptoms of RA (ACR20 at week 12: 64.1% vs. 32.4%; p<0.001).[4] In one low RoB RCT, the superiority of upadacitinib monotherapy versus MTX monotherapy was shown at 12 weeks (ACR50: 15 mg, 52% vs. 28%; p<0.001 and 30 mg, 56% vs. 28%; p<0.001).[4] Another low RoB RCT showed upadacitinib at 7.5 mg, 15 mg and 30 mg combined with csDMARDs was more effective than placebo combined with csDMARD for clinical outcomes at 12 weeks (ACR20 7.5mg 75.5% vs. 42.9%; p <0.001; ACR20 15 mg 83.7% vs. 42.9%; p<000.1; ACR20 30 mg 80% vs. 42.9%; p<0.001).[4] Filgotinib in combination with csDMARDs was superior to placebo (one low RoB RCT) in achieving ACR20 at 12 weeks (100 mg, 57.5% vs. 31.1%; p<0.001 and 200 mg, 66% vs. 31.1%; p<0.001).[4] In another low RoB RCT, filgotinib combined with MTX was superior to MTX monotherapy in achieving ACR20 at 24 weeks (100mg, 80.2% vs. 71.4%; p<0.001 and 200mg, 81% vs. 71.4%; p<0.001).[4] However, filgotinib 200 mg once daily as monotherapy was not superior to MTX monotherapy at week 24 (ACR20 78.1% vs. 71.4%; p=0.058).[4]

- *Head-to-Head Comparisons: Targeted Synthetic Disease Modifying Anti-Rheumatic Drugs versus Biologic Disease Modifying Anti-Rheumatic Drugs*

Three head-to-head trials compared tsDMARDs to bDMARDs.[4] Upadacitinib 15 mg once daily in combination with MTX showed superiority in ACR50 response over adalimumab 40 mg every 2 weeks combined with MTX at week 12 (45% vs. 29%; p>0.001; low RoB).[4] Upadacitinib-treated patients had significantly less radiographic damage progression compared with placebo, while results were comparable to adalimumab at week 26.[4] In a high RoB RCT patients were either randomized to abatacept (125 mg weekly) or upadacitinib 15 mg once daily (both in combination with csDMARDs).[4] Upadacitinib plus csDMARDs was superior to abatacept plus csDMARDs at week 12 in disease activity score-28 (DAS28)-CRP.[4] Another head-to-head trial (low RoB) investigating filgotinib 200 mg once daily in combination with MTX demonstrated non-inferiority in achieving DAS28-CRP ≤3.2 responses at week 12 when compared with adalimumab 40 mg every 2 weeks in combination with MTX (49.7% vs. 43.3%; p<0.001).[4]

In summary, recently published evidence for the efficacy of rituximab plus leflunomide versus monotherapy with leflunomide in RA did not show a statistically significant difference between treatments (low RoB).[4] JAKi (baricitinib, upadacitinib, filgotinib) combined with MTX or csDMARDs improved RA symptoms compared to MTX monotherapy.[4] Monotherapy with filgotinib was not more effective than MTX in achieving ACR20 at week 24 (low RoB).[4] In head-to-head comparisons, upadacitinib combined with MTX was more effective than adalimumab with MTX in achieving ACR50 response at week 12 (low RoB).[4] Upadacitinib combined with csDMARDs was superior to abatacept combined with csDMARDs in reducing the severity of RA symptoms as assessed by the DAS28-CRP at week 12 (low RoB).[4] Filgotinib 200 mg once daily plus MTX was noninferior to adalimumab 40 mg every 2 weeks plus MTX in achieving DAS28-CRP ≤3.2 at 12 weeks (low RoB).[4]

Safety Of Targeted Synthetic and Biologic Disease Modifying Anti-Rheumatic Drugs for Management of Rheumatoid Arthritis

A 2022 a second systematic literature review informed the 2022 update of EULAR recommendations for the management of RA.[5] Literature was searched through January 14, 2022 to identify relevant articles investigating the safety of all DMARDs (csDMARDs, bDMARDs, tsDMARDs) used to manage RA in adults.[5] Fifty-nine observational studies, primarily cohort/registry studies, 2 RCTs with a primary safety outcome, and 28 RCTs/long term extensions (LTEs) met inclusion criteria.[5] The following safety outcomes were considered: infections (including serious infections, opportunistic infections such as tuberculosis [TB] and herpes zoster), malignancies, mortality, MACEs, venous thromboembolism (VTE) including pulmonary embolism/deep venous thrombosis, changes in lipid levels, elevations of creatine phosphokinase, impairments in renal function, elevations of liver enzymes, hematological abnormalities, gastrointestinal side effects,

demyelinating disease, and induction of autoimmune disease.[5] The RoB of each included study was assessed using the Hayden-tool for observational studies and the Cochrane Collaboration's tool for RCTs.[5] For the purposes of this literature scan, evidence for the safety of bDMARDs (TNFi, IL-6i) and tsDMARDs (JAKi) will be highlighted.

- *Infections*

Of 27 observational studies addressing the risk of infections, 3 studies compared bDMARDs/JAKi to the general population, 8 studies compared bDMARDs/JAKi to csDMARDs, 3 studies compared risks across csDMARDs, and 13 studies compared risks across bDMARDs/JAKi.[5] The risk of serious infections was increased with bDMARDs compared with the general population in one study (adjusted HR [aHR] 4.1; 95% CI 3.6 to 4.7), and compared with csDMARDs in 2 studies. All studies had unclear RoB.[5] Seven studies reported a similar risk of serious infections across bDMARDs and 2 studies showed a lower infection risk with abatacept.[5] Of note, the latter result was not seen in 5 other studies, including one at low RoB from a Danish registry.[5] Serious infections were not more common with tofacitinib than with bDMARDs in 3 studies, including one with low RoB, from the Consortium of Rheumatology Researchers of North America (CORRONA registry) (aHR 0.99; 95% CI 0.75 to 1.30).[5]

The risk of any opportunistic infection was not increased with TNFi plus MTX compared with triple csDMARD therapy, and across bDMARDs (2 studies at high and 1 at unclear RoB).[5] In one study at low RoB from a German registry, patients on JAKi (aHR 3.66; 95% CI 2.38 to 5.63), TNFi (aHR 1.63; 95% CI 1.17 to 2.28), and rituximab (aHR 1.57; 95% CI 1.03 to 2.40), but not on other bDMARDs, were more likely to be infected by herpes zoster than patients on csDMARDs.[5] In 3 studies (one at low RoB) infections by herpes zoster were more frequent with tofacitinib than with bDMARDs.[5]

The risk of TB was not increased with bDMARDs compared with the general population in an observational study from Slovenia, where strict procedures for screening and treatment of latent TB were in place (one study at high RoB).[5] Another observational study at high RoB found a similar risk of TB with abatacept compared with other b/tsDMARDs.[5] Reactivation of the hepatitis B virus was more common with abatacept and rituximab (but not tocilizumab) than with TNFi in one observational study at unclear RoB.[5]

In one RCT, the ORAL-Surveillance trial, the risk of serious infections was increased with tofacitinib 10 mg twice daily compared with TNFi, while the risk of infections by herpes zoster was increased with both tofacitinib 10 mg and 5 mg.[5] In two RCTs, infections by herpes zoster were more common with filgotinib and upadacitinib than with placebo.[5] In 5 active-controlled RCTs, the number of infections caused by herpes zoster was higher with upadacitinib (range: 0.8%–3%) than with an active comparator (0.3%–1.3%), but similar with filgotinib (0.4%–1.0%) versus an active comparator (0.6%–1%).[5]

- *Malignancies*

Nine observational studies evaluated the risk of malignancies with bDMARDs. One study compared bDMARDs with the tsDMARD, tofacitinib.[5] In 2 observational studies, the risk of malignancies was not increased with bDMARD compared with the general population.[5] In one study at low RoB, from the Swedish Rheumatology Quality Register, there was a higher risk of lymphomas both in bDMARD-naïve (aHR 1.56; 95% CI 1.37 to 1.78) and in bDMARD-treated (aHR 1.65; 95% CI 1.31 to 2.08) patients compared with the general population.[5] In this study, the risk was lower with bDMARDs (TNFi and non-TNFi analyzed together) than with MTX (aHR 0.52; 95% CI 0.32 to 0.83).[5] One study at high RoB, found no difference in the risk of malignancies between TNFi and csDMARDs and another, at low RoB, found no difference between tofacitinib and bDMARDs.[5] The risk of malignancies was, in general, similar across bDMARDs in 5 studies, with conflicting data for abatacept.[5]

Compared with TNFi, tofacitinib was associated with an increased risk of malignancies (HR 1.48; 95% CI 1.04 to 2.09) over 5.5 years in the RCT, ORAL-Surveillance.[5] In subgroup analyses, the incidence of malignancies was higher across all arms for patients 65 years and older compared with patients less than 65 years of age (range: 1.1–1.9/100 person-years vs. 0.6–0.9/100 person-years).[5] In two LTE trials up to 52 weeks, the incidence of malignancies was similar with JAKi (filgotinib and upadacitinib) and adalimumab in patients who, by design, did not had to have malignancy risk factors.[5]

- *Major Cardiovascular Events*

Thirteen observational studies evaluated the risk of MACEs.[5] In one study, at unclear RoB, patients on infliximab, etanercept and abatacept, but not on other bDMARDs or tofacitinib, had a lower risk of MACE compared with patients on csDMARDs.[5] In another study, the risk of MACE was lower if a bDMARD was combined with MTX than with a bDMARD alone.[5] The risk of MACE was similar with tofacitinib and bDMARDs in one study, at low RoB (aHR 0.61; 95% CI 0.34 to 1.06).[5] In another study with high RoB, the risk of MACE was also similar with tofacitinib and TNFi both in a population representing real-world patients (aHR 1.01; 95% CI 0.83 to 1.23), and in patients 50 years or older and with at least one cardiovascular risk factor (aHR 1.24; 95% CI 0.90 to 1.69).[5]

Four observational studies with high RoB, evaluated the risk of VTE with csDMARDs and b/tsDMARDs.[5] There was no difference in the risk of VTE between bDMARDs and csDMARDs in 2 studies.[5] In one of these, there was an increased risk only in patients who switched to a second b/tsDMARD compared with patients on csDMARDs.[5] Finally, in one study, the risk of VTE was similar with tofacitinib and TNFi (aHR 1.13; 95% CI 0.77 to 1.65).[5]

Compared with TNFi, tofacitinib was associated with an increased risk of MACE (HR 1.33; 95% CI 0.91 to 1.94) over 5.5 years in the RCT, ORAL-Surveillance (not statistically significant).[5] Non-inferiority of tofacitinib could not be claimed for MACE.[5] In subgroup analyses, the incidence of MACE was higher across all arms for patients 65 years and older compared with patients less than 65 years of age (0.9–1.9/100 person-years vs. 0.7/100 person-years).[5] In another RCT, tocilizumab was non-inferior to etanercept for the risk of MACE over a mean follow-up of 3.2 years (HR 1.05; 95% CI 0.77 to 1.43).[5] In ORAL-Surveillance, the risk of VTE was increased only with tofacitinib 10 mg compared with TNFi.[5] In two LTE studies up to 52 weeks, the incidence of MACE was similar with JAKi (filgotinib and upadacitinib) and adalimumab in patients who, by design, did not had to have cardiovascular risk factors.[5]

- *Other Adverse Events*

Intestinal perforations and neuroinflammatory events were assessed in 2 observational studies, each in patients on bDMARDs.[5] In a large study with low RoB, lower intestinal perforations were uncommon but more frequent with tocilizumab (0.45/100 person-years) than with TNFi (0.18/100 person-years) (aHR 2.61; 95% CI 1.61 to 4.24).[5] In another study with low RoB, diverticular perforations (but not of other etiologies) occurred more often with tocilizumab than with rituximab/abatacept (HR 3.8; 95% CI 1.1 to 13.6).[5] No studies evaluating the risk of intestinal perforations with other IL-6i could be included.[5] In the RCT, ORAL-Surveillance, intestinal perforations were uncommon (tofacitinib 5 mg 0.17/100 person-years; tofacitinib 10 mg 0.10/100 person-years; TNFi 0.08/100 person-years) and did not occur significantly more frequently with tofacitinib 5 mg (HR 2.20; 95% CI 0.68 to 7.15) nor with tofacitinib 10 mg (HR 1.29; 95% CI 0.35 to 4.80) than with TNFi.[5] No cases of intestinal perforation occurred in 2 other RCTs on IL-6Ri and in 5 out of 8 trials on JAKi.[5]

All-cause mortality with bDMARDs was assessed in 7 observational studies. The standardized mortality rate was similarly high for bDMARD users (HR 1.8; 95% CI 1.7 to 2.0) and non-users (HR 1.5; 95% CI 1.4 to 1.5) in one study at high RoB.[5] Another study, at low RoB, found a lower risk of death with bDMARDs than with csDMARDs, and 2 studies (one at low RoB) found no difference between tofacitinib and bDMARDs.[5] In ORAL-Surveillance, the risk of mortality was increased only with tofacitinib 10 mg compared with TNFi.[5] Neuroinflammatory events were not more common with TNFi compared with the general population and with csDMARDs.[5] Seven studies addressed withdrawals due to adverse events with bDMARDs one with JAKi.[5] These studies reported results in line with the known safety profile of b/tsDMARDs.[5]

- *Summary*

This systematic review found the risk of malignancies and MACE is similar, or even decreased, with bDMARDs compared with csDMARDs.[5] However, these adverse outcomes occurred more frequently with tofacitinib than with TNFi in patients who had certain cardiovascular risk factors.[5] The risk of serious infections is increased with bDMARDs compared with csDMARDs and is similar across bDMARDs and tofacitinib.[5] Of note, herpes zoster is more common with JAKi than with csDMARDs or bDMARDs, with the possible exception of filgotinib.[5] Lower intestinal perforations are rare but occur more often with tocilizumab than with other bDMARDs.[5] Whether the overall safety profile differs across JAKi and across IL-6i remains unknown.[5]

Efficacy And Safety of Pharmacological Treatment of Psoriatic Arthritis

A 2024 systematic review supported the 2023 update of the EULAR recommendations for the management of PsA.[6] Literature was searched through December 28, 2022 for evidence assessing the safety and efficacy of csDMARDs (leflunomide, MTX); bDMARDs (TNFi, IL-17i, IL-23i, IL-12/23i); and tsDMARDs (JAKi, PDE-4i, TYK2i) in patients with PsA.[6] Thirty RCTs assessed efficacy and 24 articles (15 observational studies and 9 LTE trials) evaluated safety.[6] Of the 30 RCTs, 19 (63.3%) had low RoB and 7 (23.3%) had high RoB due to an open-label or single-blinded trial design.[6] Two trials (6.6%) had an unclear RoB due to insufficient reporting of randomization sequence generation and allocation concealment methods.[6] Of the 24 observational studies, 8/24 (33.3%) had a low RoB, 1/24 (4.2%) with unclear RoB and 10/24 (37.5%) with a high RoB.[6] For the purposes of this literature scan, evidence for the safety of bDMARDs and tsDMARDs will be highlighted.

- *Efficacy Of Biologic Disease Modifying Anti-Rheumatic Drugs*

In total, 13 placebo-controlled RCTs investigating FDA-approved bDMARDs (one golimumab RCT, one ustekinumab RCT, 4 secukinumab RCTs, 2 bimekizumab RCTs, 3 guselkumab RCTs, 2 risankizumab RCTs) with or without concomitant csDMARDs met inclusion critiera.[6] In one low RoB RCT, MTX plus placebo were compared with MTX plus the TNFi, golimumab, in patients naïve to MTX and bDMARD treatment with active dactylitis.[6] Significantly higher median reduction in the dactylitis severity score at week 24 (primary endpoint) was observed for the MTX plus golimumab arm (n=21) compared with the MTX plus placebo (n=23) arm (−5 points vs. −2 points; p=0.026).[6] In a non-inferiority low RoB trial, ustekinumab plus MTX (n=88) was non-inferior to ustekinumab plus placebo (n=85) in PsA patients naïve to ustekinumab for the primary outcome of mean Disease Activity Score-28 with Erythrocyte Sedimentation Rate [DAS28-ESR] at 24 weeks.[6] No meaningful differences in secondary outcomes were observed between the groups.[6]

Four RCTs (2 with low RoB, two with unclear RoB) investigated secukinumab, an iL-17i treatment.[6] One RCT with an unclear RoB demonstrated superior efficacy of secukinumab 300 mg (but not secukinumab 150 mg) every 4 weeks versus placebo (ACR20 at week 16 for secukinumab 300 mg, 51.5% vs. 36.9%; p<0.001 and for secukinumab 150 mg, 23.1% vs. 36.9%; p=0.10) in a biological naïve PsA population.[6] Another RCT with an unclear RoB investigated the change of ultrasound synovitis in biological naïve patients treated with secukinumab 300 mg every 4 weeks, 150 mg every 4 weeks or placebo.[6] The primary endpoint (the ultrasound Global EULAR and Synovitis Score mean change from baseline to week 12) was met with higher response rates in secukinumab (150 mg/300 mg combined group) treated patients versus placebo.[6] A third RCT with low RoB demonstrated superior efficacy of secukinumab 300 mg or 150 mg every 4 weeks when compared with placebo, meeting the study's primary endpoint, ASAS20 response at week 12 (63% vs. 66% vs. 31%, respectively; p<0.001).[6] The fourth RCT with low RoB compared secukinumab 150 mg every 4 weeks with and without loading (i.e., secukinumab 150 mg at weeks 0, 1, 2 and 3) to placebo.[6] Both regimens showed superior efficacy compared with placebo with no meaningful differences between the active treatment arms.[6]

Another IL-17i, bimekizumab, was investigated in two placebo-controlled RCTs.[6] The first low RoB investigated patients naïve to bDMARDs, and bimekizumab 160 mg every 4 weeks improved ACR50 response compared to placebo at week 16 (44% vs. 10%; p<0.001).[6] Reduction of signs and symptoms of other PsA manifestations like skin disease, enthesitis, dactylitis and radiographic damage progression were also noted with bimekizumab over placebo. A second RCT with similar design showed bimekizumab improved PsA symptoms versus placebo in patients with insufficient response to TNFi.[6]

Three RCTs investigated guselkumab, an IL-23i.[6] One low RoB, phase 3, double-blind RCT investigated patients with and without prior TNFi exposure.[6] The ACR 20% response at week 24 (primary endpoint) was significantly higher in guselkumab-treated patients compared with placebo (guselkumab 100 mg every 4 weeks: 59% vs. 22%; p<0.001 and guselkumab 100 mg every 8 weeks: 52% vs. 22%; p<0.001).[6] In another low RoB RCT only patients who were naïve to bDMARDs were included.[6] Guselkumab treatment was superior to placebo for ACR20 at week 24 (guselkumab 100 mg every 4 weeks 64% vs. placebo 33%; p<0.001 and guselkumab 100 mg every 8 weeks 64% vs. placebo 33%; p<0.001).[6] In the third RCT, with an unclear RoB, guselkumab 100 mg every 8 weeks was superior to placebo in patients who were insufficient responders to TNFi for the primary endpoint of ACR 20 at week 24 (44.4% vs 19.8%; p<0.001) as well as all other secondary endpoints (physical function, skin disease, enthesitis, dactylitis and fatigue).[6]

The efficacy and safety of risankizumab, another IL-23i, was investigated in 2 RCTs (both low RoB).[6] In patients with insufficient response to csDMARDs, patients were randomized to risankizumab 150 mg subcutaneously (at weeks 0, 4 and 16) or placebo.[6] At week 24 more patients receiving risankizumab met the primary endpoint of ACR 20 response compared with placebo (57.3% vs. 33.5%; p<0.001).[6] In another low RoB RCT, half of the patients had received bDMARD therapy prior to the study.[6] In this RCT, more patients receiving risankizumab met the primary endpoint of ACR 20 response at week 24 compared with placebo (51.3% vs. 26.5%; p<0.001).[6] Improvements in patient-reported outcomes, work productivity and health-related quality of life were observed in patients treated with risankizumab compared with placebo.[6]

- *Efficacy Of Targeted Synthetic Disease Modifying Anti-Rheumatic Drugs*

Two trials investigating the efficacy of tsDMARDs were identified.[6] In patients with prior insufficient response to bDMARDs, upadacitinib 15 and 30 mg daily improved ACR20 response at week 12 compared to placebo (15 mg once daily 56.9% vs. 30 mg once daily 63.8% vs. placebo 24.1%; p<0.001).[6] Deucravacitinib, a selective, oral TYK2 inhibitor, was investigated in a phase 2 double-blind RCT (low RoB) in patients with insufficient response to ≥1 previous NSAID or DMARD therapy.[6] The ACR 20 response at week 16 (primary endpoint) was higher for deucravacitinib 6 mg once daily versus placebo (52.9% vs. 31.8%; p=0.013) and deucravacitinib 12 mg once daily versus placebo (62.7% vs. 31.8%; p<0.001).[6]

- *Head-to-Head Comparisons: Targeted Synthetic Disease Modifying Anti-Rheumatic Drugs versus Biologic Disease Modifying Anti-Rheumatic Drugs*

Three head-to-head RCTs assessed comparative efficacy of tsDMARDs with bDMARDs.[6] One high RoB, assessor-blinded, RCT compared open-label ixekizumab to adalimumab in bDMARD naïve patients with insufficient response to csDMARDs. The primary endpoint was defined as simultaneous achievement of ACR50 and Psoriasis Area and Severity Index (PASI) 100 response at week 24.[6] Significantly more patients achieved the primary outcome in the ixekizumab group compared to adalimumab (36% vs. 27.9%; p=0.036).[6] No significant difference was found between the arms when comparing ACR (20/50/70) response rates, HAQ-DI or dactylitis remission. The results were maintained until week 54, with a significantly higher proportion of patients achieving a simultaneous ACR50 and PASI 100 response with ixekizumab versus adalimumab (39% vs. 26%; p<0.001).[6]

In a low RoB, double-blind RCT, bDMARD naïve patients were randomized to monotherapy with secukinumab 300 mg every 4 weeks or adalimumab 40 mg every 2 weeks. The study was powered to show superiority of secukinumab over adalimumab in achieving an ACR20 response at week 52, but there was no difference between groups with an ACR20 response of 67% versus 62% (p=0.072) for secukinumab and adalimumab, respectively.[6] Another low RoB, double-blind RCT compared upadacitinib 15 mg once daily and 30 mg once daily to adalimumab 40 mg every 2 weeks and placebo in patients with insufficient response to csDMARDs.[6] ACR20 response rates at week 12 were 70.6%, 78.5%, 65.0% and 36.2% for upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, adalimumab 40 mg every 2 weeks and placebo. All active treatment arms showed superiority compared with placebo (p<0.001).[6] Both upadacitinib dosages were non-inferior compared with adalimumab (with a margin 15%), while testing for superiority (versus adalimumab was only shown for upadacitinib 30 mg once daily [p<0.001]) and not for upadacitinib 15 mg once daily (hierarchical testing failed, no p-value reported).[6]

- *Infections*

A comparison of secukinumab with adalimumab showed similar rates of serious infections (secukinumab 7/426 [1.6%] and adalimumab 6/427 [1.4%]; however, candida infections were numerically more frequently in secukinumab-treated patients (secukinumab 16/426 [4%] and adalimumab 7/427 [2%]).[6] Two cases of candida skin infection were observed in tildrakizumab-treated patients (compared with none in the placebo arm).[6] Candida and other fungal infections were also more frequent in bimekizumab-treated patients compared with placebo in 2 RCTs (bimekizumab 7/267 [3%] vs. placebo 0, [0%]; and bimekizumab 20/431 [5%] vs. placebo 4/281 [1%] vs. adalimumab 1/140, [<1%]) with no systemic fungal infections observed.[6] No serious infections, herpes zoster or opportunistic infections were observed in the deucravacitinib phase 2 trial until week 16.[6] Rates of candida and fungal infections were very low in studies investigating IL-23i, with few cases of local skin candidiasis.[6] In an integrated safety analyses of guselkumab, 3 cases of opportunistic infections were observed in a 52-week RCT, with an otherwise consistent safety profile compared with the placebo-controlled period, no cases of active TB, and no signal for increased rates of serious infections.[6] Long-term safety of PsA patients in the upadacitinib trial program (comparing upadacitinib 15 mg once daily (n=907) to adalimumab 40 mg every 2 weeks (n=429); low RoB) showed higher rates for upadacitinib 15 mg for serious infections (exposure adjusted event rate [EAER] upadacitinib 15mg once daily, 3.9; 95% CI 3.1 to 4.9 and EAER adalimumab, 1.4; 95% CI, 0.8 to 2.5), opportunistic infections (EAER upadacitinib 15mg, 0.5; 95% CI, 0.2 to 0.9 and EAER adalimumab, 0) and herpes zoster rates (EAER upadacitinib 15mg, 3.6; 95% CI, 2.8 to 4.6 and EAER adalimumab 0.4, 95% CI, 0.1 to 1.1).[6] No cases of active TB occurred in both groups.[6] Data for upadacitinib 30 mg once daily was not reported.[6]

- *Major Adverse Cardiovascular Events and Arterial Thrombotic Events*

During the placebo controlled period of the SELECT PsA trials, in SELECT PsA 1, no MACEs occurred in the upadacitinib treatment arms, one in the placebo, and 2 in the adalimumab arm.[6] In the SELECT PsA 2 RCT, one MACE occurred in upadacitinib 15 mg-treated patients (compared with none in the placebo and upadacitinib 30 mg arm).[6] No MACE was seen in the deucravacitinib phase 2 trial.[6] During the long-term safety period comparing upadacitinib 15 mg once daily (n=907) to adalimumab 40 mg every 2 weeks (n=429) rates of adjudicated MACE were similar between both groups (EAER UPA 15 mg 0.3; 95% CI 0.1 to 0.6 and EAER adalimumab 0.3; 95% CI 0.1 to 1.0).[6] Analysis of the long-term safety data of PsA patients treated with tofacitinib (high RoB) showed 1/347 cases of arterial thromboembolisms in the tofacitinib 5 mg twice daily arm (incidence rate 0.5; 95% CI 0.01 to 2.78), and 2/106 in the adalimumab arm (incidence rate 2.16, 95% CI 0.26 to 7.82) and no events in the tofacitinib 10 mg BID arm.[6] No signal for MACE was identified in trials investigating risankizumab or in the integrated safety analyses of guselkumab.[6]

- *Malignancies*

During the placebo-controlled period of SELECT-PsA 1, five malignancies (excluding non-melanoma skin cancer) were observed: one in the upadacitinib 15 mg arm (neuroendocrine carcinoma), one in the upadacitinib 30 mg arm (malignant lung neoplasm) and 3 in the adalimumab 40 mg every 2 weeks arm (colon cancer, ovarian cancer, uterine cancer), with none in the placebo arm.[6] In the placebo controlled period of the SELECT-PsA 2 trial, malignancies observed in each of the upadacitinib arms were: one prostate cancer, one rectal cancer in the upadacitinib 15 mg (n=2); one rectal adenocarcinoma and one ovarian/endometrial cancer in the upadacitinib 30 mg arm (n=2), compared with none in the placebo arm.[6] In the upadacitinib LTE trial, rates of malignancies (excluding non-melanoma skin cancer) were similar (upadacitinib 15 mg, HR 0.6; 95% CI, 0.3 to 1.1 and adalimumab, HR 0.4; 95% CI, 0.1 to 1.1). Higher age (HR, 3.1; 95% CI, 1.7 to 5.8) and body mass index (HR 1.1; 95% CI, 1.03 to 1.15) were significant predictors for development of malignancies in patients receiving upadacitinib 15 mg once daily.[6] Rates of non-melanoma skin cancer were numerically higher in patients treated with upadacitinib (HR 0.8; 95% CI 0.4 to 1.3) compared to adalimumab (0.2; 95% CI 0 to 0.8).[6] No malignancy occurred during the 16 weeks of the deucravacitinib phase 2 trial.[6]

In the secukinumab trial database, secukinumab was associated with a cumulative incidence of 51/4,902 malignancies in PsA patients (exposure-adjusted incidence rates per 100 patient year 1.04; 95% CI, 0.77 to 1.37), with non-melanoma skin cancer (basal cell carcinoma, n=15; squamous cell carcinoma, n=2)

being the most prevalent.[6] The incidence rate was comparable to the expected rate of the general population (standardized incidence rate 1.16; 95% CI, 0.80 to 1.62).[6] No signal for an increased risk for malignancies was found in the integrated safety analysis of guselkumab.[6]

- *Other Adverse Events*

In the EXCEED RCT, new cases of IBD were more frequent in the secukinumab arm compared with adalimumab (2 cases vs. none).[6] In the placebo-controlled period (until week 16) of the phase 2 trial investigating deucravacitinib, acne was reported in 2 of 70 (2.9%) patients receiving deucravacitinib 6 mg once daily and 1 of 67 (1.5%) in the 12 mg once daily arm compared with none in the placebo group.[6] Also, acneiform dermatitis was reported in 2 of 70 (2.9%), 2 of 67 (3%) patients in deucravacitinib 6 mg/12 mg once daily groups compared with none in the PBO arm.[6]

In the DISCOVER-1 and DISCOVER-2 trials, similar rates of suicidal ideation in guselkumab-treated patients, compared with placebo were observed, with no events occurring in the studies investigating bimekizumab and tildrakizumab.[6] In the COSMOS RCT, one patient in the guselkumab arm experienced 2 events of conversion disorder, which resolved after discontinuation of guselkumab.[6] Another patient with a previous history of a suicidal attempt did report depressive symptoms after receiving guselkumab after the study drug was discontinued, and no further follow-up occurred.[6] Trials investigating brodalumab were terminated early following a sponsor's decision due to events of suicidal ideation and behavior observed in the study program.[6] In the integrated safety analyses of guselkumab, no cases of IBD or anaphylactic reactions were observed.[6] No risk for MACE or malignancies was observed in the placebo and long-term extension period for apremilast-treated patients.[6] Also, investigation of long-term safety from the ustekinumab PsA trial database did not reveal any new signal regarding the safety of MACE, malignancies or TB.[6]

- *Summary*

In this systematic review the efficacy of the bDMARDs (golimumab, secukinumab, ustekinumab, and golimumab) compared with placebo in treating PsA was confirmed.[6] Non-inferiority of ustekinumab monotherapy compared with ustekinumab plus MTX combination therapy was shown one RCT.[6] Head-to-head comparisons of the IL17i (secukinumab and ixekizumab), compared with TNFi (adalimumab) showed comparable ACR response rates, but better skin responses in IL-17i-treated patients.[6] Studies investigating newer IL-23i (guselkumab, risankizumab, tildrakizumab) and IL-17i (bimekizumab), showed superior efficacy when compared with placebo across many disease domains (including arthritis, enthesitis, dactylitis, skin and nail disease) as well as improvement of physical function.[6] The RCTs on novel tsDMARDs, deucravacitinib (TYK2) and upadacitinib (JAKi), showed significantly higher response rates compared with placebo treatment, as well as superiority of upadacitinib 30 mg (but not 15 mg) once daily compared with adalimumab 40 mg every 2 weeks at the expense of more adverse events.[6]

In regard to safety, 2 observational studies found higher rates of hospitalized infections in IL-17i-treated patients (compared with TNFi), while another study did not show an increased risk.[6] Fungal infections occurred more frequently in patients receiving IL-17i compared with placebo and TNFi treatment.[6] Only very few cases of fungal infections were observed in IL23-treated patients.[6] Higher event rates in upadacitinib-treated patients of serious infections, opportunistic infections, and herpes zoster rates were observed, compared with adalimumab, while rates of MACE and VTEs were similar.[6] Also, decreases of hemoglobin levels were higher in upadacitinib-treated patients, while they increased on adalimumab.[6] Increased rates of acne and acneiform rashes were reported in deucravacitinib-treated patients.[6] Results of the safety analysis also highlighted the importance of comorbidities in PsA patients, with higher risks of serious infections especially in patients with one or more comorbidities compared with patients without comorbidities, a higher risk for VTEs in patients with cardiovascular or VTE risk factors.[6] While not associated with any specific DMARD therapy, an increased risk for non-melanoma skin cancer in PsA patients was observed, as well as an increased all-cause mortality and death from coronary heart disease.[6]

Risk of Candida Infection and Serious Infections in Patients with Moderate-to-Severe Plaque Psoriasis Receiving Biologics

A 2022 systematic review and meta-analysis assessed the infection risks of TIMs used to manage moderate-to-severe PsO.[7] Three main classes of biologic agents, including TNFi (adalimumab, infliximab, and etanercept); IL-12/23i (ustekinumab and guselkumab); and IL-17i (secukinumab, ixekizumab, and brodalumab) were included in the literature search.[7] Literature was searched through December 2021 for RCTs that reported the outcome of *Candida* and other infections in adults receiving TIMs.[7] Data from 52 RCTs (n=27,297) met inclusion criteria.[7] The control group included at least one of the following therapies: another biological agent, or conventional systematic therapy, or placebo.[7] There were 51 RCTs that reported the number of serious infections, with 10 RCTs (19.6%) that had no serious infection in either study arm.[7] Eighteen RCTs (34.6%) provided the number of patients who developed *Candida* infection.[7] In all RCTs the randomized controlled phase lasted 12–52 weeks.[7]

Forty-five RCTs (86.53%) described the methods of patient randomization, 44 RCTs (84.61%) reported concealment of allocation, 40 RCTs (76.92%) described blinding of participants and personnel, and 31 RCTs (59.61%) mentioned blinding of the outcomes assessors.[7] Incomplete outcome data were well balanced in 49 RCTs (94.23%).[7] Selective outcome reporting and other sources of bias were not identified in 38 RCTs (73.08%) and 31 RCTs (59.61%), respectively.[7] Most of the RCTs included in the meta-analysis were funded by the pharmaceutical industry in the implementation and data analysis stage but not for the writing of the manuscript and publication stage.[7] The quality of most evidence was low or very low (except for high-quality evidence for secukinumab versus placebo, moderate-quality evidence for anti-IL-17 agents versus anti-IL-12/23 agents for Candida infection, and guselkumab versus placebo for serious infections).[7]

- *Interleukin-17 Inhibitors versus Placebo: Risk of Candida Infections*

There were 11 RCTs that evaluated IL-17i versus placebo.[7] The reported *Candida i*nfection rate was 1.53% in the IL-17i arm (n=7,387, including 2,030 cases treated with secukinumab, 2,328 cases treated with ixekizumab, and 3,029 cases treated with brodalumab) and was 0.53% in the placebo arm (n=2,465).[7] The pooled odds ratio (OR) from 10 RCTs was 2.30 (95% CI 1.54 to 3.45, P<0.0001), showing that IL-17i significantly increased the risk of *Candida* infection compared to placebo, with no evidence of significant heterogeneity (I^2 = 0%).[7] A stratified meta-analysis demonstrated that secukinumab significantly increased the risk of *Candida* infection) compared with placebo, without significant heterogeneity (OR 3.22, 95% CI 1.79 to 5.80, P<0.0001; I^2 = 0%).[7] Only one RCT compared ixekizumab with placebo and more patients who developed *Candida* infections received ixekizumab than placebo (the *Candida* infection rate was 0.99% in the ixekizumab arm and was 0.51% in the placebo arm).[7] There was no significant difference in the risk of *Candida* infection between the brodalumab and placebo groups and no evidence of significant heterogeneity (OR 1.66, 95% CI 0.80 to 3.44, P=0.17; I^2 = 0%).[7]

- *Interleukin 17 Inhibitors versus Interleukin 12/23 Inhibitors: Risk of Candida Infections*

Six RCTs evaluated the risk of *Candida* infection with IL-17i (n= 3,975, including 846 cases treated with secukinumab, 654 cases treated with ixekizumab, and 2475 cases treated with brodalumab) in comparison to anti-IL-12/23 agents (n=2,155 patients, including 1,115 cases treated with ustekinumab and 1,040 cases treated with guselkumab).[7] The reported *Candida* infection rate was 2.11% in the IL-17i arm and 1.06% in the IL-12/23i arm.[7] The pooled analysis of these 6 RCTs indicated that IL-17i agents significantly increased the risk of *Candida* infection compared to ustekinumab (OR 2.44, 95% CI 1.40 to 4.25, P=0.002) and guselkumab (OR 2.68, 95% CI 1.47 to 4.88, P=0.001), with no evidence of significant heterogeneity (I^2 = 0%).[7]

- *Interluekin-17 Inhibitors versus Tumor Necrosis Factor Inhibitors: Risk of Candida Infections*

Two RCTs compared IL-17i (n=3,246, 936 cases treated with secukinumab and 2,328 cases treated with ixekizumab) with TNFi (1,063 patients in the etanercept group) reporting a *Candida* infection rate of 1.50% in the IL-17i arm and 0.85% in the etanercept arm, with no significant difference between these 2 arms (OR 1.68, 95% CI 0.92 to 3.07, P=0.09) and low heterogeneity (I^2 = 34%).[7]

- *Targeted Immune Modulators versus Placebo: Risk of Serious Infections*

Based on 47 RCTs comparing placebo and TIMs, the risk of serious infection was 0.50% (85/16,981) in the TIMs arm and 0.38% (31/8,117) in the placebo arm.[7] The pooled OR for all biological agents versus placebo was 1.38 (95% CI 0.93 to 2.06, P=0.11), with no significant difference in the risk of serious infection and no evidence of significant heterogeneity (I^2 = 0%).[7] In a subgroup analysis, there was no statistically significant difference in the risk of serious infection for patients receiving TNFi (OR 1.38, 95% CI 0.77 to 2.50, P=0.28); IL-17i (OR 1.41, 95% CI 0.72 to 2.76, P=0.32) or IL-12/23i (OR 1.33, 95% CI 0.55 to 3.23, P=0.53) compared to placebo.[7] No evidence of significant heterogeneity was found across different TIMs (I^2 = 8% for ustekinumab, I^2 = 37% for etanercept, and I^2 = 0% for all other TIMs).[7]

- *Head-to-Head Targeted Immune Modulator Comparisons: Risk of Serious Infections*

A total of 11 RCTs assessed the risk of serious infection between biological agents, of which two RCTs compared IL-17i versus TNFi (OR 0.99, 95% CI 0.42 to 2.34, P=0.98), 5 RCTs compared IL-17i versus IL-12/23i agents (OR 0.95, 95% CI 0.44 to 2.05, P=0.90), and 4 RCTs compared IL-12/23i and TNFi (OR 1.67, 95% CI 0.63 to 4.42, P=0.31).[7] No significant difference in the risk of serious infection and no evidence of significant heterogeneity (I^2 = 0% for all comparisons) were found.[7] Two RCTs assessed the difference in the risk of serious infections between TIMs and methotrexate.[7] However, no serious infection events occurred in any of the treatment arms.[7]

- *Summary*

The IL-17i were associated with an increased risk of *Candida* infections in adults with moderate-to-severe PsO compared with placebo (95% CI 1.54 to 3.45, P<0.0001).[7] Secukinumab, but not ixekizumab or brodalumab, significantly increased the risk of *Candida* infection.[7] Compared to placebo, the incidence of *Candida* infection was 0.83%–5.08% for secukinumab, 0.99% for brodalumab, and 0.88%–1.47% for ixekizumab.[7] There was no difference in *Candida* infection risk between IL-17i and TNFi (95% CI, 0.92 to 3.07, P=0.09).[7] There was no evidence that the TIMs increased the risk of serious infections in adults with PsO or that the TIMs differed in the risk of serious infections.[7]

After review, 80 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Assessment of SpondyloArthritis International Society/European Alliance of Associations for Rheumatology: Management of Axial Spondyloarthritis

Two systematic reviews[2,3] support the updated recommendations for management of axSpA issued by the joint ASAS-EULAR Task Force in 2022.[8] Axial spondyloarthritis comprises the whole spectrum of patients with and without radiographic sacroiliitis, that is, r-axSpA and nr-axSpA, respectively.[8] The availability of TNFi, as well as IL-17i and JAKi, provides more therapeutic options for management of axSpA.[8] Data on the different treatment options come mainly from placebo-controlled trials, with no relevant head-to-head studies performed in axSpA at this time of this publication.[8] Recommendations for management of axSpA are presented in **Table 2**. Levels of evidence and strength of recommendations referenced in the ASAS-EULAR guidance are outlined in **Table 1.**

In patients with persistently high disease activity (ASDAS ≥ 2.1) despite conventional treatment, TNFi, IL-17i or JAKi should be considered.[8] All 3 drug classes have demonstrated efficacy in axSpA trials.[8] In the absence of head-to-head trials, it is difficult to prioritize any treatment based on efficacy.[8] Current practice is

to start a TNFi or an IL-17i.[8] This recommendation reflects the longer experience with the use of these drugs, with a larger evidence base, use in patients with multiple co-morbidities (frequently excluded from RCTs) and more knowledge about drug safety.[8]

Observational data and experience from daily clinical practice with JAKi in axSpA are missing, thus precluding the consideration of JAKi in current practice part of the recommendation.[8] Observational data and experience with JAKi should help in addressing concerns with regard to safety, such as those identified with tofacitinib in patients with RA.[8] In axSpA, such signals had not been described at the time of this guideline publication.[8] Therefore, it is unclear whether the increased risk of cardiovascular events and malignancies is specific to RA, and whether it will apply to axSpA, as well as whether these adverse events are specific to tofacitinib or reflect a JAKi class effect.[8] Until more data become available, the task force recommends being restrictive with starting JAKi in patients above the age of 50 years with one or more additional cardiovascular risk factors, and to those above the age of 65 years.[8]

An important element of differentiation across the treatment options is their effect on extra musculoskeletal manifestations (i.e., uveitis, IBD, psoriasis) leading to a new recommendation based on presence of these comorbid conditions.[8] In patients with previous uveitis, TNFi (infliximab, adalimumab, certolizumab pegol, golimumab) have been efficacious in preventing recurrence of uveitis, whereas etanercept showed contradictory results.[8] In comparative analyses from registry data, most TNFi are more efficacious in prevention of uveitis flares than etanercept or secukinumab.[8] Additionally, secukinumab has been tried, unsuccessfully, in patients with non-infectious uveitis.[8] These data led the task force to recommend TNFi in patients with a history of recurrent uveitis.[8] In patients with IBD, existing data support similar conclusions, namely the efficacy of almost all TNFi and the lack of efficacy of etanercept and secukinumab.[8] Thus, TNFi are also preferred in patients with IBD.[8] The IL-17i are contraindicated in patients with active IBD.[8] Although there are no specific comparative data on PsO in patients with axSpA, there are clear data on PsA.[8] Two head-to-head trials have been conducted comparing IL-17i (secukinumab and ixekizumab) with TNFi (adalimumab in both trials), showing superiority of IL-17i in the achievement of robust skin outcomes.[8] Therefore, an IL-17i may be preferred in patients with significant PsO.[8]

When one treatment fails and the patient still fulfils the criteria to start a new treatment, a switch should be considered.[8] However, evidence for efficacy of a given drug (or drug class) after failure of a previous one is very limited.[8] No RCT has been conducted with evaluating use of a second TNFi in people with insufficient response to TNFi.[8] Observational data suggest that a second TNFi can still be efficacious in TNFi-IR patients, although the level of efficacy may be lower than with the first TNFi.[8] The IL-17i have shown to be efficacious in TNFi-IR patients, also with a lower efficacy than in TNFi-naïve patients (direct comparisons only available for secukinumab).[8] Data on JAKi separately in bDMARD-IR were not available at the time of this guideline.[8] There are no data on the efficacy of TNFi after IL-17i or JAKi failure, on IL-17i after a JAKi failure, or on JAKi after TNFi or IL-17i failure.[8]

Table 1. EULAR Levels of Evidence and Strength of Recommendations[8]

A. Levels of Evidence	
Category	***Evidence***
1a	Systematic Review with Homogeneity of RCTs
1b	Individual RCT (With Narrow CI)
2a	Systematic Review (With Homogeneity) Of Cohort Studies
2b	Individual Cohort Study (Including Low-Quality RCT)
3a	Systematic Review (With Homogeneity) Of Case-Control Studies
3b	Individual Case-Control Study
4	Case Series (and Poor-Quality Cohort and Case-Control Studies)
5	Expert Opinion with Explicit Critical Appraisal

B. Strength of Recommendations	
Strength	***Based Upon***
A	Consistent Level 1 Studies
B	Consistent Level 2 or 3 Studies or Extrapolations from Level 1 Studies
C	Level 4 Studies or Extrapolations from Level 2 or 3 Studies
D	Level 5 Evidence or Troublingly Inconsistent or Inconclusive Studies of Any Level
Abbreviations: CI=confidence interval; EULAR=European Alliance of Associations for Rheumatology; RCT = randomized controlled trial	

Table 2. ASAS-EULAR Recommendations for Management of Axial Spondyloarthritis[8]

Recommendation	Level of Evidence	Strength of Recommendation
Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physiotherapy should be considered.	2b (education, exercise) 5 (smoking cessation) 1a (physiotherapy)	B (education, exercise) D (smoking cessation) A (physiotherapy)
Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs, continuous use is preferred if needed to control symptoms.	1a	A
Analgesics, such as acetaminophen and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated	5	D
Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic GCs.	2 (injections) 5 (long-term systemic GCs)	B (injections) D (long-terms systemic GCs)
Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazine may be considered in patients with peripheral arthritis.	1a (sulfasalazine, MTX) 1b (leflunomide) 4 (other csDMARDs) 1a (sulfasalazine: peripheral disease)	A (all csDMARDs)
TNFi, IL-17i or JAKi should be considered in patients with persistently high disease activity (ASDAS $\geq$ 2.1) despite conventional treatments; current practice is to start a TNFi or IL-17i.	1a	A
If there is a history of recurrent uveitis or active IBD, preference should be given to a TNFi. In patients with significant psoriasis, an IL-17i may be preferred.	2b (uveitis, IBD) 1a (psoriasis)	B for all conditions
Absence of response to treatment should prompt re-evaluation of the diagnosis and consideration of the presence of comorbidities.	5	D
Following a first b/tsDMARD failure, switching to another bDMARD (TNFi or IL-17i) or a JAKi should be considered.	2b (TNFi after TNFi failure) 1b (IL-17i after TNFi failure) 5 (all other switches)	B (TNFi after TNFi failure) A (IL-17i after TNFi failure) D (all other switches)
If a patient is in sustained remission, tapering a bDMARD can be considered.	1a (TNFi) 5 (IL-17i)	B (TNFi) D (IL-17i)
Abbreviations: ASAS=Assessment of SpondyloArthritis International Society; ASDAS=Ankylosing Spondylitis Disease Activity Score; axSpA=axial spondyloarthritis; bDMARD=biologic disease-modifying anti-rhematic drug; csDMARD conventional synthetic DMARDs; EULAR=European Alliance of Associations for Rheumatology;		

GCs=glucocorticoids; IBD=irritable bowel disease; IL-17i=interleukin-17 inhibitors; JAKi=Janus kinase inhibitors; NSAID=non-steroidal anti-inflammatory drug; TNFi=tumor necrosis factor inhibitors; tsDMARD=targeted synthetic DMARD

European Alliance of Associations for Rheumatology: Management of Rheumatoid Arthritis

A EULAR Task Force issued updated recommendations for pharmacologic management of RA in 2022.[11] Three systematic literature reviews were conducted covering the areas of efficacy and safety of DMARD treatment and utilization of GCs in RA to support the recommendations.[11] Compared to previous years, new drug classes have not emerged since the 2019 update of the recommendations.[11] The Task Force focused on the new data, particularly safety data for existing drugs, which led to significant changes in the 2019 recommendations.[11]

Two primary publications were incorporated into the current recommendations.[11] First, in 2021, the FDA released a document and warning regarding cardiovascular and malignancy risks of tofacitinib in comparison with TNFi, based on analyses of a randomized trial in patients with RA.[11] In 2019, JAKi were similarly recommended as bDMARDs in terms of effectiveness and safety.[11] However, recommendations were updated based on the data of the ORAL-Surveillance trial in patients with RA > 50 years of age with cardiovascular risk factors, which demonstrated tofacitinib had more MACEs and higher malignancy rates compared with TNF-inhibitors.[63] While similar findings were not reported from LTEs and registries, results of a single RCT convey a higher level of evidence compared with other non-trial data; in addition, the trial was performed in a population with specific risk factors.[11] Second, in the most recent update of the ACR management guidelines for RA, use of glucocorticoids (GCs) was distinctly discouraged as toxicity of GCs outweighs the benefits, even though the evidence level for this new guideline was low to moderate.[11]

Methotrexate should be part of the first treatment strategy in RA.[11] Leflunomide or sulfasalazine are recommended when MTX is contraindicated. Data from an RCT published more than 30 years ago clearly showed a substantial difference in progression of joint damage between sulfasalazine and hydroxychloroquine, suggesting that hydroxychloroquine may only be a very weak DMARD.[11] Thus, hydroxychloroquine is only recommended in patients with early, mild disease (i.e., without poor prognostic factors) in whom the other 3 csDMARDs (MTX, leflunomide, sulfasalazine) are contraindicated or not tolerated.[11] Of note, hydroxychloroquine is widely used in other diseases, but not for the purpose of inhibiting joint damage progression.[11] Consequently, this drug is not mentioned among the recommendations, because the task force did not wish to suggest that MTX could be replaced by hydroxychloroquine.[11] **Table 3** provides a summary of recommendations for management of RA based upon EULAR standard operating procedures (**Table 1)**.

Table 3. EULAR Recommendations for Management of Rheumatoid Arthritis[11]

Recommendation	Level of Evidence	Strength of Recommendation
Therapy with DMARDs should be started as soon as the diagnosis of RA is made.	1a	A
Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.	1a	A
Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.	2b	B
MTX should be part of the first treatment strategy.	1a	A
In patients with contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.	1a	A
Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible.	1a	A

If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered.	5	D
If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAK-inhibitors may be considered, but pertinent risk factors*** must be considered.	1a (efficacy) 1b (safety)	A (efficacy) B (safety)
bDMARDs and tsDMARD should be combined with a csDMARD; in patients who cannot use csDMARDs as co-medication, IL-6 pathway inhibitors (sarilumab, tocilizumab) and tsDMARDs may have some advantages compared with other bDMARDs.	1a	A
If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNFi/IL-6R-inhibitor**.	1a (efficacy) 1b (safety) *5 **3	A (efficacy) D (tsDMARD) B (safety) C (IL-6R inhibition)
After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs/tsDMARDs and/or csDMARDs) may be considered.	1b	A
***The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAKi: Age over 65 years, history of current or past smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated non-melanoma skin cancer), risk factors for thromboembolic events (history of myocardial infarction or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or immobility). Abbreviations: bDMARDs = biological disease-modifying antirheumatic drug; cs/tsDMARDs = conventional synthetic/targeted synthetic disease-modifying antirheumatic drug; EULAR = European Alliance of Associations for Rheumatology; IL-6 = interleukin-6; JAK = Janus kinase; MTX = methotrexate; RA = rheumatoid arthritis; TNFi = tumor necrosis factor inhibitor		

American Gastroenterological Association: Pharmacological Management of Moderate-to-Severe Ulcerative Colitis

In December 2024 the AGA guideline panel published updated guidance for the management of UC.[18] Moderate to severely active UC is defined as: 1) patients with corticosteroid-dependence or who are refractory to oral corticosteroids; 2) patients with mild symptoms, but with a high burden of inflammation or poor prognostic features; or 3) moderate to severe symptoms with Mayo endoscopy sub-score of 2 or 3.[18]

Considerations for specific TIMs are included in the recommendations:

- JAKi (tofacitinib, filgotinib, upadacitinib) have restricted use in advanced therapy-naïve patients. The FDA label recommends the use of JAKi in patients with prior failure or intolerance to TNFi. JAK inhibitors may be associated with higher risk of MACEs and cancer than TNFi in older adults with cardiovascular risk factors (e.g., smoking, prior cardiovascular disease).[18]
- Biosimilars of infliximab, adalimumab, and ustekinumab are equally effective to their originator drug in terms of therapy selection.[18]
- Subcutaneous formulations of infliximab and vedolizumab have comparable efficacy to the respective intravenous (IV) maintenance doses.[18]
- Vedolizumab and anti-IL therapies may be associated with a lower rate of infectious complications compared to TNFi. They may be preferred in patients who may be at higher risk of immunosuppression-related infections or malignancies.[18]
- There is limited data on the safety of JAKi and S1P receptor modulators in pregnancy. These drugs should be avoided in women of childbearing age contemplating pregnancy.[18]
- Lower-efficacy medications may require longer duration of treatment for response in patients with multiple prior biologic failures.[18]
- While there is no direct RCT evidence, observational studies demonstrate that infliximab and golimumab are effective at inducing remission in patients with prior exposure to advanced therapies.[18]

- To decrease risk of serious infections with immunosuppressive therapies, vaccination against influenza, pneumococcal pneumonia, and herpes zoster (particularly before S1P receptor modulator or JAK inhibitor use) should be considered.[18]

Recommendations and certainty of evidence use of TIMs are as follows:

- In adult outpatients with moderate-to-severe UC, the use of infliximab, golimumab, vedolizumab, tofacitinib, upadacitinib, ustekinumab, ozanimod, etrasimod, risankizumab and guselkumab is recommended over no treatment (strong recommendation, moderate to high certainty of evidence).[18]
- In adult outpatients with moderate-to-severe UC, the use of adalimumab, filgotinib or mirikizumab is suggested over no treatment (conditional recommendation, moderate certainty of evidence).[18]
- In adult outpatients with moderate-to-severe UC who are *naïve to advanced therapies*, using a HIGHER efficacy medication (infliximab, vedolizumab, ozanimod, etrasimod, upadacitinib, risankizumab, guselkumab) OR an INTERMEDIATE efficacy medication (golimumab, ustekinumab, tofacitinib, filgotinib, mirikizumab), is suggested rather than a LOWER efficacy medication (adalimumab) (conditional recommendation, low certainty of evidence).[18]
- In adult outpatients with moderate-to-severe UC who have previously been exposed to 1 or more advanced therapies, particularly TNFi, using a HIGHER efficacy medication (tofacitinib, upadacitinib, ustekinumab) OR an INTERMEDIATE efficacy medication (filgotinib, mirikizumab, risankizumab, guselkumab), is suggested rather than a LOWER efficacy medication (adalimumab, vedolizumab, ozanimod, etrasimod) (conditional recommendation, low certainty of evidence).[18]
- In adult outpatients with moderate-to-severe UC, the use of infliximab in combination with an immunomodulator is suggested over infliximab or an immunomodulator alone (conditional recommendation, moderate certainty of evidence).[18]
- In adult outpatients with moderate-to-severe UC, the use of adalimumab or golimumab in combination with an immunomodulator is suggested over adalimumab, golimumab or immunomodulator monotherapy (conditional recommendation, low certainty of evidence).[18]

National Institute for Health and Care Excellence

Since the last P & T Committee review, NICE has issued 7 recommendations for the use of specific TIMs in autoimmune conditions as presented below.

6/25: Spesolimab for Generalized Pustular Psoriasis Flares

Generalized pustular psoriasis is a rare form of psoriasis.[19] In the United Kingdom (UK), there is no licensed standard care for GPP flares.[19] Usual treatment includes topical steroids, cyclosporin, acitretin, or MTX as first-line treatment (week 1), which are used to treat other forms of psoriasis.[19] Infliximab and MTX are second-line treatments (weeks 2 to 4).[19] Biological treatments including guselkumab, ustekinumab or secukinumab are third-line treatments (week 5 and later).[19] Clinical trial evidence shows that spesolimab resolves moderate to severe GPP flares faster than placebo.[19] However, it is uncertain how spesolimab affects the proportion of people who need hospital and intensive care admissions, or the length of hospital stays.[19] There is no evidence comparing spesolimab with usual treatments used for GPP flares in the UK.[19] The NICE recommendations suggest using the GPPGA assessment for initiating treatment with spesolimab. A description of the GPPGA scoring is included in **Appendix 2.**

NICE recommendations:

Spesolimab is recommended as an option for treating GPP flares in adults, only if it is used to treat:

- Initial moderate to severe flares when:
    - the GPPGA total score is 3 or more, and
    - there are fresh pustules (new appearance or worsening of existing pustules), and

    - the GPPGA pustulation subscore is at least 2, and
    - at least 5% of the body's surface area is covered with erythema (abnormal redness of the skin or mucous membranes) and has pustules.[19]
- Subsequent flares with a GPPGA pustulation subscore of 2 or more, if the last flare was treated with spesolimab and resolved to a GPPGA pustulation subscore of 0 or 1 (clear or almost clear skin).[19]
- A second dose of spesolimab can be used after 8 days if a flare has not resolved to a GPPGA pustulation subscore of 0 or 1.[19]
- Consider how skin color could affect the GPPGA score and make any adjustments as needed.[19]

3/24: Etrasimod for Moderately to Severely Active Ulcerative Colitis in People Aged 16 And Over

After conventional treatment fails, people with moderately to severely active UC progress to advanced treatment, such as a bDMARD or JAKi.[15] Etrasimod is an S1P receptor agonist, which would be offered after failure of conventional treatment.[15] Clinical trial evidence shows that etrasimod is more effective than placebo for treating moderately to severely active UC.[15] Etrasimod has not been directly compared with other bDMARDs or JAKi for UC.[15]

NICE recommendation:

- Etrasimod is recommended as an option for moderately to severely active UC in people aged 16 years and over when conventional or biological treatments cannot be tolerated or the condition has not responded well enough, or lost response to treatment.[15]

9/24: Risankizumab for Moderately to Severely Active Ulcerative Colitis

The most frequently used biological treatments for moderately to severely active UC are TNFi.[16] When TNFi have not worked, or are not tolerated, an alternative treatment option is ustekinumab.[16] Risankizumab works in a similar way to ustekinumab and would be offered to the same population.[16] Clinical trial evidence shows that risankizumab is more effective than placebo for treating moderately to severely active UC.[16] Risankizumab has not been directly compared with ustekinumab in a clinical trial in this population.[16]

NICE recommendation:

- Risankizumab is recommended as an option for treating moderately to severely active UC in adults when conventional or biological treatment cannot be tolerated, or the condition has not responded well enough or has lost response to treatment, only if a TNFi has not worked (i.e., the condition has not responded well enough or has lost response to treatment), cannot be tolerated, or is not suitable.[16]

10/23: Tofacitinib for Active Ankylosing Spondylitis

People with active AS that is not controlled well enough with conventional therapy (NSAIDs) are usually offered TNFi.[9] If TNFi are not suitable or do not control the condition well enough, people are usually offered an IL-17i (secukinumab or ixekizumab).[9] The main adverse effects associated with existing bDMARDs are fatigue and an increased frequency of infections, and with IL-17 inhibitors there is an increased risk of gastritis [9] Tofacitinib is an alternative to secukinumab or ixekizumab, but it might not be as safe for some people with AS, for example, people who are over 65 or who smoke.[9] Clinical trial evidence shows that tofacitinib is more effective than placebo for treating active AS.[9] Tofacitinib has not been compared directly with secukinumab or ixekizumab in people with AS.[9]

10/23 NICE recommendations:

- Tofacitinib is recommended as an option for treating active AS that is not controlled well enough with conventional therapy in adults, only if TNFi are not suitable or do not control the condition well enough.[9]
- Assess response to tofacitinib after 16 weeks of treatment. Continue treatment only if there is clear evidence of response, defined as:
    - a reduction in the BASDAI score to 50% of the pre-treatment value or by 2 or more units and
    - a reduction in the spinal pain VAS by 2 cm or more.[9]

10/23: Bimekizumab for Treating Axial Spondyloarthritis

- Bimekizumab is recommended as an option in adults for treating active AS when conventional therapy has not worked well enough or is not tolerated, or for active nr-axSpA with objective signs of inflammation (shown by elevated C-reactive protein or magnetic resonance imaging [MRI]) when NSAIDs and TNFi have not worked well enough or are not tolerated.[10]
- Assess response to bimekizumab after 16 weeks of treatment. Continue treatment only if there is clear evidence of response, defined as:
    - a reduction in the BASDAI score to 50% of the pre-treatment value or by 2 or more units, and
    - a reduction in the spinal pain VAS by 2 cm or more.[10]

10/23: Bimekizumab for Active Psoriatic Arthritis

The TNFi (etanercept, infliximab and adalimumab) are all recommended for treatment of adults with active and progressive PsA.[64] Second-line options include the IL-17i, ixekizumab and secukinumab.[12] Bimekizumab works in a similar way to the IL-17i treatments and would be offered to the same population.[12] Clinical evidence shows that bimekizumab is more effective than placebo.[12] Bimekizumab has not been compared directly with ixekizumab in people with PsA.[12]

NICE recommendations:

- Bimekizumab alone or with MTX, is recommended as an option for treating active PsA (defined as peripheral arthritis with 3 or more tender joints and 3 or more swollen joints) in adults whose condition has not responded well enough to DMARDs or who cannot tolerate them. It is recommended only if they have had 2 conventional DMARDs and:
    - at least 1 biological DMARD (golimumab, ustekinumab, guselkumab, ixekizumab, risankizumab, certolizumab pegol, secukinumab) or
    - TNFis (etanercept, infliximab, adalimumab) are contraindicated but would otherwise be considered.[12]
- Assess response to bimekizumab after 16 weeks of treatment. Stop bimekizumab if the PsA has not responded adequately using the Psoriatic Arthritis Response Criteria (PsARC; an adequate response is an improvement in at least 2 of the 4 criteria, 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria). If the PsARC response is not adequate but there is a Psoriasis Area and Severity Index (PASI) 75 response, a dermatologist should decide whether continuing treatment is appropriate based on skin response.[12]
- Consider how skin color could affect the PASI score and make any adjustments as needed.[12]

12/23: Secukinumab for Moderate to Severe Hidradenitis Suppurativa

Hidradenitis suppurativa is a painful, long-term skin condition that causes abscesses and scarring.[21] The exact cause of HS is unknown but it occurs in skin folds where there are sweat glands, in particular the groin and armpits.[21] Early HS symptoms include isolated, painful nodules; with or without intermittent inflammation.[21] Symptoms may progress to abscesses and pus-discharging tunnels, known as sinus tracts and fistulas.[21] Guidelines published by the British Association of Dermatologists recommend starting treatment for HS with conventional systemic treatment.[21] This includes offering oral tetracyclines for at least 12 weeks, followed by oral clindamycin and rifampin when oral tetracyclines have not worked.[21] The guidelines recommend that retinoids such as acitretin or the anti-inflammatory antibiotic, dapsone, may be considered when earlier treatments have not worked.[21] Dapsone is rarely used because it needs extensive monitoring for hemolytic anemia.[21] Rifampin may be used but has many drug interactions.[21] Retinoids, such as acitretin, may be offered as monotherapy or in combination with antibiotics, but these are contraindicated for people of childbearing age.[21] People often cycle through multiple courses of tetracycline antibiotics but these rarely control moderate to severe HS.[21] Current treatment for people with moderate to severe HS when conventional systemic treatment (oral antibiotics) has not worked well enough is adalimumab.[21] Evidence from 2 clinical trials shows that secukinumab generally improves symptoms of moderate to severe HS more than placebo.[21]

NICE recommendations:

- Secukinumab is recommended as an option for treating active moderate to severe hidradenitis suppurativa in adults when it has not responded well enough to conventional systemic treatment, only if adalimumab is not suitable, did not work or has stopped working.[21]
- Assess response to secukinumab after the first 16 weeks of treatment, and only continue if there is clear evidence of a response, defined as:
    - a reduction of 25% or more in the total abscess and inflammatory nodule count, and
    - no increase in abscesses and draining fistulas.[21]

Canada's Drug Agency

Since the previous P & T Committee review of TIMs, Canada's Drug Agency has published 5 reimbursement reviews for the use TIMs in GPP, PsA, UC, HS, and PsO. The recommendations, evidence summary and quality of evidence (where provided) are summarized below.

1/25: Spesolimab for Generalized Pustular Psoriasis

The IL-36 receptor inhibitor, spesolimab, was the first treatment available in Canada indicated for GPP.[20] In current Canadian clinical practice, GPP is managed by treatments that are indicated for PsO and are used off label for GPP.[20] Evidence from 2 pivotal studies (Effisayil-1 and Effisayil-2) demonstrated that treatment with spesolimab resulted in a clinical benefit for patients with GPP compared to placebo.[20] The Effisayil-1 and Effisayil-2 trials were double-blind, multicenter phase 2 and 2b RCTs, respectively.[20] There is a lack of evidence for the use of spesolimab in combination with off-label treatments for GPP.[20] The committee acknowledged the rarity of GPP and limited guidance available for the treatment of GPP, which may result in variable approaches to treatment; however, they noted that in the Effisayil trials, the following medications were not permitted: biologics, phototherapy, topical corticosteroids, systemic immunomodulating treatments (e.g., corticosteroids and cyclophosphamide), tofacitinib, apremilast and other systemic psoriasis treatments (e.g., fumarates and any other drug known to possibly benefit psoriasis), photochemotherapy (e.g., psoralen plus ultraviolet A therapy), IL-36i, and investigational products for psoriasis.[20] Therefore the Committee concluded that there is no evidence to support the use of spesolimab in combination with these treatments.[20] Evidence was not available to assess the impact of treatment with spesolimab on reduction in hospitalization and mortality.[20] In addition, there is a lack of long-term data beyond the 2 studies, particularly for the use of spesolimab for the prevention of flares which is limited to 48 weeks.[20] Given the unpredictable and severe nature of GPP, the Committee noted it is important to continue monitoring patients and consider the risks and benefits of continued treatment.[20]

CDA recommendations:

- The use of spesolimab is recommended for acute treatment of GPP flares and for the prevention of GPP flares for patients with a history of flares in adults and pediatric patients aged 12 years and older and weighing at least 40 kg.[20]
- Spesolimab should be prescribed by clinicians (dermatologists and rheumatologists) with expertise in managing GPP and other types of psoriasis.[20]
- For prevention of flares, the initial authorization should be for 6 months of treatment.[20]
- For continued renewal of spesolimab for the prevention of flares, the severity of GPP as measured by the GPPGA total score at initiation should be maintained (not worsen), patient should experience fewer flares compared to baseline, and the reduction in the number of flares should be sustained.[20]
- Spesolimab is recommended as monotherapy not combined with other TIMs to manage and prevent GPP flares.[20]

6/24: Bimekizumab for Psoriatic Arthritis

The CDA Committee noted bimekizumab is an additional treatment option for adult patients with active PsA.[13] However, due to the lack of direct evidence with relevant comparators is uncertain whether bimekizumab has any particular advantages over existing bDMARD or tsDMARD treatment options for active PsA.[13] In addition, the study results were collected over a relatively short duration.[13] Because PsA is a chronic condition that requires lifelong treatment, there is uncertainty regarding the long-term effectiveness and safety of bimekizumab over other currently available bDMARDs or tsDMARDs for the treatment of active

PsA.[13] Any patient with active PsA could receive bimekizumab, particularly those with coexisting severe psoriasis, but the drug should be avoided in those with IBD, severe uveitis, or active infection.[13]
CDA recommendations:

- Bimekizumab is recommended as monotherapy or in combination with MTX to treat adults with active PsA.[13]
- Must be prescribed by a rheumatologist or a clinician with experience in treating adults with PsA.[13]
- Should not be used in combination with another TIM approved for managing PsA.[13]
- Should be avoided in patients with PsA and IBD, severe uveitis, or active infection.[13]

8/24: Etrasimod for Ulcerative Colitis
Evidence from 2 clinical trials demonstrated that more patients treated with etrasimod showed clinical remission and endoscopic improvement compared to patients treated with placebo which was maintained for up to 1 year.[17] In addition, more patients treated with etrasimod had corticosteroid-free clinical remission than those treated with placebo, which reduced reliance on systemic corticosteroids.[17]
CDA Recommendations:

- Etrasimod is recommended for the treatment of adults with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or an advanced treatment (i.e., biologics, S1P receptor modulators, JAKi).[17]
- Must be prescribed by a clinician with experience in treating UC.[17]
- Should not be used in combination with another TIM approved for managing UC.[17]
- For continued renewal the patient's condition must respond to treatment in the first 12 weeks of therapy to continue receiving the drug.[17]

10/24: Secukinumab for Hidradenitis Suppurativa
Moderate-quality evidence from two phase 3, double-blind, RCTs, SUNSHINE (N = 541) and SUNRISE (N = 543), demonstrated that secukinumab improved HS symptoms compared to placebo in adults living with moderate to severe HS.[22] Secukinumab improved the proportion of patients with at least a 50% decrease in abscesses and inflammatory nodules (AN count) with no increase in the number of abscesses and/or in the number of draining fistulas according to the Hidradenitis Suppurative Clinical Response (HiSCR50) after 16 weeks of treatment.[22] Response to treatment (HiSCR50 achievement) was defined as at least a 50% reduction in provider-assessed AN count with no increase in the number of abscesses and/or in the number of draining fistulas.[22] The 2 RCTs also demonstrated that secukinumab decreased AN count, decreased the proportion of patients experiencing flares, and increased the proportion of patients with at least a 30% reduction and at least 2 units reduction from baseline in skin pain on the Numerical Rating Scale (NRS30) compared with placebo.[22] The NRS is a patient-reported, segmented numeric version of the VAS that is used to measure the intensity of skin pain at its worst as well as the average intensity of skin pain due to HS in the last 24 hours.[22] The range of the NRS includes whole numbers from 0 (no skin pain) to 10 (skin pain as bad as you can imagine).[22]

At baseline in these RCTs, most patients had prior experience with at least 1 therapy for HS. There is limited evidence to support the use of secukinumab as a first-line therapy before conventional therapy options.[22] The effect of secukinumab compared with adalimumab, after 12 to 16 weeks of treatment was uncertain based on the evidence from 1 indirect treatment comparison.[22]
CDA recommendations:

- Secukinumab is recommended for the treatment of adults with moderate to severe HS who have responded inadequately to conventional systemic HS therapy (i.e., oral antibiotics).[22]

- Secukinumab should be prescribed to treat moderate to severe HS defined as: Hurley Stage II or III, with a total abscess and nodule count of 5 or greater and lesions in at least 2 separate areas of the body.[22] Provider must provide a baseline assessment of HS symptoms at time of initial request for coverage.[22]
- Must be prescribed by a clinician with experience in treating HS.[65]
- Should not be used together with another TIM approved for managing HS.[65]
- For renewal after initial authorization, physicians must provide proof of beneficial clinical effect defined as at least a 50% reduction in abscess and inflammatory nodule count with no increased in abscess or draining fistula count.

- *8/23 Deucravacitinib for Plaque Psoriasis*

In 2 double-blind, phase 3 RCTs, 53% to 58% of adults in the deucravacitinib groups achieved a PASI 75 response, 27% to 36% achieved a PASI 90 response, and 10% to 14% achieved a PASI score reduced by 100% (PASI 100) response at week 16.[14] However, the clinical relevance of these results within the Canadian treatment landscape is uncertain.[14] Based on clinical expert input, although PASI 75 is accepted as a clinically relevant minimal response threshold in clinical trials, available biologics are expected to achieve a PASI 90 or PASI 100 response in clinical practice.[14] Patients in the POETYK PSO-1 and POETYK PSO-2 trials were not required to fail on conventional treatment options before enrollment, and, as a result, it is uncertain if the outcomes demonstrated in these trials can be extrapolated to the advanced treatment clinical landscape.[14]

The evidence from 2 clinical trials was insufficient to determine that deucravacitinib offered treatment benefits over the currently available advanced treatments in Canada for the treatment of moderate to severe plaque PsO in adults.[14] No evidence was found that directly compared deucravacitinib to newer IL-17i and IL-23i, and the indirect evidence suggested that deucravacitinib was less effective at improving skin plaques than several biologics (including IL-17i and IL-23i) that are available in Canada.[14] There was not enough evidence to show that deucravacitinib met the needs of patients with moderate to severe PsO not already addressed by other available treatments.[14]

CDA recommendation:

- The use of deucravacitinib is not recommended for the treatment of adults with moderate to severe PsO who are candidates for systemic therapy or phototherapy.[14]

European Alliance of Associations for Rheumatology: Treatment of Systemic Sclerosis

In 2023, the EULAR Task Force updated guidance for treatment of systemic sclerosis.[23] The recommendations include the place on therapy for mycophenolate mofetil, rituximab and tocilizumab for the treatment of key fibrotic manifestations of systemic sclerosis.[23] Systemic sclerosis is a rare connective tissue disorder characterized by the association of autoimmune features with vascular manifestations and culminating in tissue and vascular fibrosis of the skin and internal organs, with highly variable outcomes.[23] Type and severity of organ involvement drive the heterogeneous prognosis, but overall systemic sclerosis remains the rheumatic disease with the highest morbidity and mortality, despite recent improvement in survival.[23] Recommendations that discuss csDMARDs or TIMs are summarized below using the EULAR standard operating procedures for level of evidence (LoE) and strength of recommendation (SoR) presented in **Table 1**.

- Methotrexate (1B), mycophenolate mofetil (1B) and/or rituximab (1A) should be considered for systemic sclerosis skin fibrosis (LoE: 1a-b; SoR: A/B).[23]
- Tocilizumab may be considered for skin fibrosis in patients with early, inflammatory diffuse cutaneous systemic sclerosis (LoE: 1b; SoR: C).[23]
- Mycophenolate mofetil (1A), cyclophosphamide (1A) or rituximab (1A) should be considered for systemic sclerosis-interstitial lung disease (LoE: 1a; SoR: A).[23]
- Tocilizumab should be considered for systemic sclerosis-interstitial lung disease (LoE:1b; SoR: B).[23]

European Alliance of Associations for Rheumatology/American College of Rheumatology: Management of Interleukin-1 Mediated Autoinflammatory Diseases

In 2021, a EULAR Task Force developed evidence-based recommendations for treat of IL-1 mediated systemic autoinflammatory diseases, including the cryopyrin- associated periodic syndromes (CAPS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD) and deficiency of the IL-1 receptor antagonist (DIRA).[24] These conditions rare immune system diseases that primarily present in early childhood with variable multiorgan involvement.[24] The current standard of care for patients with CAPS, TRAPS, MKD, and DIRA is subcutaneous IL-1 targeted biologic therapy when available.[24] While the specific pharmacologic mechanisms, pharmacokinetics, disease indications and costs differ for each of the three available drugs, anakinra, rilonacept and canakinumab, each blocks the effect of IL-1β on the IL-1 receptor and downstream signaling resulting in improved symptom control, as well as reduced systemic and tissue/organ inflammation.[24]

Ongoing efficacy and a beneficial long-term safety profile have been demonstrated for the long-term use of all three IL-1 blockers (anakinra, rilonacept and canakinumab) in CAPS, although direct comparative studies are lacking.[24] Anakinra may have a clinical advantage for patients with severe CAPS, especially for those with neurologic disease.[24] Some patients with CAPS may require more frequent or higher doses of these medicines than that approved by FDA, such as dosing of canakinumab more often than the approved frequency of every 8 weeks, if patients have not achieved remission.[24] On-demand regimens may be used in selected patients with MKD, TRAPS and familial cold autoinflammatory syndrome (FCAS) who have very mild disease and/or episodic disease manifestations and who maintain normal inflammatory markers in between episodes.[24] A large body of evidence suggests that IL-1 inhibitors should be considered as the preferred treatment for TRAPS.[24] Although anakinra was the first IL-1 blocker successfully used in patients with TRAPS in small series and observational registries, the long-acting anti-IL-1β monoclonal antibody, canakinumab is currently the only IL-1 blocker that the FDA has approved for the treatment of patients with TRAPS.[24] Anakinra and canakinumab have been used in children with MKD with success, but only canakinumab has been evaluated in a randomized study and approved by the FDA.[24] Anakinra and rilonacept both block IL-1α and IL-1β and should be used for patients with DIRA.[24] The FDA recently approved both anakinra and rilonacept for treatment of DIRA.[24] While anakinra has been used initially in all patients with DIRA to achieve disease control, rilonacept can be used to maintain remission.[24] EULAR recommendations for treatment of CAPS, TRAPS, MKD, and DIRA are summarized in **Table 5.** The EULAR standard operating procedures for levels of evidence and recommendation grading are presented in **Table 1**.

Table 4. EULAR Recommendations for Treatment of CAPS, TRAPS, MKD, and DIRA

Recommendations	**Level of Evidence**	**Strength of Recommendation**
IL-1 blocking therapy has become the preferred treatment and a therapeutic trial with IL-1 blocking treatment may be started when a strong clinical suspicion of a diagnosis of CAPS, TRAPS, MKD or DIRA is entertained.	4	C
CAPS Specific		
Treatment with IL-1 blockers is recommended standard of care and currently includes anakinra, canakinumab and rilonacept.	Anakinra (2b) Canakinumab (1b) Rilonacept (1b)	Anakinra (A) Canakinumab (B) Rilonacept (B)
Anakinra may be the most effective anti-IL-1 treatment for CNS disease.	2	B
Higher and more frequent dosing with IL-1 blockers may be required to control disease activity in more severe cases and/or younger children to prevent complications. Less frequent dosing may be appropriate for patients with milder disease.	1	B
TRAPS Specific		

Anti-IL-1 drugs are more effective than traditional and other biologic DMARDS in achieving disease remission and preventing long-term complications.	4	C
MKD Specific		
In children with MKD, IL-1 blocking therapy is generally required. In patients without chronic systemic inflammation, on-demand IL-1 blockade should be attempted at the onset of flares.	4	C
If anti-IL-1 is not effective or available, then anti-TNF agents should be considered.	3	B
Glucocorticoids on demand may be effective in treating acute flares; however, frequent or long-term use is limited by side effects.	2	B
DIRA Specific		
In patients with DIRA, treatment with agents that block both IL-1α and IL-1β is recommended and includes anakinra and rilonacept. Both have shown benefit in controlling disease flares and in preventing long-term complications.	4	C
Abbreviations: CAPS = cryopyrin- associated periodic syndromes; CNS = central nervous system; DIRA = deficiency of the IL-1 receptor antagonist; DMARDS = disease-modifying antirheumatic drugs; IL = interleukin; MKD = mevalonate kinase deficiency; TNF = tumor necrosis factor; TRAPS = tumor necrosis factor receptor-associated periodic syndrome		

European Alliance of Associations for Rheumatology: Screening and Prophylaxis of Chronic and Opportunistic Infections in Adults with Autoimmune Inflammatory Rheumatic Diseases.[25]

In 2022, a EULAR Task Force issued guidance for screening and prophylaxis of infections in adults with autoimmune conditions.[25] Opportunistic and chronic infections, are encountered in the setting of autoimmune inflammatory rheumatic diseases and are often associated with immunosuppressive and immunomodulatory treatments used for these diseases.[25] The Task Force reached consensus on the use of a four-category system as follows: (1) all bDMARDs and tsDMARDs: (except apremilast), (2) csDMARDs: MTX, leflunomide (sulfasalazine and hydroxychloroquine were exempted from this category, as it was thought that they only have a mild immunomodulatory/immunosuppressive effect), (3) other immunosuppressants: cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporin, tacrolimus, and 4) glucocorticoids.[25]

Eight recommendations were developed (**Table 5**) based upon EULAR standard operating procedures (**Table 1).**[25] In addition to b/tsDMARDs for which screening for latent tuberculosis (TB) should be performed, screening could be considered also before starting csDMARDs, glucocorticoids and immunosuppressants.[25] Hepatitis B (HBV) antiviral treatment should be guided by HBV status defined prior to starting antirheumatic drugs. All patients positive for hepatitis-C-RNA should be referred for antiviral treatment.[25] Patients who are non-immune to varicella zoster virus should be informed about the availability of postexposure prophylaxis should they have contact with this pathogen. Prophylaxis against *Pneumocystis jirovecii* seems to be beneficial in patients treated with daily doses >15–30 mg of prednisolone or equivalent for >2–4 weeks.[25]

Table 5. EULAR Recommendations for Screening and Prophylaxis of Opportunistic Infections[25]

Recommendations	Level of Evidence	Strength of Recommendation
Screening for latent tuberculosis is recommended in patients prior to starting bDMARDs or tsDMARDs*. Screening should also be considered in patients with increased risk for latent tuberculosis prior to starting csDMARDs, immunosuppressants* and/or glucocorticoids (according to dose and duration).	2b *5	B *D
Screening for latent tuberculosis should follow national and/or international guidelines and would typically include a chest X-ray* and Interferon-gamma release assay over tuberculin skin test where available.	2b *5	B *D

Choice and timing of latent tuberculosis therapy should be guided by national and/or international guidelines. Special attention should be given to interactions with drugs commonly used to treat autoimmune inflammatory rheumatic diseases.	5	D
All patients being considered for treatment with csDMARDs, bDMARDs, tsDMARDs*, immunosuppressants* and glucocorticoids (according to dose and duration) should be screened for HBV.	2a *2b	C *C
Screening for chronic hepatitis C should be considered in patients prior to starting csDMARDs, bDMARDs, tsDMARDs*, immunosuppressants and glucocorticoids* (according to dose and duration). Screening is recommended for patients with elevated alanine aminotransferase or those with known risk factors.	2b *5	C *D
Screening for HIV is recommended prior to treatment with bDMARDs and should be considered prior to treatment with csDMARDs, tsDMARDs, immunosuppressants and glucocorticoids (according to dose and duration).	5	D
All patients commencing csDMARDs, bDMARDs, tsDMARDs, immunosuppressants and/or glucocorticoids (according to dose and duration) who are non-immune to VZV should be informed about post-exposure prophylaxis following contact with VZV.	5	D
Prophylaxis against PCP should be considered in patients with autoimmune inflammatory disease in whom high doses of glucocorticoids are used, especially in combination with immunosuppressants* and depending on the risk–benefit ratio.	2b *5	B *D
Abbreviations: bDMARDs =biological disease-modifying antirheumatic drugs; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; HBV = hepatitis B virus; HIV = human immunodeficiency virus; PCP = pneumocystis pneumonia; tsDMARDs = targeted synthetic DMARDs; VZV =varicella zoster virus		

After review, 6 guidelines were excluded due to poor quality.[66-71]

New Formulations and Indications:

New Formulations

- Eight new intravenous and subcutaneous biosimilar products for the reference product of STELARA (ustekinumab) received FDA approval in 2024 and 2025. These products include: OTULFI (ustekinumab-aauz), IMULDOSA (ustekinumab-srlf), SELARSDI (ustekinumab-aekn), YESTINTEK (ustekinumab-kfce), STEQEYMA (ustekinumab-stba), WEZLANA (ustekinumab-auub), PYCHIVA (ustekinumab-ttwe) and STARJEMZA (ustekinumab-hmny).[26] All of the STELARA biosimilar products have FDA interchangeable status except for IMULDOSA.[26] The means they can be substituted for STELARA at the pharmacy level without requiring a prescription change from the healthcare provider. All the ustekinumab biosimilar products are indicated for treatment of adults with moderate to severe PsO, CD, UC, or active PsA and pediatric patients 6 years and older with moderate to severe PsO or active PsA.[27]
- In 2025 a biosimilar for tocilizumab, AVTOZMA (tocilizumab-anoh) received FDA approval for treatment of adults with RA, giant cell arteritis, or coronavirus disease and pediatric patients 2 years of age and older with juvenile idiopathic arthritis (JIA).[28]
- An autoinjector device for OMVOH (mirikizumab) was approved 3/25.[29] The device is available in 100 mg/mL and 200 mg/2 mL prefilled pens as dosing varies according to the UC or CD indications.[29]

New Indications

- 8/25: OTZELA (apremilast) received an expanded FDA-approved indication for the treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with active PsA.[30] Prior to this recent approval, apremilast was FDA-approved for treatment of adults with active PsA, PsO, or oral ulcers associated with Bechet's Disease.[30] The pediatric indication was for children aged 6 years of age and older and weighing 20 kg with moderate-to-severe PsO.[30] The safety and effectiveness apremilast in pediatric patients is supported by evidence from RCTs conducted in adults with PsA, pharmacokinetic data from adult patients with PsA, adult patients with PsO, and pediatric patients with PsO and safety data from a clinical trial in 245 pediatric patients 6 to 17 years of age with PsO.[30]

- 8/24: The HUMIRA biosimilar product, YUFLYMA (adalimumab-aaty) received expanded approval for treatment of adults with uveitis.[31] The other FDA-approved indications for YUFLYMA include adults with RA, PsA, AS, UC, PsO, or HS and pediatric patients aged 2 years and older with JIA, or pediatric patients aged 6 years and older with CD.[31]

- 9/24: TREMFYA (guselkumab) received expanded approved for treatment of adults with moderately to severely active UC.[32] Approval for treatment of adults with moderate to severely active CD occurred 3/25.[32] Prior to these expanded indications, guselkumab was FDA-approved for treatment of adults with moderate-to-severe PsO or active PsA.[32]

  Guselkumab was studied up to 12 weeks in subjects with moderately to severely active UC in a double-blind, placebo-controlled induction RCT (UC1; n=701).[32] In subjects who responded to induction therapy, long-term safety and efficacy up to 44 weeks was evaluated in a double-blind, placebo-controlled maintenance RCT (UC2; n=568).[32] Patients with inadequate response, loss of response, or intolerance to corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine), biologic therapy (TNFi, vedolizumab), and/or Janus kinase (JAK) inhibitors were enrolled in the RCT.[32] Disease activity was assessed by the modified Mayo score (mMS), a 3-component Mayo score (0-9) which consists of the following subscores (0 to 3 for each subscore): stool frequency, rectal bleeding, and findings on centrally reviewed endoscopy (ES).[32] An ES of 2 was defined by marked erythema, lack of vascular pattern, friability, and/or erosions; an ES of 3 was defined by spontaneous bleeding and ulceration. Enrolled subjects with a mMS between 5 and 9 and an ES of 2 or 3 were classified as having moderately to severely active ulcerative colitis.[32] Enrolled subjects were permitted to use stable doses of oral aminosalicylates, immunomodulators and/or oral corticosteroids (up to 20 mg/day prednisone or equivalent).[32]

  In UC1, the primary endpoint was clinical remission at Week 12 as defined by the mMS.[32] At Week 12, 23% of patients who received guselkumab 200 mg IV every 4 weeks for 3 doses had achieved remission, compared with 8% of placebo-treated patients (treatment difference [TD], 15%; 95% CI 10 to 20).[32] Subjects were re-randomized to receive a subcutaneous (SC) maintenance regimen of either guselkumab 100 mg every 8 weeks, guselkumab 200 mg every 4 weeks, or placebo for up to an additional 44 weeks after induction therapy.[32] In UC2, 45% of patients who received guselkumab 100 mg SC every 8 weeks and 50% of patients who received guselkumab 200 mg SC every 4 weeks achieved remission at Week 44, compared with 19% of placebo-treated patients (TD for 100 mg, 25%; 95% CI 16 to 34%; and for 200 mg, 30%; 95% CI 21 to 38%).[32] The FDA-approved UC dose is an IV induction dose of 200 mg every 4 weeks at Week 0, 4, and 8 followed by a maintenance dose of 100 mg SC at Week 16 and every 8 weeks thereafter or 200 mg SC at Week 12 and every 4 weeks thereafter.[32] It is recommended to use the lowest effective dose to maintain therapeutic response.[32]

  Guselkumab was studied in 3 clinical trials in subjects with moderately to severely active CD disease. In 2 double-blind, placebo-controlled RCTs (CD1; n= 361, CD2; n=360) patients received 200 mg IV guselkumab at weeks 0, 4, and 8 over 12 weeks.[32] In a double-blind, placebo-controlled RCT (CD3; n=340), patients received 400 mg SC guselkumab at weeks 0, 4, and 8 followed by one of two recommended SC guselkumab dosing regimens (100 mg every 8 weeks or 200 mg every 4 weeks) for up to 48 weeks.[32] Adults who had a history of inadequate response, loss of response, or intolerance to oral corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, MTX), and/or biologic therapy (TNFi or vedolizumab) met inclusion criteria.[32] Moderately to severely active Crohn's disease was defined as a Crohn's Disease Activity Index (CDAI) score of ≥220 and a Simple Endoscopic Score for Crohn's Disease (SES-CD) of ≥6 (or ≥4 for subjects with isolated ileal disease).[32] Subjects were permitted to use stable doses of oral corticosteroids (prednisone ≤40 mg/day or equivalent), immunomodulators and/or aminosalicylates.[32]

In CD1, 47% of guselkumab-treated patients achieved clinical remission at week 12, compared to 20% of placebo-treated patients (treatment difference 27%; 95% CI 17 to 38%).[32] Similar results were observed in CD2 in patients who received guselkumab versus placebo (47% vs. 15%; TD 31%; 95% CI 21 to 41%).[32] In CD3, the co-primary endpoints were clinical remission at week 48 and endoscopic response at week 48 compared to placebo.[32] At week 48, 59% of guselkumab 100 mg every 8 weeks treated patients achieved clinical remission compared to 17% of placebo-treated patients (TD 41%; 95% CI 30 to 52%), and guselkumab 100 mg every 8 weeks was more effective than placebo at achieving an endoscopic response (39% vs. 5%; TD 34%; 95% CI 24 to 44).[32] Similar results were observed when guselkumab was administered as 200 mg SC every 4 weeks beginning at 12 weeks.[32] The FDA-approved CD induction dose is 200 mg via IV infusion over at least one hour at weeks 0, 4, and 8 or 400 mg subcutaneously at weeks 0, 4, and 8.[32] Maintenance dosing is 100 mg administered by SC injection at week 16 and every 8 weeks thereafter, or 200 mg SC at week 12 and every 4 weeks thereafter.[32] Use the lowest effective recommended dosage to maintain therapeutic response.[32] Reported adverse events with guselkumab in the UC and CD RCTs included hypersensitivity reactions, infections, and hepatotoxicity.[32]

- 9/24: CIMZIA (certolizumab pegol) received expanded approved for treatment of polyarticular JIA (pJIA) in patients aged 2 years and older.[33] Prior to this expanded approval, certolizumab pegol was FDA-approved for treatment of adults with CD, PsA, PsO, AS, and nr-axSpA.[33] The efficacy of certolizumab in pediatric patients with pJIA is based on pharmacokinetic exposure and extrapolation of the established efficacy of certolizumab in RA patients.[33] The efficacy of certolizumab was also assessed in a multi-center, open-label study NCT01550003 in 193 patients 2 to 17 years of age with JIA with active polyarthritis with an inadequate response or intolerance to at least 1 DMARD (nonbiologic or biologic).[33] The patients had the following subtypes of JIA: polyarthritis rheumatoid factor-positive (20.0%), polyarthritis rheumatoid factor-negative (44.8%), extended oligoarthritis (13.3%), juvenile psoriatic arthritis (4.8%), and enthesitis-related arthritis (19.0%).[33] Patients could be on stable MTX, glucocorticoids, and/or NSAIDs.[33] Efficacy was assessed as secondary endpoints through Week 24.[33] The safety and efficacy was generally consistent with responses in patients with RA.[33]

- 9/24 and 11/24: BIMZELX (bimekizumab) received expanded approval for 4 indications: adults with active PsA, adults with active AS and nr-axSpA, and patients with HS.[34] Prior to these approvals, bimekizumab was only approved for treatment of adults with moderate to severe PsO. Bimekizumab dosing for adults with PsO is 320 mg SC at Weeks 0, 4, 8, 12, and 16 and then every 8 weeks thereafter.[34] In contrast, dosing for patients with PsA, AS, or nr-axSpA is 160 mg SC every 4 weeks.[34] The HS dosing regimen is unique, starting with 320 mg SC every 2 weeks for 4 months followed by 320 mg every 4 weeks thereafter.[34] As with other IL-17i, bimekizumab should not be administered in patients with active IBD.[34] Other serious adverse events include suicidal ideation and behavior, infections, and liver biochemical abnormalities.[34]

  The efficacy of bimekizumab in PsA patients was assessed in 2 double-blind, placebo-controlled RCTs (Trial PsA-1 and Trial PsA-2) in adults 18 years and older.[34] The PsA-1 study evaluated 852 biologic-naïve subjects, who were treated with either bimekizumab 160 mg SC every 4 weeks up to week 52, adalimumab 40 mg SC every 2 weeks up to week 52, or placebo.[34] An active reference (adalimumab) group was included to enable an assessment of the benefit–risk profile of bimekizumab alongside a commonly used standard-of-care treatment and to allow masking to the active treatment.[72] The study was not powered for statistical comparisons of adalimumab to bimekizumab or placebo.[72] Subjects receiving placebo were switched to bimekizumab every 4 weeks at week 16 to week 52.[34] In this study, 78% of subjects had received prior treatment with at least one csDMARDs, and 22% of subjects had no prior treatment with csDMARDs.[34] At baseline, 58% of subjects were receiving concomitant MTX, 11% were receiving concomitant csDMARDs other than MTX, and 31% were receiving no csDMARDs.[34] The PsA-2 study evaluated 400 adults with inadequate response or intolerance to treatment with a TNFi, who were treated with bimekizumab 160 mg every 4 weeks or placebo up to week 16.[34] In this study, 43% of subjects were receiving concomitant MTX, 8% were receiving concomitant csDMARDs other than MTX, and 50% were receiving no csDMARDs.[34] For both studies, the primary endpoint was the proportion of subjects who achieved an ACR50 response at week 16.[34] In Trial PsA-1, 44% of bimekizumab-treated patients achieved ACR50 at Week 16 compared with

10% of placebo-treated patients (TD =38%; 95% CI 31.6 to 45.1) and 47% of adalimumab-treated patients (statistical assessment not reported).[72] In Trial PsA-2, 67% of bimekizumab-treated patients achieved ACR50 versus 15.8% of placebo-treated patients (TD = 51.3%; 95% CI 42.9 to 59.6).[34]

The efficacy of bimekizumab in adults with nr-axSpA was evaluated in one double-blind, placebo-controlled RCT (n=254).[34] Patients also had a history of inadequate response to 2 different NSAIDs, or intolerance or contraindication to NSAIDs. Approximately 24% of patients were on concomitant csDMARDs.[34] Overall, 11% of patients had received previous TNFi treatment (i.e., inadequate response or intolerance to TNFi).[34] The primary endpoint was at least 40% improvement in the ASAS score at week 16 (see **Appendix 1**).[34] More bimekizumab-treated patients achieved ASAS40 responses at week 16 compared with placebo (47.7% vs. 21.4%; TD = 26.2%; 95% CI 15 to 37.5).[34]

The efficacy of bimekizumab in adults with AS was evaluated in one double-blind, placebo-controlled RCT (n=332).[34] Patients also had a history of inadequate response to 2 different NSAIDs, or intolerance or contraindication to NSAIDs.[34] Approximately 20% of subjects were on concomitant csDMARDs. Overall, 16% of subjects had received previous TNFi treatment (i.e., inadequate response or intolerance to TNFi).[34] The primary endpoint was at least 40% improvement in the ASAS score.[34] At week 16, 44.8% of bimekizumab-treated patients achieved ASAS40 response versus 22.5% of placebo-treated patients (TD = 22.3%; 95% CI 12.1 to 32.4).[34]

The efficacy of bimekizumab in adults with HS was assessed in 2 double blind, placebo-controlled RCTs (Trial HS-1 and Trial HS-2).[34] Adults (n=1,014) with moderate to severe HS of at least 6 months with Hurley Stage II or Hurley Stage III disease, and with ≥5 inflammatory lesions [i.e., number of abscesses plus number of inflammatory nodules (AN count)], and a history of inadequate response to a course of systemic antibiotics for the treatment of HS met inclusion criteria.[34] Patients received bimekizumab 320 mg every 2 weeks (Q2W) for 48 weeks, or bimekizumab 320 mg every 4 weeks (Q4W) up to week 48, or bimekizumab 320 mg Q2W to week 16, followed by 320 mg Q4W up to week 48, or placebo.[34] At week 16, subjects receiving placebo were switched to bimekizumab 320 mg Q2W to week 48. Concomitant oral doxycycline, minocycline, or an equivalent systemic tetracycline for HS was allowed if the subject was on a stable dose regimen for 28 days prior to baseline.[34] The primary efficacy endpoint in both trials was the Hidradenitis Suppurativa Clinical Response 50 (HiSCR50) at week 16, defined by at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess or draining tunnel count relative to baseline.[34] In both trials, a higher proportion of patients who received bimekizumab 320 mg every 2 weeks achieved HiSCR50 compared to placebo (Trial HS-1 48% vs. 29%; OR 2.23; 97.5% CI, 1.16 to 4.31; p=0.006 and Trial HS-2 52% vs. 32%; OR 2.29; 97.5% CI, 1.22 to 4.29; p=0.0032).[73] In both trials, HiSCR50 was also met in the group who were administered bimekizumab 320 mg every 4 weeks (Trial HS-1 45% vs. 21%; OR 2.00; 97.5% CI, 0.98 to 4.09; p=0.03 and Trial HS-2 54% vs 32% OR 2.42; 97.5% CI, 1.22 to 4.80; p=0.0038).[73]

- 1/25: OMVOH (mirikizumab) received approval for treatment of adults with moderate to severely active CD.[29] Prior to this approval, mirikizumab was approved to treat adults with moderately to severely active UC.[29] For patients with UC, mirikizumab is initiated with an induction dose of 300 mg via IV infusion at week 0, 4 and 8.[29] The maintenance dose for UC is 200 mg SC starting at week 12 and every 4 weeks thereafter.[29] Induction dosing for CD with mirikizumab begins with a 900 mg IV infusion at week 0, 4, and 8.[29] The maintenance dose for CD is 300 mg SC starting at week 12 and every 4 week thereafter.[29]

  The efficacy of mirikizumab was evaluated in a double-blind, placebo-controlled RCT (CD-1) adults (n=679) with moderately to severely active CD who had an inadequate response, loss of response, or intolerance to corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, and MTX), and/or biologics (TNFi, integrin receptor antagonists).[29] Patients were randomized 3:1 at week 0 to receive placebo or mirikizumab 900 mg via IV infusion at week 0, 4, and 8 followed by a dosage of 300 mg by SC injection at week 12 and then every 4 weeks for 40 weeks.[29] Patients were permitted to use stable doses of oral

corticosteroids (prednisone ≤30 mg/day or equivalent, extended-release budesonide 9 mg/day), immunomodulators (6-mercatopurine, azathioprine, or MTX) and/or aminosalicylates.[29] At baseline, 31% of subjects were receiving oral corticosteroids, 26% were receiving immunomodulators, and 44% were receiving aminosalicylates.[29] Disease activity at baseline was assessed by the Crohn's Disease Activity Index (CDAI) and the Simple Endoscopic Score for Crohn's disease (SES-CD). Moderately to severely active CD was defined by a CDAI of ≥220 and an SES-CD ≥7 (centrally read) for subjects with ileal-colonic disease or ≥4 for subjects with isolated ileal disease. At baseline, patients had a median CDAI of 329 and SES-CD of 12.[29]

The coprimary endpoints of clinical remission by CDAI and endoscopic response by SES-CD were assessed at week 52.[29] More mirikizumab-treated patients achieved clinical remission at week 52 compared with placebo (53% vs. 36%; TD 17%; 95% CI 9 to 25%).[29] Similar results were observed with endoscopic response at week 52 between mirikizumab and placebo (46% vs. 23%; TD 23%; 95% CI 15 to 30%).[29] The common adverse events reported in this trial with mirikizumab included upper respiratory tract infections (28%), injection site reactions (10%), headache (6%), arthralgia (6%), and elevated liver function tests (5%).[29]

New FDA Safety Alerts:

Table 6. Description of New FDA Safety Alerts[74]

Generic Name	Brand Name	Month/Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Apremilast	OTEZLA	12/2021	Warnings and Precautions	*Hypersensitivity* Hypersensitivity reactions, including cases of angioedema and anaphylaxis, have been reported during post marketing surveillance. Avoid the use of apremilast in patients with known hypersensitivity to apremilast or to any of the excipients in the formulation. If signs or symptoms of serious hypersensitivity reactions develop during treatment, discontinue apremilast and institute appropriate therapy.
		4/2024	Warnings and Precautions	*Weight Loss in Pediatric Patients* During the placebo-controlled period of the clinical trial in pediatric subjects 6 to 17 years of age with moderate to severe plaque psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (19/163) of pediatric subjects treated with apremilast compared to 2.5% (2/80) of pediatric subjects treated with placebo. Weight decrease of greater than or equal to 10% of body weight occurred in 1% (1/163) of pediatric subjects treated with apremilast twice daily compared to 0% (0/80) of pediatric subjects treated with placebo. Closely monitor growth (height and weight) in apremilast-treated pediatric patients. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted.
Risankizumab-rzaa	SKYRIZI	6/2022 and 6/2024	Warnings and Precautions	*Hepatotoxicity in Treatment of Inflammatory Bowel Disease*

		(Ulcerative Colitis added to warning)		A serious adverse reaction of drug-induced liver injury was reported in a patient with Crohn's disease (ALT 54x ULN, AST 30x ULN, and total bilirubin 2.2x ULN) following two intravenous doses of risankizumab 600 mg in conjunction with a rash that required hospitalization. The liver test abnormalities resolved following administration of steroids. Risankizumab was subsequently discontinued. For the treatment of Crohn's disease and ulcerative colitis, evaluate liver enzymes and bilirubin at baseline, and during induction for at least 12 weeks of treatment. Monitor thereafter according to routine patient management. Consider other treatment options in patients with evidence of liver cirrhosis. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of hepatic dysfunction.
Secukinumab	COSENTYX	7/2023 10/2024	Warnings and Precautions	*Hypersensitivity Reactions* Anaphylaxis and cases of anaphylaxis, angioedema, and urticaria occurred in secukinumab treated subjects in clinical trials and in the post-marketing setting. If an anaphylactic or other serious allergic reaction occurs, administration of secukinumab should be discontinued immediately and appropriate therapy initiated. *Eczematous Eruptions* In postmarketing reports, cases of severe eczematous eruptions, including atopic dermatitis-like eruptions, dyshidrotic eczema, and erythroderma, were reported in patients receiving secukinumab; some cases resulted in hospitalization. The onset of eczematous eruptions was variable, ranging from days to months after the first dose of secukinumab. Treatment may need to be discontinued to resolve the eczematous eruption. Some patients were successfully treated for eczematous eruptions while continuing secukinumab *Risk of Hypersensitivity in Latex-Sensitive Individuals* The removable caps of the COSENTYX 150 mg/mL Sensoready pen and the COSENTYX 1 mL and 0.5 mL prefilled syringes contain natural rubber latex, which may cause an allergic reaction in latex-sensitive individuals. The safe use of COSENTYX 150 mg/mL Sensoready pen or 1 mL and 0.5 mL prefilled syringes in latex-sensitive individuals has not been studied.

		8/2024	Warnings and Precautions	*Infections* In the postmarketing setting, serious bacterial, viral, fungal opportunistic infections, and some fatal infections have been reported in patients receiving IL-17 inhibitors including secukinumab. Cases of Hepatitis B virus reactivation have been reported. If signs of Hepatitis B virus reactivation occur, consult a hepatitis specialist. Secukinumab is not recommended for use in patients with active viral hepatitis.
Canakinumab	ILARIS	11/2024	Warnings and Precautions	*Hypersensitivity Reactions* During clinical trials, no anaphylactic reactions attributable to treatment with canakinumab have been reported. It should be recognized that symptoms of the underlying disease being treated may be similar to symptoms of hypersensitivity. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), characterized by serious skin eruptions, has been reported in patients with autoinflammatory conditions treated with canakinumab. If a severe hypersensitivity reaction occurs, immediately discontinue canakinumab; treat promptly and monitor until signs and symptoms resolve.
Ixekizumab	TALTZ	7/2024	Warnings and Precautions	*Infections* In the postmarketing setting, serious bacterial, viral, and fungal opportunistic infections have been reported in patients receiving IL-17 inhibitors including ixekizumab. *Eczematous Eruptions* In the postmarketing setting, cases of severe eczematous eruptions, including atopic dermatitis-like eruptions, dyshidrotic eczema, and erythroderma were reported in patients receiving ixekizumab; some cases resulted in hospitalization. The onset of eczematous eruptions was variable, ranging from days to months after the first dose of ixekizumab. Treatment may need to be discontinued to resolve the eczematous eruption. Some patients with limited psoriasis treatment options were successfully treated for eczema while continuing ixekizumab.
Bimekizumab	Bimzelx	11/2024	Warnings and Precautions	*Suicidal Ideation and Behavior* An increased incidence of new onset or worsening suicidal ideation and behavior was observed in subjects treated with bimekizumab. A causal association between treatment with bimekizumab and increased risk of suicidal ideation and behavior has not been definitively established.

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Appendix 1: FDA-Approved Targeted Immune Modulators

Table 1. FDA-Approved Targeted Immune Modulators for Selected Auto-Immune Conditions[27,75]

Drug – Route of Administration	Molecular Target	Common Approved Indication(s)
Biologic DMARDs		
Adalimumab (HUMIRA) - SC	TNF	AS, RA, PsA, PsO, CD, UC
Certolizumab Pegol (CIMZIA) - SC		AS, RA PsA, PsO, CD
Etanercept (ENBREL) - SC		AS, RA, PsA, PsO
Golimumab - (SIMPONI and SIMPONI ARIA) - IV or SC		AS, RA, PsA, UC
Infliximab (REMICADE) - IV		AS, RA, PsA, PsO, CD, UC
Anakinra (KINERET) - SC	IL-1	RA
Sarilumab (KEVZARA) - SC	IL-6	RA
Tocilizumab (ACTEMRA) – IV or SC		RA
Ustekinumab (STELARA) – IV or SC	IL-12 and IL-23	PsA, PsO, CD, UC
Bimekizumab (BIMZELX) - SC	IL-17	AS, PsO, PsA
Brodalumab (SILIQ) - SC		PsO
Ixekizumab (TALTZ) - SC		AS, PsA, PsO
Secukinumab (COSYNTEX) - SC		AS, PsA, PsO
Guselkumab (TREMFYA) - SC	IL-23	PsA, PsO, CD, UC
Mirikizumab (OMVOH) – IV (initial dose) followed by SC		UC, CD
Risankizumab (SKYRIZI) - SC		PsA, PsO, CD, UC
Tildrakizumab (ILUMYA) - SC		PsO
Vedolizumab (ENTYVIO) – IV	Integrin receptor	CD, UC
Natalizumab (TYSABRI) – IV		CD
Abatacept (ORENCIA) - IV or SC	T-lymphocyte	RA, PsA
Rituximab (RITUXAN) - IV	B-lymphocyte	RA
Spesolimab (SPEVIGO) – IV for acute flares, SC for maintenance to prevent flairs	IL-36	GPP
Targeted Synthetic DMARDs		
Baricitinib (OLUMIANT) - PO	JAK 1,2	RA
Tofacitinib (XELJANZ)- PO	JAK 1,2,3	RA, PsA, UC
Upadacitinib (RINVOQ) - PO	JAK 1	RA, CD, UC
Apremilast (OTEZLA) - PO	PDE4	PsA, PsO
Ozanimod (ZEPOSIA) – PO	S1P receptor	UC
Etrasimod (VELSIPITY)– PO		UC

Deucravacitinib (SOTYKU) – PO	TYK2	PsO

Abbreviations: AS=ankylosing spondylitis; CD=Crohn's Disease; DMARD=Disease-Modifying Antirheumatic Drug; FDA=Food and Drug Administration; IL=interleukin; GPP= Generalized Pustular Psoriasis; IV=intravenous; JAK=Janus Kinase; PDE=phosphodiesterase; PO=oral; PsA=psoriatic arthritis; PsO=plaque psoriasis; S1P=sphingosine 1-phosphate; RA=rheumatoid arthritis; SC=subcutaneous; TNF=tumor necrosis factor; TYK2=tyrosine kinase 2; UC=Ulcerative Colitis

Appendix 2: Outcomes Used for Assessment of Disease Progression in Clinical Trials

Table 2. Selected Outcomes Used for Assessment of Disease Progression[20,76-79]

Ankylosing Spondylitis		
Outcome Measure	**Domains**	**Scale and Scoring**
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Level of symptoms: 1. Fatigue 2. Pain in hips, back and neck 3. Pain in joints other than hips, back or neck 4. Discomfort in areas tender to touch or pressure Mean measurements of: 5. Intensity of morning stiffness 6. Duration of morning stiffness (0 to 2 hours scored on a 0-10 scale)	VAS scale 0-10: 0 is no symptoms, 10 is very severe BASDAI score calculation: 1. Add scores for the first 4 questions 2. Add one half of the sum of question 5 and 6 3. Divide the result by 5 A BASDAI score ≥ 4 (on a scale of 0-10) indicates active disease that warrants consideration of therapy
BASDAI50	• ≥ 50% improvement in BASDAI	
Bath Ankylosing Spondylitis Functional Index (BASFI)	Severity of 10 functional abilities: 1. Putting on socks 2. Bend from the waist to pick up a pen from the floor 3. Reaching up to a high shelf 4. Getting up from an armless chair 5. Getting up off the floor 6. Standing unsupported 7. Climbing 12-15 steps unaided 8. Looking over the shoulder 9. Doing physically demanding activities 10. Doing a full day's activities	VAS scale 0-10: easy (0) to impossible (10) BASFI score calculation: Total all 10 items and divide by 10 for final score Reported as change in score from baseline
Assessment of Spondyloarthritis International Society (ASAS) Response	Combines measures of symptoms and disability in 4 disease measures: 1. Spinal inflammation (BASDAI questions 5 and 6) 2. Spinal pain 3. Patient global assessment of spondylitis 4. Functional impairment (BASFI score)	Scale of 0-10: 0 is no symptoms, 10 is very severe
ASAS20	• Improvement of ≥ 20% and ≥ 1 unit in ≥ 3 of disease measures above • No worsening of ≥ 20% and ≥ 1 unit in remaining unimproved measure	Assessment of response to therapy by percent in symptom improvement
ASAS40	• Improvement of ≥ 40% and ≥ 2 units in ≥ 3 of disease measures above	
ASAS Partial Remission	• No worsening at all in remaining measure	Value of ≤ 2 in each of the 4 domains

	• Reflects low disease activity	
Ankylosing Spondylitis Disease Activity Score (ASDAS) ASDAS Calculator: http://www.asas-group.org/clinical-instruments/asdas_calculator/asdas.html	Measures severity of symptoms and signs of inflammation including: 1. Back pain 2. Patient global assessment of spondylitis 3. Peripheral pain and swelling (BASDAI score) 4. Duration of morning stiffness (BASDAI score) 5. CRP or ESR	Scale of 0-10: 0 is no symptoms, 10 is very severe ASDAS scores: < 1.3 – Inactive Disease 1.4 to 2.1 – Moderate Disease Activity 2.2 to 3.4 – High Disease Activity >3.5 – Very High Disease Activity Improvement Criteria: Change ≥ 1.1 – Clinically Important Improvement Change ≥ 2.0 – Major Improvement
Spondyloarthritis Research Consortium of Canada (SPARCC)	Assessment of inflammation in the sacroiliac joints on magnetic resonance imaging (MRI). • Six coronal slices are assessed. • The sacroiliac joints are divided into 4 quadrants (upper lilac, lower iliac, upper sacral, and lower sacral). • The presence of increased signals in each quadrant is recorded. The maximum score for 2 sacroiliac joints in each coronal slice is 8. Maximum score for 6 coronal slices = 48 • A score for "intense" is assigned each sacroiliac joint on each slice. A score of 1 is assigned if "intense signal" is seen in any quadrant of any joint on a single slice. Maximum score per slice is 2, and for 6 slices = 12 • A score for "deep" may be assigned each joint on each slice. A score of 1 is assigned if "deep" signal is seen in any quadrant of a sacroiliac joint on a single slice. Maximum score per slide is 2, and for 6 slices =12.	Maximum score is 72 points • Presence of bone marrow edema = 48 • Presence of intense edema = 12 • Presence of deep edema = 12
Rheumatoid Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**
Disease Activity Score (DAS)-28 DAS-28 calculator https://www.das-score.nl/das28/DAScalculators/dasculators.html	Clinical assessment of disease activity in combination with an acute phase reactant level 1. Assessment of 28 joints for swelling and tenderness - swollen joint count (SJC) - tender joint count (TJC) 2. General health (GH) - patient assessment of disease on a 0-100 scale where 100 means maximal disease activity 3. Either ESR or CRP adjusted with SJC and TJC scores	DAS-28 scoring ranges from 0 to 9.4: <2.6: Remission ≥2.6 and ≤3.2: Low Disease Activity >3.2 and ≤5.1: Moderate Disease Activity >5.1: High disease activity • DAS-28 reduction by 0.6 represents a moderate improvement. • DAS-28 reduction more than 1.2 represents a major improvement.

Health Assessment Questionnaire Disability Index (HAQ-DI)	Assess 8 domains of daily activity – patient self-reported 1. Dressing and Grooming 2. Arising 3. Eating 4. Walking 5. Hygiene 6. Reach 7. Grip 8. Chores or Activities	Scored 0 to 3: 0 - no difficulty 1 - with some difficulty 2 - with much difficulty 3 - unable to do HAQ-DI calculation: Sum of all domains then divided by 8 to give total score ranging from 0 (best) to 3 (worst*)*

American College of Rheumatology (ACR)
 	
ACR 20
 	
ACR 50
 	
ACR 70
	Definition of improvement in RA symptoms
	
	• 20% improvement in tender and swollen joint counts
	• 20% improvement in 3 of 5 remaining ACR core set measures
	  ○ patient global assessment (VAS score)
	  ○ physician global assessment (VAS score)
	  ○ self-reported physical disability (HAQ score)
	  ○ an acute phase reactant (ESR or CRP)
	  ○ patient pain assessment (VAS score)
	
	• 50% improvement in tender and swollen joint counts
	• 50% improvement in 3 of 5 remaining ACR core measures
	
	• 70% improvement in tender and swollen joint counts
	• 70% improvement in 3 of 5 remaining ACR core set measures
		
		20% improvement
		
		50% improvement
		
		70% improvement

Plaque Psoriasis, Psoriatic Arthritis, and Generalized Pustular Psoriasis		
Outcome Measure	**Domains**	**Scale and Scoring**
Static Physician's Global Assessment Scale (sPGA)	The static PGA is a 0-5 ordinal rating ranging from "clear" to "very severe psoriasis" as evaluated by the provider	Scale of 0 – 5: 0 = clear; scores 1–5 = increasing severity Response to therapy indicated by a score of 0 or 1
Psoriasis Symptom Inventory (PSI)	Patient reported outcome in 8 areas: 1. Itch 2. Redness 3. Scaling 4. Burning 5. Cracking 6. Stinging 7. Flaking 8. Pain of Lesions	Scale of 0-4: 0 = not at all severe, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe Score ranges from 0 – 32 Response to therapy indicated by scores < 8 with no single item rated higher than 1

Psoriasis Area and Severity Index (PASI) PASI-75 PASI-90	Measure of overall psoriasis severity and coverage on Head, Upper Extremities, Trunk and Lower Extremities • Erythema • Induration • Scaling 75% Improvement in PASI score 90% Improvement in PASI score – clear or almost clear skin	Scale of 0-4: 0 is clear, 1-4 increasing severity PASI score: 1. Sum rows 1, 2, and 3 for each area of the body using a 0-4 scale 2. Add an area score based on percentage involvement from 0 (clear) to 6 (≥90% coverage) 3. Multiply score as rated for each body area (0.1, 0.2, 0.3, 0.4 for head, arms, trunk, and legs, respectively) 4. Add all the scores together Composite score ranges from 0 -72: 0 = normal 72 = maximal disease
PsA Response Criteria (PsARC)	Used by the National Institute of Health Care Excellence (NICE) to continue TNF inhibitor therapy with an assessment at baseline and 12 weeks 1. 66 swollen joint score 2. 68 tender joint score 3. Patient global assessment 4. Physician global assessment	**Response** = improvement in ≥ 2 of the 4 tests: -One of which must be the joint tenderness or swelling score -No worsening in any of the four measures • **Improvement** is defined as a decrease ≥ 30% in the swollen or tender joint score and ≥1 in either of the global assessments
Dermatology Quality of Life (DQLI)	10 question patient self-reported assessment 1. How itchy has your skin been? 2. How embarrassed are because of your skin? 3. Has your skin interfered with activities? 4. Has your skin influenced the clothes you wear/ 5. Has your skin affected social activities? 6. How your skin impacted your ability to participate in a sport? 7. Has your skin prevented you from working? 8. Has your skin caused any problems with friends? 9. Has your skin impacted sexual activities? 10. How much has the treatment for your skin affected your daily activities?	Scale of 0-3: 0 not at all, 1 a little, 2 a lot, and 3 very much Interpretation of DQLI score: 0 – 1 no effect at all on patient's life 2 – 5 small effects on patient's life 6 – 10 moderate effects on patient's life 11 – 20 very large effect on patient's life 21 – 30 extremely large effect on patient's life
Generalized Pustular Psoriasis Global Assessment (GPPGA)	Clinician scores 3 components on a 5-point scale (0 = clear to 4 = severe): 1. Erythema 2. Pustules 3. Lesion scaling	Scoring: Ranges from 0 to 4 0 = clear 1 = almost clear 2 = mild disease: bright red erythema, discrete moderate-density pustules, fine scaling or crusting 3 = moderate disease: bright red erythema, high-density pustules, moderate scaling or crusting covering most or all lesions

		4 = severe disease: deep, fiery red erythema, very high-density pustules with pustular lakes, and severe scaling or crusting cover most or all lesions
Crohn's Disease and Ulcerative Colitis		
Outcome Measure	**Domains**	**Scale and Scoring**
Crohn's Disease Activity Score (CDAI)	Evaluation of 8 clinical factors (each weighted and summed to reach a total score) 1. Number of liquid or soft stools each day for 1 week (weight x 2) 2. Abdominal pain (graded on a severity scale of 0-3) for 1 week (weight x 5) 3. General Well-being (subjective score of 0-4) for 1 week (weight x 7) 4. Presence of complications (weight x 20) 5. Use of diphenoxylate/atropine or opiates for diarrhea (weight x 30) 6. Presence of abdominal mass (graded as 0 [none], 2 [questionable] or 5 [definite]) (weight x 10) 7. Absolute deviation of Hematocrit from 47% (men) or 42% (women) (weight x 6) 8. Percentage deviation from standard weight (weight x 1)	Each factor is weighted and summed to achieve a total score • Scores ≤150 indicate minimal disease • Scores >150 indicate active disease • Scores >450 indicate extremely severe disease

Mayo Clinic score (MCS) for grading activity of ulcerative colitis	Assessment — Points **1. Stool Frequency** -Patient reporting a normal number of daily stools -3-4 more stools than normal — 2 -≥ 5 more stools than normal — 3 **2. Rectal Bleeding** -None — 0 -Blood streaks seen with stool less than half the time — 1 -Blood with most stools — 2 -Pure blood passed — 3 **3. Endoscopic Findings** -Normal or inactive colitis — 0 -Mild friability, erythema, decreased vascularity — 1 -Friability, marked erythema, absent vascular pattern, erosions — 2 -Ulcerations and spontaneous bleeding — 3 **4. Physician Global Assessment** -Normal — 0 -Mild colitis — 1 -Moderate colitis — 2 -Severe colitis — 3	The score can range from 0-12 with higher scores indicating worse severity. A critical component of this score is the endoscopic findings. Patients with lower scores but with an endoscopic score of 2 or greater are considered more severe regardless of the final score.
Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analog scale		

Appendix 3: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
adalimumab	HUMIRA PEN	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN CROHN'S-UC-HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN PSOR-UV-ADOL HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA	SUBCUT	SYRINGEKIT	Y
adalimumab	HUMIRA(CF)	SUBCUT	SYRINGEKIT	Y
adalimumab-atto	AMJEVITA(CF) AUTOINJECTOR	SUBCUT	AUTO INJCT	Y
adalimumab-atto	AMJEVITA(CF)	SUBCUT	SYRINGE	Y
adalimumab-fkjp	ADALIMUMAB-FKJP(CF) PEN	SUBCUT	PEN IJ KIT	Y
adalimumab-fkjp	ADALIMUMAB-FKJP(CF) PEN	SUBCUT	PEN INJCTR	Y
adalimumab-fkjp	ADALIMUMAB-FKJP(CF)	SUBCUT	SYRINGE	Y
adalimumab-fkjp	ADALIMUMAB-FKJP(CF)	SUBCUT	SYRINGEKIT	Y
adalimumab-ryvk	SIMLANDI(CF) AUTOINJECTOR	SUBCUT	AUTOINJKIT	Y
adalimumab-ryvk	SIMLANDI(CF)	SUBCUT	SYRINGEKIT	Y
apremilast	OTEZLA	ORAL	TAB DS PK	Y
apremilast	OTEZLA	ORAL	TABLET	Y
etanercept	ENBREL MINI	SUBCUT	CARTRIDGE	Y
etanercept	ENBREL SURECLICK	SUBCUT	PEN INJCTR	Y
etanercept	ENBREL	SUBCUT	SYRINGE	Y
etanercept	ENBREL	SUBCUT	VIAL	Y
infliximab-axxq	AVSOLA	INTRAVEN	VIAL	Y
ixekizumab	TALTZ AUTOINJECTOR	SUBCUT	AUTO INJCT	Y
ixekizumab	TALTZ AUTOINJECTOR (2 PACK)	SUBCUT	AUTO INJCT	Y
ixekizumab	TALTZ AUTOINJECTOR (3 PACK)	SUBCUT	AUTO INJCT	Y
ixekizumab	TALTZ SYRINGE	SUBCUT	SYRINGE	Y
tofacitinib citrate	XELJANZ	ORAL	SOLUTION	Y
tofacitinib citrate	XELJANZ XR	ORAL	TAB ER 24H	Y
tofacitinib citrate	XELJANZ	ORAL	TABLET	Y
abatacept	ORENCIA CLICKJECT	SUBCUT	AUTO INJCT	N
abatacept	ORENCIA	SUBCUT	SYRINGE	N
abatacept/maltose	ORENCIA	INTRAVEN	VIAL	N
adalimumab-aacf	ADALIMUMAB-AACF(CF) PEN (2 PK)	SUBCUT	PEN IJ KIT	N
adalimumab-aacf	ADALIMUMAB-AACF(CF) PEN CROHNS	SUBCUT	PEN IJ KIT	N
adalimumab-aacf	ADALIMUMAB-AACF(CF) PEN PS-UV	SUBCUT	PEN IJ KIT	N
adalimumab-aacf	IDACIO(CF) PEN (2 PACK)	SUBCUT	PEN IJ KIT	N
adalimumab-aacf	IDACIO(CF) PEN CROHN'S-UC(6PK)	SUBCUT	PEN IJ KIT	N
adalimumab-aacf	IDACIO(CF) PEN PSORIASIS (4PK)	SUBCUT	PEN IJ KIT	N
adalimumab-aacf	IDACIO(CF) PEN	SUBCUT	PEN INJCTR	N

adalimumab-aacf	ADALIMUMAB-AACF(CF)	SUBCUT	SYRINGE	N
adalimumab-aacf	ADALIMUMAB-AACF(CF) (2 PK)	SUBCUT	SYRINGEKIT	N
adalimumab-aacf	IDACIO(CF) (2 PACK)	SUBCUT	SYRINGEKIT	N
adalimumab-aaty	ADALIMUMAB-AATY(CF) AI CROHNS	SUBCUT	AUTOINJKIT	N
adalimumab-aaty	ADALIMUMAB-AATY(CF) AUTOINJ (2)	SUBCUT	AUTOINJKIT	N
adalimumab-aaty	ADALIMUMAB-AATY(CF) AUTOINJECT	SUBCUT	AUTOINJKIT	N
adalimumab-aaty	YUFLYMA(CF) AI CROHN'S-UC-HS	SUBCUT	AUTOINJKIT	N
adalimumab-aaty	YUFLYMA(CF) AUTOINJECT (2 PCK)	SUBCUT	AUTOINJKIT	N
adalimumab-aaty	YUFLYMA(CF) AUTOINJECTOR	SUBCUT	AUTOINJKIT	N
adalimumab-aaty	ADALIMUMAB-AATY(CF) (2 PACK)	SUBCUT	SYRINGEKIT	N
adalimumab-aaty	ADALIMUMAB-AATY(CF) (2 PK)	SUBCUT	SYRINGEKIT	N
adalimumab-aaty	YUFLYMA(CF) (2 PACK)	SUBCUT	SYRINGEKIT	N
adalimumab-adaz	ADALIMUMAB-ADAZ(CF) PEN	SUBCUT	PEN INJCTR	N
adalimumab-adaz	HYRIMOZ(CF) PEN	SUBCUT	PEN INJCTR	N
adalimumab-adaz	HYRIMOZ(CF) PEN CROHN-UC START	SUBCUT	PEN INJCTR	N
adalimumab-adaz	HYRIMOZ(CF) PEN PSORIASIS	SUBCUT	PEN INJCTR	N
adalimumab-adaz	ADALIMUMAB-ADAZ(CF)	SUBCUT	SYRINGE	N
adalimumab-adaz	HYRIMOZ(CF)	SUBCUT	SYRINGE	N
adalimumab-adaz	HYRIMOZ(CF) PEDIATRIC CROHN'S	SUBCUT	SYRINGE	N
adalimumab-adbm	ADALIMUMAB-ADBM(CF) PEN	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	ADALIMUMAB-ADBM(CF) PEN CROHNS	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	ADALIMUMAB-ADBM(CF) PEN PS-UV	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	ADALIMUMAB-ADBM(CF)PEN	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	CYLTEZO(CF) PEN	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	CYLTEZO(CF) PEN CROHN'S-UC-HS	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	CYLTEZO(CF) PEN PSORIASIS-UV	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	ADALIMUMAB-ADBM(CF)	SUBCUT	SYRINGEKIT	N
adalimumab-adbm	CYLTEZO(CF)	SUBCUT	SYRINGEKIT	N
adalimumab-afzb	ABRILADA(CF) PEN	SUBCUT	PEN IJ KIT	N
adalimumab-afzb	ABRILADA(CF) PEN (2 PACK)	SUBCUT	PEN IJ KIT	N
adalimumab-afzb	ABRILADA(CF)	SUBCUT	SYRINGEKIT	N
adalimumab-aqvh	YUSIMRY(CF) PEN	SUBCUT	PEN INJCTR	N
adalimumab-atto	AMJEVITA(CF) AUTOINJECTOR	SUBCUT	AUTO INJCT	N
adalimumab-atto	AMJEVITA(CF)	SUBCUT	SYRINGE	N
adalimumab-bwwd	HADLIMA PUSHTOUCH	SUBCUT	AUTO INJCT	N
adalimumab-bwwd	HADLIMA(CF) PUSHTOUCH	SUBCUT	AUTO INJCT	N
adalimumab-bwwd	HADLIMA	SUBCUT	SYRINGE	N
adalimumab-bwwd	HADLIMA(CF)	SUBCUT	SYRINGE	N
adalimumab-fkjp	HULIO(CF) PEN	SUBCUT	PEN IJ KIT	N
adalimumab-fkjp	HULIO(CF) PEN	SUBCUT	PEN INJCTR	N

adalimumab-fkjp	HULIO(CF)	SUBCUT	SYRINGE	N
adalimumab-fkjp	HULIO(CF)	SUBCUT	SYRINGEKIT	N
adalimumab-ryvk	ADALIMUMAB-RYVK(CF) AUTOINJECT	SUBCUT	AUTOINJKIT	N
adalimumab-ryvk	ADALIMUMAB-RYVK(CF)	SUBCUT	SYRINGEKIT	N
anakinra	KINERET	SUBCUT	SYRINGE	N
baricitinib	OLUMIANT	ORAL	TABLET	N
bimekizumab-bkzx	BIMZELX AUTOINJECTOR	SUBCUT	AUTO INJCT	N
bimekizumab-bkzx	BIMZELX	SUBCUT	SYRINGE	N
brodalumab	SILIQ	SUBCUT	SYRINGE	N
canakinumab/PF	ILARIS	SUBCUT	VIAL	N
certolizumab pegol	CIMZIA (2 PACK)	SUBCUT	KIT	N
certolizumab pegol	CIMZIA	SUBCUT	SYRINGEKIT	N
certolizumab pegol	CIMZIA (2 PACK)	SUBCUT	SYRINGEKIT	N
deucravacitinib	SOTYKTU	ORAL	TABLET	N
etrasimod arginine	VELSIPITY	ORAL	TABLET	N
golimumab	SIMPONI ARIA	INTRAVEN	VIAL	N
golimumab	SIMPONI	SUBCUT	PEN INJCTR	N
golimumab	SIMPONI	SUBCUT	SYRINGE	N
guselkumab	TREMFYA	INTRAVEN	VIAL	N
guselkumab	TREMFYA ONE-PRESS	SUBCUT	AUTO INJCT	N
guselkumab	TREMFYA PEN	SUBCUT	PEN INJCTR	N
guselkumab	TREMFYA PEN INDUCTION PK-CROHN	SUBCUT	PEN INJCTR	N
guselkumab	TREMFYA	SUBCUT	SYRINGE	N
infliximab	INFLIXIMAB	INTRAVEN	VIAL	N
infliximab	REMICADE	INTRAVEN	VIAL	N
infliximab-abda	RENFLEXIS	INTRAVEN	VIAL	N
infliximab-dyyb	INFLECTRA	INTRAVEN	VIAL	N
infliximab-dyyb	ZYMFENTRA	SUBCUT	PEN IJ KIT	N
infliximab-dyyb	ZYMFENTRA PEN (2 PACK)	SUBCUT	PEN IJ KIT	N
infliximab-dyyb	ZYMFENTRA (2 PACK)	SUBCUT	SYRINGEKIT	N
mirikizumab-mrkz	OMVOH	INTRAVEN	VIAL	N
mirikizumab-mrkz	OMVOH PEN	SUBCUT	PEN INJCTR	N
mirikizumab-mrkz	OMVOH	SUBCUT	SYRINGE	N
natalizumab	TYSABRI	INTRAVEN	VIAL	N
risankizumab-rzaa	SKYRIZI	INTRAVEN	VIAL	N
risankizumab-rzaa	SKYRIZI PEN	SUBCUT	PEN INJCTR	N
risankizumab-rzaa	SKYRIZI	SUBCUT	SYRINGE	N
risankizumab-rzaa	SKYRIZI ON-BODY	SUBCUT	WEAR INJCT	N
rituximab	RITUXAN	INTRAVEN	VIAL	N
rituximab-abbs	TRUXIMA	INTRAVEN	VIAL	N

rituximab-arrx	RIABNI	INTRAVEN	VIAL	N
rituximab-pvvr	RUXIENCE	INTRAVEN	VIAL	N
sarilumab	KEVZARA	SUBCUT	PEN INJCTR	N
sarilumab	KEVZARA	SUBCUT	SYRINGE	N
secukinumab	COSENTYX	INTRAVEN	VIAL	N
secukinumab	COSENTYX SENSOREADY (2 PENS)	SUBCUT	PEN INJCTR	N
secukinumab	COSENTYX SENSOREADY PEN	SUBCUT	PEN INJCTR	N
secukinumab	COSENTYX UNOREADY PEN	SUBCUT	PEN INJCTR	N
secukinumab	COSENTYX (2 SYRINGES)	SUBCUT	SYRINGE	N
secukinumab	COSENTYX SYRINGE	SUBCUT	SYRINGE	N
spesolimab-sbzo	SPEVIGO	INTRAVEN	VIAL	N
spesolimab-sbzo	SPEVIGO	SUBCUT	SYRINGE	N
tildrakizumab-asmn	ILUMYA	SUBCUT	SYRINGE	N
tocilizumab	ACTEMRA	INTRAVEN	VIAL	N
tocilizumab	ACTEMRA ACTPEN	SUBCUT	PEN INJCTR	N
tocilizumab	ACTEMRA	SUBCUT	SYRINGE	N
tocilizumab-aazg	TYENNE	INTRAVEN	VIAL	N
tocilizumab-aazg	TYENNE AUTOINJECTOR	SUBCUT	PEN INJCTR	N
tocilizumab-aazg	TYENNE	SUBCUT	SYRINGE	N
tocilizumab-bavi	TOFIDENCE	INTRAVEN	VIAL	N
upadacitinib	RINVOQ LQ	ORAL	SOLUTION	N
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N
ustekinumab	STELARA	INTRAVEN	VIAL	N
ustekinumab	USTEKINUMAB	INTRAVEN	VIAL	N
ustekinumab	STELARA	SUBCUT	SYRINGE	N
ustekinumab	USTEKINUMAB	SUBCUT	SYRINGE	N
ustekinumab	STELARA	SUBCUT	VIAL	N
ustekinumab	USTEKINUMAB	SUBCUT	VIAL	N
ustekinumab-aauz	OTULFI	INTRAVEN	VIAL	N
ustekinumab-aauz	OTULFI	SUBCUT	SYRINGE	N
ustekinumab-aekn	SELARSDI	INTRAVEN	VIAL	N
ustekinumab-aekn	SELARSDI	SUBCUT	SYRINGE	N
ustekinumab-aekn	USTEKINUMAB-AEKN	SUBCUT	SYRINGE	N
ustekinumab-kfce	YESINTEK	INTRAVEN	VIAL	N
ustekinumab-kfce	YESINTEK	SUBCUT	SYRINGE	N
ustekinumab-kfce	YESINTEK	SUBCUT	VIAL	N
ustekinumab-stba	STEQEYMA	INTRAVEN	VIAL	N
ustekinumab-stba	STEQEYMA	SUBCUT	SYRINGE	N
ustekinumab-ttwe	PYZCHIVA	INTRAVEN	VIAL	N
ustekinumab-ttwe	USTEKINUMAB-TTWE	INTRAVEN	VIAL	N

ustekinumab-ttwe	PYZCHIVA	SUBCUT	SYRINGE	N
ustekinumab-ttwe	USTEKINUMAB-TTWE	SUBCUT	SYRINGE	N
vedolizumab	ENTYVIO	INTRAVEN	VIAL	N
vedolizumab	ENTYVIO PEN	SUBCUT	PEN INJCTR	N

Appendix 4: New Comparative Clinical Trials

A total of 530 citations were manually reviewed from the initial literature search. After further review, 527 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Werth, et al[80] DB, MC, RCT	1.Rituximab 1000 mg IV on days 1, 15, 168, and 182 (n=67) plus twice-daily oral placebo 2.Mycophenolate mofetil 1 gm PO twice daily (n=68) plus placebo infusions on days 1, 15, 168, and 182 Both groups received the same regimen of tapering GCs for first 24 weeks	-Adults aged 18 to 75 yo with a diagnosis of pemphigus vulgaris within the previous 24 months -PDAI score ≥ 15 (moderate to severe disease activity)	Sustained remission at week 52: PDAI activity score of 0 (on a scale of 0 to 250) for at least 16 weeks without the use of GCs	Sustained Remission at Week 52 1.25/62 (40%) 2.6/63 (10%) Difference: 31% 95% CI 15 to 45 P<0.001 Rituximab was superior to mycophenolate mofetil in producing sustained complete remission, but more patients who received rituximab had serious adverse events than those who received mycophenolate mofetil	-Sponsored by manufacturer of rituximab -Trial designed with 80% power to detect a difference of 25% between groups -More attrition in the mycophenolate group vs. rituximab group (15% vs. 1%) -More patients in the mycophenolate group received rescue therapy compared with rituximab (38% vs. 4%) and were excluded from primary efficacy analysis -Serious adverse events occurred in 15 (22%) of rituximab-treated patients compared with 10 (15%) of mycophenolate-treated patients
Peyrin-Biroulet et al[81] MC, OL, RCT	1.Risankizumab 600 mg IV at weeks 0, 4, and 8 followed by 360 mg SC every 8 weeks from week 12 to week 48 (n=262) 2.Ustekinumab weight based IV induction dose (260 mg to 520 mg) at week 0 followed by 90 mg SC every 8 weeks from week 8 to week 48 (n=265)	-Adults aged 18 to 80 yo with moderate-to-severe CD who had failed at least one TNFi -Baseline CDAI score 220 to 450	The two primary end points, which were tested sequentially, were: 1. Clinical remission at week 24: defined as a CDAI score of <150 which was analyzed in the first 50% of patients to complete the week 24 visit, with a noninferiority margin of 10 percentage points and 2. Endoscopic remission at week 48 (defined as a score of ≤4, a decrease of ≥2 points from baseline, and no subscore >1 in any individual variable on the	A. Clinical remission at Week 24 1. 75/128 (58.6%) 2.54/137 (39.5%) Adjusted difference: 18.4% 95% CI 6.6 to 30.3 NI margin met B. Endoscopic remission at Week 48 1. 81/255 (31.8%) 2.43/265 (16.2%) Adjusted difference: 15.6% 95% CI 8.4 to 22.9 P<0.01	-Funded by manufacturer of risankizumab -Open label study design -More risankizumab-treated patients completed the study compared with ustekinumab-treated patients (90% vs. 73%) due to adverse events (risankizumab) or lack of efficacy (ustekinumab).

			Simple Endoscopic Score for Crohn's Disease [range, 0 to 56, with higher scores indicating more severe disease]), which was analyzed for superiority in 100% of the patients.	Risankizumab was non-inferior to ustekinumab with respect to clinical remission at week 24 and superior with respect to endoscopic remission at week 48.	
Talarico et al[82] MC, single-blind, RCT	1.Infliximab 5 mg/kg IV at weeks 0, 2 and 6 and then every 6 to 8 weeks over 6 months (n=22) 2.Adalimumab 40 mg SC every 2 weeks over 6 months (n=19)	-Adults aged 18 to 65 yo with BS that occurred during treatment with azathioprine or cyclosporine for at least 3 months	Percentage of patients with remission of mucocutaneous involvement	Percentage of responders after 6 months of treatment 1.n=14/22 (64%) 2.n=17/18 (94%) P=0.023 95% CI not reported Effectiveness of both infliximab and adalimumab in achieving remission in patients with BS affected by mucocutaneous involvement was confirmed	-Small sample size -Single blinded study design (only the evaluators)
Abbreviations: BS = Behcet syndrome; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index (CDAI); CI = confidence interval; DB = double blind; GC = glucocorticoids; IV = intravenous; kg = kilograms; MC = multi-center; mg = milligrams; n = number; NI =noninferiority; OL = open label; PDAI = Pemphigus Disease Area Index; PO = oral; RCT = randomized controlled trial; TNFi = tumor necrosis factor inhibitor; yo = years old					

Appendix 5: Abstracts of Comparative Clinical Trials

Rituximab versus Mycophenolate Mofetil in Patients with Pemphigus Vulgaris[80]

Background: Rituximab and mycophenolate mofetil are used to treat pemphigus vulgaris, but they have not been adequately compared in clinical trials.

Methods: In a randomized, controlled trial, we assigned patients with moderate-to-severe pemphigus vulgaris in a 1:1 ratio to receive intravenous rituximab (1000 mg on days 1, 15, 168, and 182) or oral mycophenolate mofetil (2 g per day), in addition to an oral glucocorticoid administered on the same tapering schedule in the two groups. The primary end point was sustained complete remission at week 52, defined as the healing of lesions with no new active lesions, as reflected by a Pemphigus Disease Area Index (PDAI) activity score of 0 (on a scale of 0 to 250, with higher scores indicating greater disease severity), for at least 16 weeks without the use of glucocorticoids. Secondary end points were the cumulative dose of glucocorticoids, the number of disease flares, and the change from baseline in the score on the Dermatology Life Quality Index (DLQI; scores range from 0 to 30, with higher scores indicating greater impairment).

Results: Of the 135 patients who underwent randomization, 67 were assigned to receive rituximab and 68 to receive mycophenolate mofetil. The primary outcome was assessed in the modified intention-to-treat population: 62 patients in the rituximab group and 63 in the mycophenolate mofetil group. The median PDAI activity scores at baseline were 22.7 in the rituximab group and 18.3 in the mycophenolate mofetil group. At week 52, sustained complete remission was observed in 25 patients (40%) in the rituximab group and in 6 (10%) in the mycophenolate mofetil group (difference, 31 percentage points; 95% confidence interval [CI], 15 to 45; P<0.001). The mean cumulative glucocorticoid dose during the 52-week treatment period was 3545 mg in the rituximab group and 5140 mg in the mycophenolate mofetil group (difference, -1595 mg; 95% CI, -2838 to -353; P<0.001). There were 6 disease flares in the rituximab group and 44 in the mycophenolate mofetil group (adjusted rate ratio, 0.12; 95% CI, 0.05 to 0.29; P<0.001). The mean change in DLQI score was -8.87 points and -6.00 points, respectively (difference, -2.87 points; 95% CI, -4.58 to -1.17; P = 0.001). Serious adverse events occurred in 15 of 67 patients (22%) in the rituximab group and in 10 of 68 (15%) in the mycophenolate mofetil group.

Conclusions: Rituximab was superior to mycophenolate mofetil in producing sustained complete remission at 52 weeks in patients with pemphigus vulgaris. Rituximab resulted in a greater reduction in glucocorticoid use than mycophenolate mofetil, but more patients in the rituximab group had serious adverse events. Further trials are needed to

determine the comparative efficacy and safety of rituximab and mycophenolate mofetil beyond 52 weeks of treatment. (Funded by F. Hoffmann-La Roche; PEMPHIX ClinicalTrials.gov number, NCT02383589.)

Risankizumab versus Ustekinumab for Moderate-to-Severe Crohn's Disease[81]
Background: The efficacy and safety of risankizumab as compared with ustekinumab in patients with Crohn's disease are unknown.
Methods: In this phase 3b, multicenter, open-label, randomized, controlled trial with blinded assessment of end points, patients with moderate-to-severe Crohn's disease who had had an inadequate response to anti-tumor necrosis factor (TNF) therapy or unacceptable side effects with such therapy were randomly assigned to receive risankizumab or ustekinumab at standard doses for 48 weeks. The two primary end points, which were tested sequentially, were clinical remission at week 24 (defined as a Crohn's Disease Activity Index score of <150 [range, 0 to 600, with higher scores indicating more severe disease activity]), which was analyzed in the first 50% of patients to complete the week 24 visit, with a noninferiority margin of 10 percentage points; and endoscopic remission at week 48 (defined as a score of ≤4, a decrease of ≥2 points from baseline, and no subscore >1 in any individual variable on the Simple Endoscopic Score for Crohn's Disease [range, 0 to 56, with higher scores indicating more severe disease]), which was analyzed for superiority in 100% of the patients. Safety was assessed in all patients who received at least one dose of risankizumab or ustekinumab.
Results: In the full intention-to-treat population for the efficacy analysis, 230 of 255 patients (90.2%) who received risankizumab and 193 of 265 patients (72.8%) who received ustekinumab completed all the assigned treatments. Both primary end points were met; risankizumab was noninferior to ustekinumab with respect to clinical remission at week 24 (58.6% vs. 39.5%; adjusted difference, 18.4 percentage points; 95% confidence interval [CI], 6.6 to 30.3) and superior to ustekinumab with respect to endoscopic remission at week 48 (31.8% vs. 16.2%; adjusted difference, 15.6 percentage points; 95% CI, 8.4 to 22.9; P<0.001). The incidence of adverse events appeared to be similar in the two groups.
Conclusions: In this head-to-head clinical trial of risankizumab and ustekinumab involving patients with moderate-to-severe Crohn's disease who had had unacceptable side effects with anti-TNF therapy or an inadequate response to such therapy, risankizumab was noninferior to ustekinumab with respect to clinical remission at week 24 and superior with respect to endoscopic remission at week 48. (Funded by AbbVie; ClinicalTrials.gov number, NCT04524611.).

Efficacy And Safety of Infliximab or Adalimumab in Severe Mucocutaneous Behçet's Syndrome Refractory to Traditional Immunosuppressants[82]
Introduction: Evidence from randomized controlled trials on anti-tumor necrosis factor (TNF) agents in patients with Behçet's syndrome (BS) is low.
Method: We conducted a phase 3, multicenter, prospective, randomized, active-controlled, parallel-group study to evaluate the efficacy and safety of either infliximab (IFX) or adalimumab (ADA) in patients with BS. Adults patients with BS presenting with active mucocutaneous manifestations, occurring while on therapy with either azathioprine or cyclosporine for at least 3 months prior to study entry, were eligible. Participants were randomly assigned (1:1) to receive IFX or ADA for 6 months. The primary study outcome was the time to response of manifestations over 6-month anti-TNF alpha agents' treatment.
Results: 42 patients underwent screening visits, of whom 40 were randomly assigned to the IFX group (n=22) or to the ADA group (n=18). All patients at the time of randomization had active mucocutaneous manifestations and a smaller proportion had concomitant vital organ involvement (ie, six and three patients with ocular and neurological involvement, respectively). A total of 14 (64%) responders in the IFX group and 17 (94%) in the ADA group were observed. Retention on treatment was 95% and 94% in the IFX and in the ADA group, respectively. Quality of life resulted to be significantly improved in both groups from baseline, as well as Behçet's Disease Current Activity Form assessment. We registered two adverse events (one serious) in the ADA group and three non-serious adverse events in the IFX group.
Discussion: The overall results of this study confirm the effectiveness of both IFX and ADA in achieving remission in patients with BS affected by mucocutaneous involvement.

Appendix 6: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to June 25, 2025>

1	Adalimumab/	7596
2	Etanercept/	6699
3	tocilizumab.mp.	7829
4	Abatacept/	3553
5	Infliximab/	12728
6	Rituximab/	20484
7	golimumab.mp.	1825
8	apremilast.mp.	1350
9	tofacitinib.mp.	3953
10	certolizumab.mp.	1767
11	Certolizumab Pegol/	785
12	secukinumab.mp.	2584
13	Abatacept/	3553
14	Ustekinumab/	2114
15	Natalizumab/	2089
16	vedolizumab.mp.	2438
17	brodalumab.mp.	675
18	guselkumab.mp.	925
19	anakinra.mp.	3062
20	Canakinumab.mp.	1246
21	sarilumab.mp.	429
22	baricitinib.mp.	1995
23	guselkumab.mp.	925
24	ixekizumab.mp.	1320
25	risankizumab.mp.	720
26	tildrakizumab.mp.	382
27	upadacitinib.mp.	1479
28	Janus Kinase Inhibitors/	2489
29	bimekizumab.mp.	355
30	deucravacitinib.mp.	252
31	Sphingosine 1 Phosphate Receptor Modulators/ or etrasimod.mp.	312
32	mirikizumab.mp.	144
33	spesolimab.mp.	164
34	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	73837
35	limit 34 to (english language and humans and yr="2023 -Current" and (guideline or practice guideline or "systematic review"))	530

Targeted Immune Modulators for Autoimmune Conditions

Goal(s):

- Promote use consistent with national clinical practice guidelines and medical evidence.
- Restrict use of targeted immune modulators to OHP-funded diagnoses in adults.
- Allow case-by-case review for members covered under the EPSDT program.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators for autoimmune conditions (both pharmacy and provider administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Targeted Immune Modulators FDA-Approved for Ankylosing Spondylitis, Juvenile Idiopathic Arthritis, Rheumatoid Arthritis, and Non-Radiographic Axial Spondyloarthritis

Generic Name (BRAND NAME)	Ankylosing Spondylitis (AS)	Juvenile Idiopathic Arthritis (JIA)	Rheumatoid Arthritis (RA)	Non-Radiographic Axial Spondyloarthritis (nr-axSpA)
Tier 1 (Preferred First-Line)				
Adalimumab (HUMIRA)	≥18 y	≥2 yo	≥18 yo	
Adalimumab-atto (AMJEVITA)	≥18 y	≥2 yo	≥18 yo	
Adalimumab-fkjp 50 mg/mL (non-branded NDCs)	≥18 y	≥2 yo	≥18 yo	
Adalimumab-ryvk (SIMLANDI)	≥18 y	≥2 yo	≥18 yo	
Etanercept (ENBREL)	≥18 yo	≥2 yo	≥18 yo	
Infliximab-axxq (AVSOLA)	≥18 yo		≥18 yo	
Tier 2 (Preferred Second-Line)				
Ixekizumab (TALTZ)	≥ 18 yo			≥18 yo
Tofacitinib (XELJANZ)	≥18 yo	≥2 yo	≥18 yo	
Tier 3 (Non-Preferred Third-Line)				
Abatacept (ORENCIA)		≥2 yo	≥18 yo	
Anakinra (KINERET)			≥18 yo	

Generic Name (BRAND NAME)	Ankylosing Spondylitis (AS)	Juvenile Idiopathic Arthritis (JIA)	Rheumatoid Arthritis (RA)	Non-Radiographic Axial Spondyloarthritis (nr-axSpA)
Baricitinib (OLUMIANT)			≥18 yo	
Bimekizumab (BIMZELX)	≥18 yo			≥18 yo
Canakinumab (ILARIS)		≥2 yo		
Certolizumab (CIMZIA)	≥18 yo	≥2 yo	≥18 yo	≥18 yo
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo	≥2 yo (SIMPONI ARIA)	≥18 yo	
Infliximab (REMICADE)	≥18 yo		≥18 yo	
Rituximab (RITUXAN)			≥18 yo	
Sarilumab (KEVZARA)			≥18 yo	
Secukinumab (COSENTYX)	≥18 yo			≥18 yo
Tocilizumab (ACTEMRA)		≥2 yo	≥18 yo	
Upadacitinib (RINVOQ)	≥18 yo	≥2 yo	≥18 yo	≥18 yo

Note: Biosimilar products are Tier 3 unless specifically mentioned

Table 2. Targeted Immune Modulators FDA-Approved for Plaque Psoriasis, Psoriatic Arthritis, and Hidradenitis Suppurativa

Generic Name (BRAND NAME)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Hidradenitis Suppurativa (HS)
Tier 1 (Preferred First-Line)			
Adalimumab (HUMIRA)	≥18 yo	≥18 yo	≥ 12 yo
Adalimumab-atto (AMJEVITA)	≥18 yo	≥18 yo	≥18 yo
Adalimumab-fkjp 50 mg/mL (non-branded NDCs)	≥18 yo	≥18 yo	
Adalimumab-ryvk (SIMLANDI)	≥18 yo	≥18 yo	≥18 yo
Etanercept (ENBREL)	≥4 yo	≥2 yo	
Infliximab-axxq (AVSOLA)	≥18 yo	≥18 yo	
Tier 2 (Preferred Second-Line)			
Ixekizumab (TALTZ)	≥6 yo	≥18 yo	
Tofacitinib (XELJANZ)		≥18 yo	
Tier 3 (Non-Preferred Third-Line)			
Abatacept (ORENCIA)		≥2 yo	
Apremilast (OTEZLA)	≥ 6 yo and weighing ≥ 20 kg	≥ 6 yo and weighing ≥ 20 kg	
Bimekizumab (BIMZELX)	≥18 yo	≥18 yo	≥18 yo
Brodalumab (SILIQ)	≥18 yo		
Certolizumab (CIMZIA)	≥18 yo	≥18 yo	
Deucravacitinib (SOTYKU)	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)		≥2 yo (SIMPONI ARIA) ≥18 yo (SIMPONI)	

Generic Name (BRAND NAME)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Hidradenitis Suppurativa (HS)
Guselkumab (TREMFYA)	≥18 yo	≥18 yo	
Infliximab (REMICADE)	≥18 yo	≥18 yo	
Risankizumab (SKYRIZI)	≥18 yo	≥18 yo	
Secukinumab (COSENTYX)	≥6 yo	≥2 yo	≥18 yo
Tildrakizumab (ILUMYA)	≥18 yo		
Upadacitinib (RINVOQ)		≥2 yo	
Ustekinumab (STELARA)	≥6 yo	≥6 yo	

Note: Biosimilar products are Tier 3 unless specifically mentioned

Table 3. Targeted Immune Modulators FDA-Approved for Crohn's Disease and Ulcerative Colitis

Generic Drug Name (BRAND NAME)	Crohn's Disease	Ulcerative Colitis
Tier 1 (Preferred First-Line)		
Adalimumab (HUMIRA)	≥6 yo	≥5 yo
Adalimumab-atto (AMJEVITA)	≥6 yo	≥18 yo
Adalimumab-fkjp 50 mg/mL (non-branded NDCs)	≥6 yo	≥18 yo
Adalimumab-ryvk (SIMLANDI)	≥6 yo	≥18 yo
Infliximab-axxq (AVSOLA)	≥6 yo	≥6 yo
Tier 2 (Preferred Second-Line)		
Tofacitinib (XELJANZ)		≥18 yo
Tier 3 (Non-Preferred Third-Line)		
Certolizumab (CIMZIA)	≥18 yo	
Etrasimod (VELSIPITY)		≥18 yo
Golimumab (SIMPONI and SIMPONI ARIA)		≥18 yo (SIMPONI)
Guselkumab (TREMFYA)	≥18 yo	≥18 yo
Infliximab (REMICADE)	≥6 yo	≥6 yo
Mirikizumab (OMVOH)	≥18 yo	≥18 yo
Risankizumab (SKYRIZI)	≥18 yo	≥18 yo
Ozanimod (ZEPOSIA)		≥18 yo
Upadacitinib (RINVOQ)	≥ 18 yo	≥18 yo
Ustekinumab (STELARA)	≥ 18 yo	≥18 yo
Vedolizumab (ENTYVIO)	≥18 yo	≥18 yo

Note: Biosimilar products are Tier 3 unless specifically mentioned

Table 4. Targeted Immune Modulators FDA-Approved for Other Indications not Listed in Table 1, 2 or 3

Generic Drug Name (BRAND NAME)	Other Indications
Adalimumab (HUMIRA) & biosimilars	• Uveitis (non-infectious) ≥2 yo
Abatacept (ORENCIA)	• Acute Graft Versus Host Disease (aGVHD) ≥ 2 yo
Anakinra (KINERET)	• DIRA • COVID ≥ 18 yo (hospitalized) • NOMID
Apremilast (OTEZLA)	• Oral Ulcers associated with Behcet's Disease ≥ 18 yo
Baricitinib (OLUMIANT)	• COVID ≥ 18 yo (hospitalized)
Canakinumab (ILARIS)	• FCAS ≥4 yo • FMF ≥ 4 yo • Gout flares unresponsive to NSAIDs and colchicine ≥18 yo • HIDS ≥ 4 yo • MKD ≥ 4 yo • MWS ≥ 4 yo • Stills Disease ≥ 2 yo • TRAPS ≥ 4 yo
Rituximab (RITUXAN) and biosimilars	• BL ≥ 6 mo • BLL ≥ 6 mo • B-AL ≥ 6 mo • CLL ≥ 18 yo • DLBCL ≥ 6 mo • GPA ≥ 2yo • MPA ≥ 2 yo • NHL ≥18 yo • Pemphigus Vulgaris ≥ 18 yo (RITUXAN only)
Sarilumab (KEVZARA)	• Polymyalgia Rheumatica (PMR) ≥ 18 yo
Secukinumab (COSENTYX)	• Enthesitis-Related Arthritis (ERA) ≥ 4 yo
Spesolimab (Spevigo)	• Generalized Pustular Psoriasis Flares >12 yo and weighing >40 kg • Generalized Pustular Psoriasis after Flares >12 yo and weighing >40 kg
Tocilizumab (ACTEMRA)	• CRS ≥2 yo • COVID ≥ 18 yo (hospitalized) • GCA ≥18 yo • SSc-ILD ≥ 18 yo
Upadacitinib (RINVOQ)	• Atopic Dermatitis ≥ 12 yo

Abbreviations: BL = Burkitt Lymphoma; BLL = Burkitt-like Lymphoma; B-AL = mature B-cell acute leukemia; CLL = Chronic Lymphocytic Leukemia; COVID = Covid-19 infection; CRS = Cytokine Release Syndrome; DIRA = Deficiency of Interleukin-1 Receptor Antagonist; DLBCL = Diffuse Large B-Cell Lymphoma; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase Deficiency; mo = months old; MPA = Microscopic Polyangiitis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic

Generic Drug Name (BRAND NAME)	Other Indications
Inflammatory Disease; NSAIDs = non-steroidal anti-inflammatory drugs; SSc-ILD = Systemic Sclerosis-Associated Interstitial Lung Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old	

Table 5. First-Line Conventional Therapy Recommended for Select Conditions

Conditions	Recommended Conventional Therapy Prior To a Targeted Immune Modulator
Arthritis (Juvenile Idiopathic, Psoriatic, Rheumatoid)	• DMARD therapy: Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; AND • Concurrent DMARD therapy with plans to continue concomitant use. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.
Ankylosing Spondyloarthritis	• At least 2 NSAIDs over 4 weeks • Patients with predominant peripheral manifestations should try sulfasalazine or one glucocorticoid injection, if appropriate.
Atopic Dermatitis	• Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide), in combination with a topical calcineurin inhibitor (e.g., tacrolimus) for at least 4 weeks OR • Oral immunomodulator therapy (e.g., cyclosporine, methotrexate, or azathioprine) for at least 8 weeks
Crohn's Disease	• Mercaptopurine, methotrexate, or azathioprine for ≥6 months
Generalized Pustular Psoriasis	• Acitretin, methotrexate, or cyclosporine for ≥ 3 months
Hidradenitis Suppurativa (HS)	• 90-day trial of conventional HS therapy (e.g. oral antibiotics)
Plaque Psoriasis	• Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%) for a minimum of 4 weeks; AND • At least one other topical agent: calcipotriene, tazarotene, anthralin for a minimum of 8 weeks; AND • Phototherapy for at least 8 weeks; AND • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate for at least 16 weeks
Ulcerative Colitis	• 5-aminosalicylate products, mercaptopurine, or azathioprine for ≥6 months
Abbreviations: DMARD = Disease Modifying Anti-Rheumatic Drug; NSAID = non-steroidal anti-inflammatory drug	

Table 6. FDA-recommended Baseline Safety Tests for Sphingosine 1-Phosphate Receptor Modulators

	Negative Pregnancy Test	LFTs	CBC with lymphocyte count	Ophthalmic Exam	Baseline ECG (see notes)	Skin Exam for Malignancy	Varicella Zoster Antibodies
Etrasimod (VELSIPITY)	X	X	X	X	X	X	X
Ozanimod (ZEPOSIA)	X	X	X	X	X		X
Abbreviations: CBC=complete blood count; ECG=electrocardiogram; FDA =Food and Drug Administration; LFTs = liver function tests							

Sphingosine 1-Phosphate Receptor Modulators Clinical Notes:

- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with risk factors for bradycardia (h/o MI, age >70 yrs., electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on etrasimod or ozanimod with caution. A cardiology evaluation should be performed before considering treatment in patients with significant QT prolongation, heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension, a history of with second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sinoatrial heart block.
- An ophthalmology evaluation should be repeated 3-4 months after etrasimod or ozanimod initiation with subsequent evaluations based on clinical symptoms.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP? Notes: A. Mild-to-moderate psoriasis, plaque psoriasis, and atopic dermatitis are unfunded, severe forms are funded. B. Mild Hidradenitis Suppurativa (HS) is unfunded, moderate-to-severe HS (e.g., Hurley Stage II or III) is funded. C. Alopecia areata is unfunded. Psoriasis and atopic dermatitis are severe in nature when resulting in functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's DLQI ≥ 13 (or severe score on other validated tool) AND one or more of the following: • At least 10% body surface area involvement; OR • Hand, foot, face, or mucous membrane involvement?	**Yes:** Go to # 4	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP. If eligible for EPSDT review: Go to #3.
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny, medical necessity.
4. Is the request for a drug FDA-approved for this condition and age as defined in Table 1,2,3 or 4 above?	**Yes:** Go to #6	**No:** Go to #5

Approval Criteria		
5. Is there documentation of 1) inadequate response, contraindication or intolerance to FDA-approved targeted immune modulators AND 2) prescribing by, or in consultation with, a relevant specialist for the condition?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment? *(Note: this requirement does not apply to requests for apremilast.)	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. If patient meets all other criteria, may approve once for up to 3 months to allow time for screening for ongoing therapy to avoid interruptions in care.
7. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #8
8. Is there documentation of one of the following: • Treatment failure or inadequate response to conventional treatment in outlined Table 5 OR • contraindication or intolerance to first-line conventional treatments outlined in Table 5 OR • request is for a condition not outlined in Table 5?	**Yes:** Go to #9 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No**: Pass to RPh. Deny; medical appropriateness
9. Is the request for 1) a preferred Tier 1 product in Table 1, 2 or 3 OR 2) a preferred Tier 2 product if there is no Tier 1 product listed for the indication?	**Yes:** Go to #11	**No:** Go to #10

Approval Criteria		
10. Is there documentation that therapy with an agent from each of the preferred tiers would be inappropriate? Note: documentation could include inadequate response after ≥3 months with at least one product from each preferred tier, contraindication or intolerance to products from each preferred tier, or lack of products FDA-approved for the requested indication in tiers. Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Go to #11	**No**: Pass to RPh. Deny; medical appropriateness. Require trial of at least one product from each tier.
11. Is the request for upadacitinib for severe atopic dermatitis?	**Yes:** Go to #12	**No:** Go to #13
12. Has the provider submitted baseline assessment for the severity of atopic dermatitis: Eczema Area and Severity Index score (EASI 50) OR Dermatology Life Quality Index (DLQI) OR Investigators Global Assessment (IGA) score?	**Yes:** Document date of baseline assessment and results here_____ Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the request for a JAK inhibitor (e.g., tofacitinib, baricitinib, or upadacitinib)?	**Yes:** Go to #14	**No:** Go to #15

Approval Criteria		
14. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus OR cyclosporine? Note: Tofacitinib, baricitinib, and upadacitinib may be used concurrently with methotrexate or other nonbiologic DMARD drugs. Tofacitinib, baricitinib, or upadacitinib are not recommended to be used in combination with other JAK inhibitors, biologic DMARDs, azathioprine, or cyclosporine.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve baricitinib or upadacitinib for up to 6 months. Approve tofacitinib for up to 6 months at a maximum dose of 10 or 11 mg daily for Rheumatoid Arthritis OR 10 mg twice daily for 8 weeks then 5 or 10 mg twice daily for Ulcerative Colitis
15. Is the prescription for a sphingosine 1-phosphate receptor modulator (etrasimod or ozanimod)?	**Yes:** Go to #16	**No:** Go to #19
16. Have baseline safety assessments been completed as outlined in **Table 6**?	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness.
17. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on an anti-arrhythmic, beta-blocker, or calcium channel blocker?	**Yes:** Go to #18	**No:** Go to #19
18. Has the patient had a cardiology consultation before initiation (see clinical notes attached to **Table 6**)?	**Yes:** Go to #19	**No:** Pass to RPh. Deny; medical appropriateness.
19. Duration of initial approval based on indication	AS, Plaque psoriasis, RA, AD: 6 months HS: 12 weeks UC/Crohn's: 12 months Other: length of treatment or 1 year, whichever is longer	

Renewal Criteria		
1. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with upadacitinib therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started, OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started, OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request for continuation of adalimumab or secukinumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to #4	**No:** Go to #5
4. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: • a reduction of 25% or more in the total abscess and inflammatory nodule count, AND • no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for continuation of spesolimab to prevent flares of Generalized Pustular Psoriasis (GPP)?	**Yes:** Go to #6	**No:** Go to #8
6. Has the severity of GPP been maintained (not worsened) as assessed by: • the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) OR • a reduction in frequency and number of GPP flares?	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
~~6.~~7. Has the patient been adherent to both biologic and DMARD therapy (if DMARD therapy has been prescribed in conjunction with the biologic therapy)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
~~7.~~8. Is the request to renew therapy for Ankylosing Spondylitis?	**Yes:** Go to #9	**No:** Go to #10
9. Has the patient's condition improved as assessed by: • A reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units AND • A reduction in the spinal visual activity score (VAS) by 2 cm or more	**Yes:** Approve for 12 months	**No:** Pass to RPh; Deny; medical appropriateness
~~8.~~10. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement?	**Yes:** Approve for 12 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 10/25 (DM); 8/24; 6/23; 10/22; 6/2; 10/21; 10/20; 2/20; 5/19; 1/19; 1/18; 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12
Implementation: TBD; 1/1/25; 9/1/24; 7/1/23; 1/1/23; 7/1/22; 1/1/22; 1/1/2021; 7/1/2019; 3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 12/12