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Drug Class Update with New Drug Evaluations: Biologics for Autoimmune Conditions

Date of Review: February 2020

Generic Names: upadacitinib
risankizumab-rzaa

Date of Last Review: January 2019
Dates of Literature Search: 09/01/2018 – 10/23/2019
Brand Name (Manufacturer): Rinvoq™ (AbbVie, Inc.)
Skyrizi™ (AbbVie, Inc.)

Dossiers Received: yes

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

Purpose for Class Update: New comparative evidence for existing biologics for autoimmune conditions will be reviewed. In addition, safety and efficacy for two new biologic response modifiers recently approved by the United States (U.S.) Food and Drug Administration (FDA) will be evaluated. Oral upadacitinib is approved for treatment of adult patients with moderate-to-severe rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate (MTX). Risankizumab-rzaa is approved for subcutaneous administration in the treatment of adults with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy.

Research Questions:
1. Is there new comparative evidence that biologic response modifiers differ in effectiveness for alleviating symptoms and stabilizing disease in patients with RA, juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), or PsO?
2. Is there new comparative evidence that biologic response modifiers differ in harms?
3. Are there specific subpopulations for which one agent is better tolerated or more effective than other available agents?
4. Is upadacitinib safer or more effective then currently available agents for the treatment of adult patients with moderate-to-severe RA?
5. Is risankizumab-rzaa safer or more effective than currently available agents for the treatment of moderate-to-severe PsO?

Conclusions:
CLASS UPDATE
- The Health Evidence Review Commission (HERC) restructured the Prioritized List of Health Services in 2019. Consequently, moderate-to-severe Hidradenitis Suppurativa (HS) is now funded on line 419, effective January 2020.[1] Per Guideline Note 198, initial treatment of moderate-to-severe HS with adalimumab is limited to adults whose disease has not responded to at least a 90-day trial of conventional therapy (e.g., oral antibiotics), unless such a trial is not tolerated or contraindicated.[2]

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- Three new high quality systematic reviews evaluating safety and efficacy of specific biologic agents in CD and RA have been published since the last class update.[3-5]
- A Cochrane review evaluated the efficacy and safety of certolizumab pegol for the induction of remission in CD.[3] Moderate quality evidence showed certolizumab pegol was superior to placebo for achieving clinical remission [Relative Risk (RR) 1.36, 95% Confidence Interval (CI) 1.11 to 1.66] and clinical response at week 8 (RR 1.29, 95% CI 1.09 to 1.53).[3] Serious adverse events included worsening Crohn's disease, infections, and malignancy. Moderate quality evidence revealed serious adverse events occurred in 8.7% and 6.2% of participants in the certolizumab pegol and the placebo groups, respectively, but the difference was not statistically significant (RR 1.35, 95% CI 0.93 to 1.97).[3]
- A high quality systematic review and meta-analysis evaluated infection risk associated with Janus kinase (JAK) inhibitors administered in RA patients.[4] Estimated risk ratios of serious infections compared with placebo were not statistically significant: 1.22 (95% CI 0.60 to 2.45) for tofacitinib, 0.80 (95% CI 0.46 to 1.38) for baricitinib, and 1.14 (95% CI 0.24 to 5.43) for upadacitinib.[4] The estimated risk ratios of herpes zoster compared with placebo were 1.38 (95% CI 0.66 to 2.88) for tofacitinib, 2.86 (95% CI 1.26 to 6.50) for baricitinib and 0.78 (95% CI 0.19 to 3.22) for upadacitinib.[4] These data indicate a statistically significant difference in the risk of herpes zoster with baricitinib compared with placebo that is not seen with tofacitinib or upadacitinib.[4] Absolute values were not reported.
- A high quality systematic review and meta-analysis evaluated the impact of JAK inhibitors on risk of cardiovascular events (CVEs) in patients with RA.[5] No significant difference was observed regarding all CVE risks following JAK inhibitor administration ranging from 12 to 24 weeks [Odds Ratio (OR) 1.04, (95% CI 0.61 to 1.76), P=0.89].[5] There was no significant difference in incidence of major adverse cardiovascular events (MACEs); [OR 0.80 (95 % CI 0.36 to 1.75), P=0.57] or venous thromboembolism events (VTEs); [OR 1.16, (95 % CI 0.48 to 2.81), p = 0.74] with JAK inhibitor treatment.[5] Dose-dependent impact of JAK inhibitors on the risks of all CVEs, MACEs and VTEs was not observed with tofacitinib (5 mg vs.. 10 mg) or upadacitinib (15 mg vs.. 30 mg), whereas baricitinib 2 mg was found to be safer than 4 mg in all CVE incidence [OR 0.19 (95% CI 0.04 to 0.88), p = 0.03].[5] In summary, the existing evidence from randomized clinical trials (RCTs) could not identify significant short-term cardiovascular risk for JAK inhibitor-treated RA patients.[5] However, post-marketing data are needed to ascertain the cardiovascular safety of JAK inhibitors because of increased risk of VTE found for baricitinib at the higher 4 mg dose.[5]
- New comparative studies for selected biologics are summarized in **Table 4**, and trial abstracts are presented in **Appendix 3**.
- In the past year, the National Institute for Health and Care Excellence (NICE) developed guidance documents for tildrakizumab certolizumab pegol and risankizumab.[6-8] Tildrakizumab, certolizumab pegol or risankizumab are recommended as options for treatment of PsO in adults if PsO is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10; and PsO has not responded to other systemic treatments, including cyclosporine, MTX and phototherapy, or these options are contraindicated or not tolerated.[6-8]
- The American Academy of Dermatology-National Psoriasis Foundation (AAD-NPF) guidelines for the management and treatment of psoriasis with biologics were published April 2019.[9] High quality evidence supports the use of etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, guselkumab, or tildrakizumab at FDA-approved dosing, as monotherapy treatment options in adult patients with moderate-to-severe PsO.[9]
- Expanded indications were FDA-approved for the following medications:
    - ustekinumab for treatment of moderately to severely active ulcerative colitis
    - rituximab for treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in children 2 years of age and older in combination with glucocorticoids
    - certolizumab pegol for treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation
    - apremilast for treatment of oral ulcers associated with Behcet's Disease
    - ixekizumab for treatment of adults with AS

- tildrakizumab for use in moderate-to-severe PsO for adults
- belimumab for use in patients aged 5 years and older with active, autoantibody-positive, Systemic Lupus Erythematosus (SLE) who are receiving standard therapy.

UPADACITINIB

- Four phase 3 studies were submitted to the FDA for approval of upadacitinib.[10] Upadacitinib was compared to placebo, MTX, and adalimumab administered over 12 to 14 weeks.
- The SELECT-NEXT trial evaluated the efficacy and safety of upadacitinib compared to placebo over 12 weeks in 661 RA patients who had inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).[11] Moderate quality evidence showed more patients in the upadacitinib 15 mg (64%) and 30 mg (66%) treatment groups met the co-primary endpoint of 20% response on the American College of Rheumatology assessment (ACR20) at week 12 compared with 36% in the placebo group [15 mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, Number Needed to Treat (NNT)=4; 30 mg vs. placebo difference=31%, (95% CI 22 to 30), P<0.0001, NNT=4].[11] Moderate quality evidence showed similar results with the co-primary endpoint of Disease Activity Score/C-Reactive Protein (DAS28-CRP) less than or equal to 3.2 at week 12 in the patients receiving upadacitinib 15 mg (48%) and 30 mg (48%) compared with 17% of patients in the placebo group [15 mg vs. placebo difference=29%, (95% CI 19 to 38), P<0.0001, NNT=4; 30mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, NNT=4].[11]
- The SELECT-BEYOND trial used a similar study design to evaluate upadacitinib in 499 RA patients who had inadequate response to at least one biologic disease modifying antirheumatic drugs (bDMARD).[12] Moderate quality evidence showed more patients in the upadacitinib 15 mg (65%) and 30 mg (56%) treatment groups met the co-primary endpoint of ACR20 at week 12 compared with 28% in the placebo group [15 mg vs. placebo difference=37%, (95% CI 26 to 46), P<0.0001, NNT=3; 30 mg vs. placebo difference=28%, (95% CI 18 to 38), P<0.0001, NNT=4].[12] Significantly more patients met the co-primary endpoint of DAS28-CRP less than or equal to 3.2 at week 12 in the upadacitinib 15 mg (43%) and 30 mg (42%) groups compared with 14% in the placebo group [15 mg vs. placebo difference=29%, (95% CI 20 to 30), P<0.0001, NNT=4; 30 mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, NNT=4, moderate quality evidence).[12]
- The SELECT-COMPARE trial evaluated the efficacy and safety of upadacitinib compared to placebo and adalimumab in 1,629 patients with active RA on stable doses of MTX but with inadequate response to MTX.[13] Moderate quality evidence showed more patients in the upadacitinib 15 mg (71%) treatment group met the co-primary endpoint of ACR20 at week 12 compared with 36% in the placebo group [15 mg vs. placebo difference=34%, (95% CI 29 to 39), P≤0.001, NNT=3).[13] More patients met the co-primary endpoint of DAS28-CRP less than 2.6 at week 12 in the upadacitinib 15 mg group (29%) compared with 6% in the placebo group [15 mg vs. placebo difference=23%, (95% CI 19 to 27), P≤0.001, NNT =5; moderate quality evidence].[13] A DAS score of 2.6 is considered to correspond to remission. Moderate quality evidence demonstrated more patients receiving upadacitinib achieved ACR20 (79%) and DAS28-CRP less than 2.6 (29%) compared with 63% of patients who achieved ACR 20 with adalimumab and 11% who achieved DAS28-CRP less than 2.6 with adalimumab [ACR 20 upadacitinib vs. adalimumab difference=8%, (95% CI 1.2 to 13.8), P≤0.05, NNT=13 and DAS28-CRP upadacitinib vs. adalimumab difference=11%, (95% CI 5 to 16), P≤0.001, NNT=10).[13]
- The SELECT-MONOTHERAPY trial evaluated the efficacy and safety of switching to upadacitinib monotherapy compared with continuing MTX in 648 patients with an inadequate response to MTX.[14] Eligible patients must have shown active disease despite treatment with MTX, defined as at least six swollen joints out of 66, at least six tender joints out of 68, and more than 3 mg/L C-reactive protein (upper limit of normal 2.87 mg/L).[14] Patients were randomly assigned in a 1:1:1 ratio to receive upadacitinib 15 mg, upadacitinib 30 mg, or stabilized dose of MTX for 14 weeks. Based on moderate quality evidence, both upadacitinib groups had more responders at week 14 for the ACR20 response [15 mg (68%) and 30 mg (71%)] compared with the MTX group [15 mg vs. MTX difference=27%, (95% CI 18 to 36), P<0.0001, NNT=4; 30 mg vs. MTX difference=30% (95% CI 21 to 30), p<0.0001, NNT=4].[14] For the co-primary endpoint of DAS28-CRP less than or equal to 3.2, similar results were observed [15 mg (45%) and 30 mg (53%)] compared to the MTX

cohort (19%) [15 mg vs. MTX difference=26%, (95% CI 16 to 33); P<0.001, NNT=4; 30mg vs. MTX difference=33%, (95% CI 25 to 42), P<0.001, NNT=3 moderate quality evidence).[14]

- Reported safety data from these Phase 3 trials demonstrated that patients treated with upadacitinib 15 mg experienced a 1% or greater frequency of adverse events compared to placebo, including upper respiratory infection, nausea, cough, and pyrexia [15] Patients treated with upadacitinib 30 mg experienced a higher percentage of adverse effects that led to study drug discontinuation compared to either the upadacitinib 15 mg or placebo groups.[10] The most common adverse effect leading to discontinuation of upadacitinib was pneumonia (15 mg: 0.5 events/100 patient years, 30 mg 0.9 event/100 patient years).[10] Upadacitinib prescribing information contains FDA Black Boxed warnings for serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections.[15] Other FDA Black Boxed warnings include risk of lymphoma and thrombosis associated with JAK inhibitor administration.[15]
- There is insufficient evidence to determine differences in long-term efficacy, long-term safety, remission rates, health-related quality of life, or functional improvement with upadacitinib compared to other treatments for moderate to severe RA.

RISANKIZUMAB

- The efficacy and safety of risankizumab in patients with moderate-to-severe plaque PsO was evaluated in 2 similar double-blind, randomized, placebo-controlled and ustekinumab-controlled phase 3 trials (UltIMMa-1 and UltIMMa-2).[16] The primary objective of the 2 studies was to demonstrate superiority of risankizumab over placebo and ustekinumab. In a third phase 3 study, the IMMVent trial, risankizumab was compared with adalimumab in patients with moderate-to-severe PsO.[17]
- In both the UltIMMa-1 and UltIMMa-2 trials, more risankizumab-treated patients, compared with those receiving placebo or ustekinumab, achieved the co-primary endpoints of 90% improvement in the PASI-90 and achievement of 0 or 1 (clear or almost clear) on the static Physician's Global Assessment (sPGA scale) at week 16. Moderate quality evidence showed at week 16 in the UltIMMa-1 trial, PASI-90 was achieved by 75.3% risankizumab-treated patients compared with 4.9% placebo-treated patients and 42% ustekinumab-treated patients [risankizumab vs. placebo difference=70%, (95% CI 64 to 76), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=33%, (95% CI 22 to 44), p<0.0001, NNT=3].[16] In UltIMMa-2, 74.8% risankizumab-treated patients, compared with 2% placebo-treated patients and 47.5% ustekinumab-treated patients, achieved PASI-90 [risankizumab vs. placebo difference=72%, (95% CI 66 to 78), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=27%, (95% CI 16 to 38), p<0.0001, NNT=4, moderate quality evidence].[16] In UltIMMA-1, moderate quality evidence showed sPGA 0 or 1 was achieved by 87.5% of patients receiving risankizumab versus 7.8% receiving placebo and 63% receiving ustekinumab [risankizumab vs. placebo difference=79%, (95% CI 73 to 86), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=25%, (95% CI 15 to 35), p<0.0001, NNT=4].[16] Similar results were observed in UltIMMA-2, as sPGA 0 or 1 at week 16 was observed in 83.7% of patients receiving risankizumab versus 5.1% receiving placebo and 61.6% receiving ustekinumab [risankizumab vs. placebo difference=78%%, (95% CI 72 to 84), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=22%, (95% CI 12 to 32), p<0.0001, NNT=5, moderate quality evidence].[16]
- In the IMMVent trial at week 16, PASI 90 was achieved in 72% patients given risankizumab and 47% of patients given adalimumab (adjusted absolute difference 24.9% [95% CI 17.5 to 32.4%; p<0.0001]), and sPGA scores of 0 or 1 were achieved in 84% of patients given risankizumab and 60% patients given adalimumab (adjusted absolute difference 23.3% [95% CI 16.6–30.1; p<0.0001, moderate quality evidence]).[17]
- Analyses of the reported safety data from Phase 3 trials demonstrates that risankizumab-treated subjects experienced a 1% or greater frequency of adverse events compared to placebo, including upper respiratory infections, headache, fatigue, injection site reactions and tinea infections.[18]
- There is insufficient evidence to determine differences in long-term efficacy, long-term safety, remission rates, health-related quality of life, or functional improvement with risankizumab compared to other treatments for moderate to severe PsO.

Recommendations:

- Modify prior authorization (PA) criteria to reflect revisions to the Oregon Health Authority (OHA) Prioritized List of Health Services. Effective January 2020, adalimumab is funded for treatment of moderate-to-severe Hidradenitis suppurativa (HS) per Guideline Note 198.
- Modify PA criteria to reflect updated indications and age ranges for specific biologic response modifiers as follows:
    - Ustekinumab for treatment of moderately to severely active ulcerative colitis
    - Rituximab for treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in children 2 years of age and older in combination with glucocorticoids
    - Upadacitinib for use in moderate-to-severe RA for adults
    - Certolizumab pegol for treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation
    - Apremilast for treatment of oral ulcers associated with Behcet's Disease
    - Ixekizumab for treatment of adults with AS
    - Tildrakizumab for use in moderate-to-severe PsO for adults
    - Belimumab for use in patients aged 5 years and older with active, autoantibody-positive, Systemic Lupus Erythematosus (SLE) who are receiving standard therapy
- No PDL changes recommended based on the clinical evidence. Maintain upadacitinib and risankizumab-rzaa as non-preferred drugs on the Oregon Health Plan Preferred Drug List (PDL).
- After executive session, secukinumab was designated as a preferred agent on the PDL.

Summary of Prior Reviews and Current Policy

The last comparative review of biologic drugs for autoimmune conditions was presented to the Pharmacy and Therapeutics (P and T) Committee at the January 2019 meeting. Two biologic response modifiers, tildrakizumab and baricitinib, were added to the PA criteria for biologic agents. The preferred biologic agents on the PDL, adalimumab and etanercept, have broad indications for use including AS, JIA, PsO, PsA, and RA. Adalimumab is also approved for management of inflammatory bowel diseases including CD and UC. All the other drugs in the biologic class are non-preferred based on evidence presented at previous P and T meetings and require PA as outlined in **Appendix 4**.

OHP FFS Utilization:

In the third quarter of 2019, there were approximately 157 pharmacy claims for biologic agents in the fee-for-service (FFS) population. Seventy-seven percent of the claims were for the preferred agents etanercept and adalimumab. For the non-preferred agents, 1-3% of all claims were for ixekizumab, anakinra, tocilizumab, and ustekinumab, and 4-6% of claims were for tofacitinib, certolizumab, secukinumab, and apremilast. There were no pharmacy claims for brodalumab, canakinumab, guselkumab, or baricitinib.

Background:

<u>Rheumatoid Arthritis</u>

Rheumatoid arthritis is characterized by chronic inflammation of synovial tissues and progressive erosion of bone leading to joint destruction and disability. Approximately 1% of the general population is affected worldwide, and although RA may occur at any age, the peak incidence of onset is usually between the 4th and 6th decades, with females being 2- to 3-times more likely affected than males.[19] The 2015 American College of Rheumatology [20] and 2016 European League against Rheumatism (EULAR) [21] recommendations suggest that treatment begin with csDMARDs such as MTX as soon as diagnosis of RA is established.

The optimal dose of MTX is 25 mg once a week.[22] Patients who cannot tolerate this MTX dose because of adverse effects may improve with a lower dose.[23] Other csDMARDs include sulfasalazine, hydroxychloroquine, and leflunomide.

Biologic DMARDs or targeted synthetic DMARDs (tsDMARDs) are recommended for patients with a suboptimal response or intolerance to csDMARDs. Biologic DMARDs are proteins that must be administered parentally. Targeted synthetic DMARDs are small chemical molecules that can be given orally. The Janus kinase (JAK) inhibitors (tofacitinib, baricitinib, and upadacitinib) are classified as tsDMARDs. Monotherapy with bDMARDs or tsDMARDs or combination therapy that includes MTX can be initiated as second-line therapy, depending on the patient's response to previous therapy and any pertinent comorbidities. Over the past decade, management of RA has shifted from controlling symptoms to preventing and controlling joint damage.[24] Additionally, with the availability of bDMARDs and tsDMARDs, a "treat-to-target" approach is now recommended, where the goals of treatment include remission or low disease activity and maintenance of remission.[20] These goals have been shown to lead to better outcomes such as prevention of progression of joint damage and improved quality of life.[24]

Janus kinase inhibitors are among the newest class of treatments for RA. The JAK family plays important roles in the signalling pathways of various cytokines, growth factors, and hormones involved in immunity and hematopoiesis.[25] JAK proteins (JAK1, JAK2, and JAK3 and tyrosine kinase 2 [TYK2]) are signal-transduction factors involved in the downstream signaling of cytokines to their receptors on the cell surface and are implicated in the pathogenesis of RA.[25] Three JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) have been approved by the FDA and each has a different inhibitory profile for the JAK proteins (see **Table 1**). Upadacitinib is a selective JAK1 inhibitor, which in theory should have less side effects than tofacitinib and baricitinib. JAK1 plays a major role in signaling of inflammatory mediators, such as IL-6 and interferon. JAK inhibitors are potent immunosuppressants, and there are a number of well-known safety issues associated with use of this class of medications, including serious infections, malignancy, lymphoproliferative disorders, gastrointestinal perforations, lymphopenia, neutropenia, anemia, and lipid elevations.[10] Based upon accumulating data regarding the risk of thrombosis with JAK inhibitors, thrombosis is now also considered a class safety issue with JAK inhibitors.[10] **Table 1** summarizes the different DMARDs FDA-approved for management of RA.

Table 1. FDA-Approved Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis Treatment[23]

Drug and Maintenance Dosing Recommendations	Molecular Target	Structure	Adverse Events
Conventional Synthetic DMARDs			
Methotrexate (10-25 mg once a week)	Dihydrofolate reductase	Small chemical molecule	Nausea, stomatitis, elevated LFTs, bone marrow suppression, teratogenicity
Sulfasalazine (Azulfidine®) (2-4 g once a day)	Folate		Cutaneous hypersensitivity, nausea, diarrhea, agranulocytosis, drug-induced lupus, azoospermia
Leflunomide (Arava®) (20mg once a day)	Pyrimidine		Diarrhea, hypertension, hypersensitivity, elevated LFTs, leukocytopenia, teratogenicity
Biologic DMARDs			
Etanercept (Enbrel®) (50 mg SC once a week)	TNF	Receptor antagonist	Infections, reactivation of TB, psoriasiform skin changes, exacerbation of demyelinating diseases, drug-induced lupus, non-melanoma skin cancer, injection site or infusion reactions
Infliximab (Remicade®) (3-10mg/kg IV every 6-8 weeks)		Chimeric monoclonal antibody	
Adalimumab (Humira®) (40 mg SC every 2 weeks)		Human monoclonal antibody	
Golimumab (Simponi®) (50 mg SC once a month or 2 mg/kg IV every 8 weeks)		Human monoclonal antibody	
Certolizumab pegol (Cimzia®) (200 mg SC every 2 weeks or 400mg every 4 weeks)		Humanized monoclonal antibody	
Tocilizumab (Actemra®) (162 mg SC every 1-2 weeks or 4-8 mg/kg IV every 4 weeks)	IL-6	Humanized monoclonal antibody	Infections, reactivation of TB, bowel perforation, hypersensitivity reactions, neutropenia, injection site reactions, hyperlipidemia
Sarilumab (Kevzara®) (150 mg-200 mg every 2 weeks)		Human monoclonal antibody	
Rituximab (Rituxan®) (1000 mg IV every 6 months)	B cell	Chimeric monoclonal antibody	Hypersensitivity reactions, reactivation of hepatitis B, leukocytopenia, progressive multifocal leukoencephalopathy, tumor lysis syndrome
Abatacept (Orencia®) (125 mg SC once a week or 750-1000 mg IV every 4 weeks)	T-lymphocyte	Receptor antagonist	Infections, reactivation of TB, leukocytopenia, injection site reactions
Anakinra (Kineret®) (100 mg SC once a day)	IL-1	Receptor antagonist	Infections, injection site pain
Targeted Synthetic DMARDs			
Tofacitinib (Xeljanz®) (10 mg once a day)	JAK 1,2,3	Small chemical molecule	Infections, reactivation of TB, herpes zoster, cytopenia, hyperlipidemia, CPK level increase
Baricitinib (Olumiant®) (2-4mg once a day)	JAK 1,2		
Upadacitinib (Rinvoq™) (15 mg once a day)	JAK 1		
Abbreviations: CPK = creatine phosphokinase; DMARD = Disease-Modifying Antirheumatic Drug; FDA = Food and Drug Administration; g = grams; IL = interleukin; IV = intravenous; JAK = Janus kinase; LFT = liver function tests; mg = milligrams; SC = subcutaneous; TB = tuberculosis; tumor necrosis factor = TNF			

Primary endpoints used in RA clinical trials include the ACR response, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the Disease Activity Score 28 (DAS-28). The ACR response score is a composite endpoint with 7 domains used to calculate the proportion of patients achieving a target percentage of improvement from baseline and is a considered a measure of efficacy and overall disease activity.[26] Patients are said to meet ACR 20 criteria when they have at least 20% reductions in tender joint counts, 20% reduction swollen joint counts and 20% improvement in at least 3 of the 5 remaining domains.[26] The additional 5 domains include patient global assessment of arthritis on a visual analog scale, physician global assessment of arthritis on a visual analog scale, patient assessment of pain on a visual analog scale, patient assessment of physical functioning (e.g., health assessment questionnaire), and acute phase reactant (ESR or CRP). ACR 50 and ACR 70 criteria are similar, but with improvement of at least 50% and 70% in ACR criteria.[26] ACR 50 and 70 are considered more clinically significant than ACR 20.[26] The HAQ-DI is a widely used self-reported measure of functional capacity. Scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[27] The minimal clinically important difference (MCID) of an improvement on the HAQ-DI is a change of at least 0.22 from baseline.[12] The DAS-28 is another index of disease activity (similar to the ACR response). The DAS is a continuous composite outcome that consists of: 1) the number of painful joints (Ritchie Articular Index, 0-78 joints), 44-joint count for swollen joints, erythrocyte sedimentation rate (ESR) and patient global assessment of disease activity or general health using a visual analogue scale.[11] A DAS-28 score greater than 5.1 corresponds to high disease activity and less than 3.2 of low disease activity. A DAS score of 2.6 is considered to correspond to remission.[28]

Plaque Psoriasis

Psoriasis is a chronic, immune-mediated inflammatory disorder of the skin and/or joints that affects about 2 to 3% of the population.[29] Two peaks in age of onset have been reported: one at 20 to 30 years of age and a second peak at 50 to 60 years.[29] Plaque psoriasis accounts for about 80% to 90% of all patients with psoriasis.[30] 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. Mild PsO is not a funded condition per the Health Evidence Review Commission (HERC) Guideline Note 57.[31] Per NICE guidance, first-line agents for PsO include: topical medications including corticosteroids, vitamin D analogs (e.g., calcipotriene) , retinoids (e.g., tazarotene) or calcineurin inhibitors (e.g., tacrolimus or pimecrolimus).[32] Phototherapy is an option for patients with moderate-to-severe PsO who have not responded to topical therapy. Systemic non-biologic treatments are recommended for patients with moderate-to-severe PsO unresponsive to topical or phototherapy and include MTX, cyclosporine, or acitretin. Biologics may be added for patients with moderate-to-severe PsO not controlled by other therapies. Injectable biologic agents used to treat PsO include adalimumab, brodalumab, certolizumab, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab. An oral phosphodiesterase 4 (PD4) inhibitor, apremilast, is also approved for treatment of moderate-to-severe PSO. All the systemic products may have one or more serious adverse reactions, including malignancy, serious infections, teratogenicity, depression, nephrotoxicity, hepatotoxicity, and bone marrow suppression.[29] The various DMARDs FDA-approved to treat PsO are compared in **Table 2.**

Table 2. FDA approved Disease-Modifying Antirheumatic Drugs for Plaque Psoriasis[29]

Drug	Molecular Target	Approved Age Range for PsO	Maintenance Dosing	Warnings
Adalimumab (Humira®)	TNF	Adults	40 mg SC every other week	Serious Infections*, Malignancies including Lymphoma
Etanercept (Enbrel®)		Patients ≥ 4 years of age	50 mg SC once weekly (<63 kg, 0.8 mg/kg SC once weekly)	Serious Infections*, Malignancies including Lymphoma
Infliximab (Remicade®)		Adults	5 mg/kg IV every 8 weeks	Serious Infections*, Malignancies including Lymphoma
Certolizumab Pegol (Cimzia®)		Adults	400 mg SC every other week	Serious Infections*, Malignancies including Lymphoma
Ustekinumab (Stelara®)	IL-12 and IL-23	Patients ≥ 12 years of age	≤100 kg, 45 mg SC every 12 weeks >100 kg, 90 mg SC every 12 weeks	Serious Infections*, Malignancies including Lymphoma
Secukinumab (Cosentyx®)	IL-17	Adults	300 mg SC every 4 weeks	Crohn's Disease
Ixekizumab (Taltz®)			80 mg SC every 4 weeks	Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis)
Brodalumab (Siliq™)			210 mg SC every 2 weeks	Suicide Ideation, REMS Program, Serious Infections*, Crohn's Disease
Guselkumab (Tremfya®)	IL-23	Adults	100 mg SC every 8 weeks	Upper respiratory infections, tinea infections, and herpes simplex infections
Tildrakizumab (Ilumya™)			100 mg SC every 12 weeks	
Risankizumab-rzaa (Skyrizi™)			150 mg SC every 12 weeks	
Apremilast (Otezla®)	PDE-4	Adults	30 mg orally twice daily	Worsening depression

Abbreviations: IL=interleukin; IV=intravenous; PASI=Psoriasis Area and Severity Index; PDE=phosphodiesterase; SC = subcutaneous; TNF= tumor necrosis factor
*Serious Infections include: bacterial sepsis, tuberculosis, invasive fungal and opportunistic infections

Several tools have been developed to evaluate symptom improvement and quality of life in patients with psoriasis. 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.[33] 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.[33,34] It does not take into account 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.[33] 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.[34] 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.[35] The sPGA is another physician-reported symptom severity scale which evaluates symptom severity at a single point in time with higher scores indicating more severe disease (range 0 to 5).Responders to therapy are typically defined as patients with a sPGA score of 0 or 1, corresponding to clear or almost clear skin or patients with an improvement of at least 2 points. In clinical trials of patients with moderate to severe disease, the proportion of patients with a sPGA score of 0 or 1 has a strong correlation with a 75% improvement in PASI.[35] Finally, the PSI evaluates patient-reported rather than physician-assessed symptoms. Eight individual symptoms in the prior 24 hours are assessed including itching, redness, scaling, burning, stinging, cracking, flaking and pain.[35] Individual symptoms are rated from 0 to 4 with total scores ranging from 0 to 32 points.[35] Patients with total scores of 8 or less with no single item rated greater than 1 are generally considered responders to therapy.

Hidradenitis Suppurativa

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.[36,37] The mean age of onset is 22 years. It is characterized by inflamed nodules which occur most frequently in the axillary, inguinal, and anogenital regions of the body.[36,37] These nodules are painful, recurrent, and can result in abscesses, chronic draining sinus tracts, scarring, disfigurement, and disability. Genetic predisposition, hormonal factors, immune factors, medications such as lithium and medroxyprogesterone acetate, obesity, and smoking all are potential contributors to the etiology.[37]

There are multiple staging systems that evaluate symptoms and severity of HS. 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.[38] About 69% of patients have stage 1 disease, while approximately 28% and 4% of patients have more severe stage 2 and 3 disease.[38] The minimum clinically significant change in Hurley staging is unclear.[39]

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.[37] Surgical treatment may also be an option for Hurley stage 2 and 3 patients.[37] Pharmacological treatments for HS include antibiotics, retinoids, corticosteroids, and immunosuppressive agents such as tumor necrosis factor (TNF)-alpha inhibitors.[37,38] However, the most commonly used treatments are topical and oral antibiotics.[40] Antibiotics can be used both for the acute treatment of an infected area as well as for maintenance treatment.[36,37,41] The most commonly used oral antibiotic treatments are tetracyclines.[40]

TNF-alpha inhibitors are often reserved for patients with moderate to severe HS (e.g. Hurley Stage II or Hurley Stage III).[37,38] Guidance from NICE recommends the use of adalimumab for active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.[40] Continuation of therapy beyond 12 weeks is recommended only if there is a reduction of 25% or more in the total abscess and inflammatory nodule count as well as no increase in abscesses or draining fistulas at that time.[40] Adalimumab was approved for moderate to severe HS in September 2015 and is the only medication FDA-approved for this condition.[42] In October 2018, the indication was expanded to include patients age 12 years and older, with varied dosing based on weight.[42]

A review of the safety and efficacy of adalimumab in treating HS was presented to the P and T committee at the November 2018 meeting. At that time, medical therapy for HS was not funded by the OHA. However, in 2019 the HERC restructured the Prioritized List of Health Services. Moderate-to-severe HS is now funded on line 419, effective January 2020.[1] Mild HS is included on Line 514 and remains unfunded.[2] Per Guideline Note 198, initial treatment of moderate-to-severe HS with adalimumab is limited to adults whose disease has not responded to at least a 90-day trial of conventional therapy (e.g., oral antibiotics), unless such a trial

is not tolerated or contraindicated.[2] Treatment with adalimumab after 12 weeks is only included on Line 419 for patients with a clear evidence of response, defined as: a) a reduction of 25% or more in the total abscess and inflammatory nodule count, AND b) no increase in abscesses and draining fistulas.[2]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, 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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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.

Systematic Reviews:
After review, 6 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). [43-49]

Certolizumab pegol for induction of remission in Crohn's disease
A high quality Cochrane review published in August 2019 evaluated the efficacy and safety of certolizumab pegol for the induction of remission in CD.[3] The literature search was conducted through January 28, 2019. The main outcomes selected for analysis were clinical remission at week 8 (Crohn's Disease Activity Index [CDAI] P150), clinical response at week 8 (CDAI reduction Q 100 or clinical remission), and serious adverse events.[3] Four studies involving 1,485 participants with moderate- to-severe CD met the inclusion criteria and were used in the meta-analyses.[3] All 4 studies were randomized, double-blind, placebo-controlled multicenter trials sponsored by UCB Inc., the manufacturer of certolizumab pegol. One study was identified as high risk of bias due to a non-identical placebo while the other studies were judged to be at low risk of bias.[3]

Clinical remission at week 8 was achieved in 26.9% (225/835) of patients prescribed certolizumab pegol 100-400 mg every 2 to 4 weeks compared to 19.8% (129/650) in the placebo group, (RR 1.36, 95% CI 1.11 to 1.66; moderate certainty evidence).[3] Clinical response at week 8 was achieved in 40.2% (336/835) and 30.9% (201/650) of participants in the certolizumab pegol and the placebo groups, respectively (RR 1.29, 95% CI 1.09 to 1.53; moderate certainty evidence).[3] Serious adverse events were observed in 8.7% (73/835) and 6.2% (40/650) of participants in the certolizumab pegol and the placebo groups, respectively (RR 1.35, 95% CI 0.93 to 1.97; moderate certainty evidence).[3] Serious adverse events included worsening CD, infections, and malignancy.

In summary, moderate certainty of evidence suggests that certolizumab pegol is effective for induction of clinical remission and clinical response in people with moderate-to-severe CD. It is uncertain whether the risk of serious adverse events differs between certolizumab pegol and placebo as the 95% CI includes the possibility of a small decrease or doubling of events.[3]

Infection risk with JAK inhibitors

A high quality systematic review and meta-analysis of infection risk associated with JAK inhibitors in RA patients was published in April 2019.[4] Data from 21 trials were included in a meta-analysis of the risk for serious infection and herpes zoster associated with JAK inhibitor therapy. Eleven trials assessed tofacitinib (5,888 patients), 6 trials assessed baricitinib (3,520 patients), and 4 trials included upadacitinib (1,736 patients).[4] Assessment of study validity revealed few sources of bias.[4] All studies reported randomization and blinding of participants and clinical assessors.[4] Half of the trials did not describe methods of allocation concealment, and 3 studies did not account for incomplete outcome data.[4] The majority of the studies included patients with an inadequate response to DMARDs.[4] Six of the eleven tofacitinib trials and all of the baricitinib and upadacitinib trials recruited patients on background stable doses of MTX.[4] Patients were distributed globally.[4] Sixteen studies recruited patient from Asia, including three Japanese bridging studies.[4]

Estimates of serious infection incidence rates per 100 patient-years were 1.97 (95% CI 1.41 to 2.68) for tofacitinib, 3.16 (95% CI 2.07 to 4.63) for baricitinib, and 3.02 (95% CI 0.98 to 7.04) for upadacitinib.[4] In the pooled placebo group, estimates of incidence rates were 2.50 (95% CI 1.74 to 3.48) per 100 person-years, derived from 1.19 (95% CI 0.51 to 2.34) from the tofacitinib placebo group, 4.09 (95% CI 2.65 to 6.04) from baricitinib, and 1.75 (95% CI: 0.21 to 6.32) from upadacitinib.[4] The estimated incident risk ratios of serious infections compared with placebo in per protocol analyses were not statistically significant: 1.22 (95% CI 0.60 to 2.45) for tofacitinib, 0.80 (95% CI 0.46 to 1.38) for baricitinib and 1.14 (95% CI 0.24 to 5.43) for upadacitinib.[4]

The estimated incidence rates per 100 patient-years of herpes zoster were 2.51 (95% CI 1.87 to 3.30) for tofacitinib, 3.16 (95% CI 2.07 to 4.63) for baricitinib, and 2.41 (95% CI 0.66 to 6.18) for upadacitinib.[4] In the pooled placebo group, the incidence rate was 1.22 (95% CI 0.71 to 1.95) per 100 patient-years.[4] There were 8 serious or disseminated cases (4 with tofacitinib and 4 with baricitinib) versus 3 in the pooled placebo group.[4] Overall, these data indicate a statistically significant difference in the risk of herpes zoster with baricitinib compared with placebo (RR 2.86; 95% CI 1.26 to 6.50) that is not seen with tofacitinib (RR 1.38; 95% CI 0.66 to 2.88) or upadacitinib (RR 0.78; 95% CI 0.19 to 3.22).[4] While a statistically significant increase was not apparent with tofacitinib or upadacitinib, due to levels of uncertainty in the estimates, a true effect cannot be ruled out.[4] There are several considerations when interpreting these results. The increasing incidence of herpes zoster with age is well recognized.[4] It is a critical confounder and subtle differences in age distribution from these clinical trials could cause significant differences in herpes zoster events.[4] A geographic variation in rates of herpes zoster with JAK inhibitors exists, with highest rates seen in Japan and Korea.[4] This is relevant when examining data extrapolated from studies across different geographical regions.[4] A quarter of the studies in this meta-analysis did not recruit from countries in Asia, which may contribute to a lower overall incidence of herpes zoster.[4]

Cardiovascular event risk with JAK inhibitors

In August 2019, a high quality systematic review and meta-analysis evaluated the impact of JAK inhibitors on risk of cardiovascular events in patients with RA.[5] The literature search was conducted through October 2018. The primary outcome was the relationship between JAK inhibitors and all cardiovascular events.[5] The duration of therapy with JAK inhibitors ranged from 12 to 24 weeks. The secondary outcomes evaluated MACEs and VTEs, including pulmonary embolism (PE) and deep vein thrombosis (DVT).[5] Twenty-six RCTs (11,799 subjects) met inclusion criteria for the systematic review. No significant difference was observed regarding all CVEs risk following JAK inhibitor usage in general [OR 1.04 (95% CI 0.61 to 1.76), p = 0.89], tofacitinib [OR 0.63 (95% CI 0.26 to 1.54); p = 0.31], baricitinib [OR 1.21 (95% CI 0.51 to 2.83); p = 0.66], or upadacitinib [OR 3.29 (95% CI 0.59 to 18.44); p = 0.18].[5] Likewise, there was no significant difference for JAK inhibitor treatment overall regarding occurrence of MACEs [OR 0.80 (95 % CI 0.36 to 1.75); p = 0.57] or VTEs [OR 1.16 (95 % CI 0.48 to 2.81); p = 0.74].[5] Dose-dependent impact of JAK inhibitors on the risks of all CVEs, MACEs and VTEs were not observed with tofacitinib (5 mg vs. 10 mg) and upadacitinib (15 mg vs. 30 mg), whereas baricitinib 2 mg was found to be safer than 4 mg in all CVEs incidence [OR 0.19 (95% CI 0.04 to 0.88); p = 0.03].[5] In summary, evidence from RCTs indicate no significant short-term cardiovascular risk for JAK inhibitor-treated patients, but post-marketing data are needed to ascertain their long-term cardiovascular safety, especially at the higher doses, due to increased risk of VTE events for baricitinib at higher dosages.[5]

New Guidelines

NATIONAL INSTITUTE OF HEALTH AND CARE EXCELLENCE

The National Institute for Health and Care Excellence (NICE) has developed several guidance documents in the past year for recently marketed biologic agents approved to treat PsO. These guidelines are rated as high quality using the AGREE II Global Rating Scale. A systematic review process for new literature was performed and there was complete information to inform decision making. The recommendations are summarized below.

TILDRAKIZUMAB, CERTOLIZUMAB PEGOL, and RISANKIZUMAB

Guidance for treating moderate to severe PsO with tildrakizumab and certolizumab pegol was published in April 2019.[6,7] Guidance for treating moderate to severe PsO with risankizumab was published in August 2019.[8] Tildrakizumab, certolizumab pegol or risankizumab are recommended as options for treatment of PsO in adults if:

- PsO is severe, as defined by a total PASI of 10 or more and a DLQI of more than 10; and
- PsO has not responded to other systemic treatments, including cyclosporine, MTX and phototherapy, or these options are contraindicated or not tolerated.[6]
- Consider stopping tildrakizumab between 12 weeks and 28 weeks if there has not been at least a 50% reduction in the PASI score from when treatment started.[6]
- Stop tildrakizumab at 28 weeks if the PsO has not responded adequately. An adequate response is defined as:
  - 75% reduction in the PASI score from when treatment started; or
  - 50% reduction in the PASI score and a 5-point reduction in DLQI from when treatment started.[6]
- Lowest maintenance dosage of certolizumab pegol should be used (200 mg every 2 weeks) after the loading dose.[7]
- Stop certolizumab pegol at 16 weeks if PsO has not responded adequately. An adequate response is defined as:
  - 75% reduction in the PASI score from when treatment started or
  - 50% reduction in the PASI score and a 5-point reduction in DLQI from when treatment started.[7]
- Stop risankizumab treatment at 16 weeks if the PsO has not responded adequately. An adequate response is defined as:
  - 75% reduction in the PASI score from when treatment started or 50% reduction in the PASI score (PASI 50) and
  - 5-point reduction in DLQI from when treatment started.[8]
- If patients and their clinicians consider risankizumab to be one of a range of suitable treatments, including guselkumab, secukinumab and ixekizumab, the least expensive should be chosen (taking into account administration costs, dose, price per dose and commercial arrangements).[8]

AMERICAN ACADEMY OF DERMATOLOGY-NATIONAL PSORIASIS FOUNDATION

American Academy of Dermatology-National Psoriasis Foundation (AAD-NPF) guidelines for the management and treatment of psoriasis with biologics were published in April 2019.[9] A multidisciplinary work group of psoriasis experts consisting of dermatologists, a rheumatologist, a cardiologist, and representatives from a patient advocacy organization was convened to update the previously published 2008 AAD psoriasis guidelines.[9] The focus of the recommendations are for the use of biologic agents in the treatment of psoriasis in adults. In accordance with American Academy of Dermatology (AAD) policy, a minimum 51% of work group members did not have any relevant conflicts of interest.[9] If a potential conflict was noted, the work group members recused themselves from discussion and drafting of recommendations pertinent to the topic area of interest.[9] The efficacy and safety of etanercept, infliximab, adalimumab, certolizumab, ustekinumab, secukinumab, ixekizumab brodalumab, guselkumab, tildrakizumab, and risankizumab were evaluated as monotherapy or in combination with

other psoriasis therapies to treat moderate-to-severe psoriasis in adults.[9] A literature search was completed from January 1, 2008 through December 31, 2017 to guide development of the recommendations.

The Grade A recommendations, which are based on consistent and good-quality patient-oriented evidence, recommend etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, guselkumab, or tildrakizumab at FDA-approved dosing, as monotherapy treatment options in adult patients with moderate-to-severe PsO.[9]

Other recommendations to guide PsO treatment with biologics included:

- Certolizumab is likely to have class characteristics similar to those of other TNF-inhibitors (i.e., adalimumab, etanercept, and infliximab) regarding treatment combination, efficacy in difficult-to-treat areas, and possibly immunogenicity. However, there is no evidence available on these topics, and these statements are based on extrapolation of data from other TNF-inhibitors.[9]
- Recommendations to combine TNF inhibitors or ustekinumab with acitretin, MTX, apremilast, or cyclosporine to augment efficacy for the treatment of moderate-to-severe PsO is based on Grade B to C evidence (B=inconsistent or limited quality evidence; C = consensus or opinion based evidence). There is no evidence for systemic combination therapy with secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, or risankizumab.[9]
- Patients with a history of concomitant inflammatory bowel disease (IBD) might benefit from TNF-inhibitor therapy.[9] Adalimumab, infliximab, and certolizumab are approved for the treatment of IBD.[9]
- Patients with a history of concomitant multiple sclerosis or IBD might benefit from ustekinumab therapy.[9] Ustekinumab is FDA-approved for the treatment of Crohn's disease.
- Patients with a personal history of or active IBD might experience reactivation or worsening of their disease with administration of Il-17 inhibitors (i.e., secukinumab, ixekizumab, and brodalumab).[9] Although the number of patients presenting with this adverse effect in clinical trials was relatively small, it is recommended that the use of IL-17 inhibitors be avoided in patients with a personal history of or active IBD.[9]
- Rare cases of suicidal ideation and completed suicides have occurred with brodalumab treatment, resulting in a FDA Black Boxed warning.[9] Brodalumab should not be considered as a treatment option in patients with suicidal ideation, recent suicidal behavior, or history of suicidal ideation.[9]

New Formulations:

1. Ixifi™ (infliximab-qbtx) is biosimilar to Remicade® (infliximab) and received FDA approval December 2017. Ixifi™ is FDA-approved for all indications of Remicade® including: RA in combination with MTX, PsA, AS, CD, pediatric CD, UC, and PsO. As with infliximab, the biosimilar carries a Black Boxed warning for serious infection and malignancy risk. A second Remicade® biosimilar manufactured by Amgen, Avsola™ (infliximab-axxq) also received FDA approval December 2017.

2. Eticovo™ (etanercept-ykro) is biosimilar to Enbrel® (etanercept). The biosimilar received FDA approval April 2019 for treatment of RA, JIA in patients aged 2 years and older, PsA, AS, and PsO in patients 4 years and older. As with etanercept, the biosimilar carries a Black Boxed warning for serious infection and malignancy risk. In a 52-week phase 3 clinical study which randomized 596 patients with RA across 70 sites in 10 countries, etanercept-ykro demonstrated comparable safety and efficacy to etanercept as evidenced in ACR 20 response rate of 80.8% in the etanercept-ykro arm versus 81.5% in the etanercept arm.[50]

3. Hadlima™ (adalimumab-bwwd) is biosimilar to Humira® (adalimumab) and received FDA approval July 2019. The FDA-approved indications for Hadlima™ include: RA, JIA, PsA, AS, CD, UC, and PsO. As with adalimumab, the biosimilar carries a Black Boxed warning for serious infection and

malignancy risk. FDA approval was based on data derived from a randomized, double-blind 52-week phase 3 study in which 544 patients with moderate to severe RA despite MTX therapy were randomized to receive either adalimumab-bwwd or adalimumab. At Week 24, the ACR 20 response rate was 72.4% in the adalimumab-bwwd group versus 72.2% in the adalimumab group.[51] The safety profile of adalimumab-bwwd was comparable to adalimumab up to Week 24. The product is expected to launch in the United States in 2023.

4. Abrilada™ (adalimumab-afzb) is biosimilar to Humira® (adalimumab) and received FDA approval November 2019. Abrilada™ is FDA-approved to treat RA, JIA, PsO, PsA, AS, CD, and UC. As with adalimumab, the biosimilar carries a Black Boxed warning for serious infection and malignancy risk. Results from the REFLECTIONS B538-02 clinical comparative study found no clinically meaningful differences in efficacy, safety or immunogenicity compared to the reference product, each taken in combination with MTX, in patients with moderate to severe RA.[52]

5. Ruxience™ (rituximab-pvvr) is biosimilar to Rituxan® (rituximab). Ruxience™ received FDA approval July 2019 and is indicated for treatment of adults with Non-Hodgkins Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), and Granulomatosis with Polyangiitis (GPA) or Microscopic Polyangiitis (MPA) in combination with glucocorticoids. As with rituximab, the biosimilar carries a Black Boxed warning for infusion-related reactions, severe mucocutaneous reactions, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy. Results from the REFLECTIONS B3281006 clinical comparative study evaluated the efficacy, safety, immunogenicity, pharmacokinetics, and pharmacodynamics of rituximab-pvvr, and found no clinically meaningful differences in safety or efficacy compared to the reference product in patients with CD20-positive, low tumor burden follicular lymphoma.[53]

6. Truxima® (rituximab-abbs) is biosimilar to Rituxan® (rituximab). FDA-approval was granted November 2018. Truxima® is indicated for treatment of adults with NHL. Currently, Truxima® does not have FDA-approval for inflammatory conditions such as RA. Like rituximab, Truxima® has a label that carries a Black Boxed warning alerting providers and patients to the risk of fatal infusion reactions, skin and mouth reactions, and hepatitis B reactivation.

New Indications:

1. Stelara® (ustekinumab) received an expanded indication for treatment of moderately to severely active UC in adults in November 2019. Approval was based primarily on results from the UNIFI trial, in which subcutaneous injections of ustekinumab led to clinical remission rates of 38%-44% after 12 months, depending on the dosing interval (12 and 8 weeks, respectively), versus 24% in a placebo group.[54]

2. Rituxan® (rituximab) received FDA approval to treat GPA and MPA in patients 2 years of age and older in combination with glucocorticoids in September 2019. Previously approved indications include NHL, CLL, RA, and Pemphigus Vulgaris (PV) in adult patients.

3. Cimzia® (certolizumab pegol) received an expanded indication for treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation in March 2019.

4. Benlysta® (belimumab) received FDA approval for use in patients aged 5 years and older with active, autoantibody-positive SLE who are receiving standard therapy in April 2019.

5. Inflectra® (infliximab-dyyb) and Renflexis (infliximab-abda) received expanded indications to treat pediatric UC in patients 6 years and older in June 2019.

6. Erelzi™ (etanercept-szzs) received FDA approval for the expanded indications of PsA and PsO in October 2019.

7. Otezla® (apremilast) received an expanded indication to treat adult patients with oral ulcers associated with Behcet's Disease in July 2019.

8. Taltz® (ixekizumab) received FDA approval in August 2019 to treat adults with AS.

New FDA Safety Alerts:

Table 3. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Labeling Addition or Change	Description and Mitigation Principles (if applicable)
Infliximab-abda[55]	Renflexis®	3/2019	Warnings and Precautions	**Malignancies** Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including infliximab products. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents.[55] **Cardiovascular and Cerebrovascular Reactions** Serious cerebrovascular accidents, myocardial ischemia/infarction (some fatal), hypotension, hypertension, and arrhythmias have been reported during and within 24 hours of initiation of infliximab product infusion. Cases of transient visual loss have been reported during or within 2 hours of infusion of infliximab product. Monitor patients during infusion and if serious reaction occurs, discontinue infusion. Further management of reactions should be dictated by signs and symptoms.[55]
Guselkumab[56]	Tremfya®	4/2019 4/2019	Contraindications Warning and Precautions	Tremfya is contraindicated in patients with a history of serious hypersensitivity reaction to guselkumab or to any of the excipient.[56] Serious hypersensitivity reactions have been reported with postmarket use of Tremfya. Some cases required hospitalization. If a serious hypersensitivity reaction occurs, discontinue Tremfya® and initiate appropriate therapy.[56]
Belimumab[57]	Benlysta®	9/19	Warnings and Precautions	In controlled clinical studies, psychiatric disorders (depression, suicidal ideation and behavior) have been reported more frequently in patients receiving Benlysta®. Physicians should assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with Benlysta® and continue to monitor patients during treatment. Patients receiving Benlysta® (and caregivers if applicable) should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or behavior, or other mood changes.[57]
Ustekinumab	Stelara®	11/19	Warnings and Precautions	Stelara® may increase the risk of infections and reactivation of latent infections. Serious bacterial, mycobacterial, fungal, and viral infections were observed in patients receiving Stelara®.[58]

Randomized Controlled Trials

A total of 396 citations were manually reviewed from the initial literature search. After further review, 392 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 4 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 4. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Paul C, et al.[59] IXORA-S DB, AC, RCT Duration: 52 weeks	1. Ixekizumab 160 mg SC at week 0, followed by 80 mg every 2 weeks to week 12, then 80 mg every 4 weeks (n=131) Vs. 2. Ustekinumab 45 or 90 mg SC at weeks 0, 4, 16, 28 and 40 (n=158)	Adults with moderate to severe PsO N=302	Co-primary outcomes: Proportion of patients who achieved PASI 90 and sPGA 0/1 at week 52	PASI 90: 1. 104 (77.4%) 2. 98 (59.2%) RR 1.308 (95% CI 1.102 to 1.513; P=0.003) sPGA 0/1: 1. 110 (83.6%) 2. 108 (65.8%) RR 1.271 (95% CI 1.100 to 1.442; P=0.002)
Reich K, et al.[60] ECLIPSE DB, AC, MC, RCT Duration: 48 weeks	1. Guselkumab 100 mg SC at weeks 0 and 4, then every 8 weeks (n=534) Vs. 2. Secukinumab 300 mg SC at weeks 0, 1, 2, 3 and 4, then every 4 weeks (n=514)	Adults with moderate to severe PsO N=1048	Proportion of patients who achieved PASI 90 response at week 48	PASI 90 (ITT) 1.451 (84%) 2.360 (70%) Treatment Difference: 14% (95% CI: 9.2 to 19.2%; P<0.0001)
Sands BE, et al.[61] DB, AC, MC, RCT Duration: 50 weeks	1. Vedolizumab 300 mg IV infusion on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (n=383) Vs. 2. Adalimumab 160 mg at week 1, 80 mg at week 2 and 40 mg every 2 weeks until week 50 (n=386)	Adults with moderate to severe UC N= 769	Proportion of patients with clinical remission (defined as a total score of ≤2 on the Mayo scale [range, 0 to 12], with higher scores indicating more severe disease) at week 52	Clinical Remission: 1. 120 (31.3%) 2. 87 (22.5%) Treatment Difference: 8.8% (95% CI: 2.5 to 15.0%; P=0.006)

Mease PJ, et al[62] DB, RCT Duration: 24 weeks	1. MTX 20 mg PO plus PBO SC once a week (n=284) 2. Etanercept 50 mg SC plus PBO PO once a week (n=284) 3. Etanercept 50 mg SC plus MTX 20 mg PO once a week (n=283)	Adults with PsA N=851	Proportion of patients with ACR 20 response at week 24	ACR 20: 1. MTX: 50.7% 2. Etanercept: 60.9% 3. Etanercept + MTX: 65% 1 vs. 2: p = 0.029 1 vs... 3: p=0.005 95% CI not reported
Abbreviations: AC = Active Comparator; ACR = American College of Rheumatology; CI = confidence interval; DB = double blind; ITT = intention to treat; IV = intravenous; MC=multi-center; MTX = methotrexate; N = number; PASI = Psoriasis Area and Severity Index; PBO = placebo; PO= oral; PsA = psoriatic arthritis; PsO= plaque psoriasis; sPGA = static Physician's Global Assessment; RCT = randomized controlled trial; RR = relative risk; SC = subcutaneous				

NEW DRUG EVALUATION: Upadacitinib (Rinvoq™)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including FDA Black Boxed warnings, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Upadacitinib (Rinvoq™) is an oral JAK inhibitor indicated for the treatment of adults with moderate to severe RA who have had an inadequate response or intolerance to MTX.[15] Use of upadacitinib in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.[15] The recommended dose of upadacitinib is 15 mg orally once a day via an extended-release tablet, either as monotherapy or in combination with MTX or other non-biologic DMARDs.

Four published phase 3 studies and 1 unpublished trial were submitted to the FDA for upadacitinib approval.[10] These trials, collectively named the SELECT RA program, evaluated the efficacy and safety of upadacitinib in treating patients with moderately to severely active RA. The trials were conducted in Australia, New Zealand, Israel, South Africa, Asia, North/Central/South America, and Europe. Two doses of upadacitinib (15 mg and 30 mg once daily) were studied in clinical trials. There were numerical differences in treatment response between the two doses of upadacitinib generally favoring the 30 mg dose; however, the clinical benefit of the 30 mg dose over the 15 mg dose is small.[10] Given the increased safety concerns with the higher dose (e.g. anemia, neutropenia), the incremental benefit of the 30 mg dose does not outweigh the increased risk.[10] Therefore, the manufacturer is only marketing the 15 mg strength of upadacitinib.

Comparators to upadacitinib in the phase 3 trials included placebo, MTX, and adalimumab administered over 12 to 14 weeks. In all 5 trials, patients were switched from placebo or MTX to upadacitinib after the initial 3-month assessment with an option to participate in ongoing extension trials planned for up to 5 years. The co-primary efficacy endpoints assessed were the proportion of subjects who achieved an ACR20 response and reduced disease activity, as measured by DAS28-CRP. Secondary endpoints included ACR50 and ACR70 response rates and patient function, as assessed by improvements in the HAQ-DI score from baseline. The SELECT RA trials included patient populations known to exhibit different degrees of response based on past treatment history, with or without concurrent csDMARDs, in subjects who had an inadequate response to csDMARDs and/or bDMARDs. Results for the 4 published trial are summarized below. Additional trial details are presented in **Table 7.**

The SELECT-NEXT trial evaluated the efficacy and safety of upadacitinib in 661 RA patients who had inadequate response to csDMARDs (MTX, sulfasalazine, or leflunomide) compared to placebo over 12 weeks.[11] Patients in this trial had little or no exposure bDMARDs. Moderate quality evidence showed more patients in the upadacitinib 15 mg (64%) and 30 mg (66%) treatment groups met the co-primary endpoint of ACR20 at week 12 compared with 36% in the placebo group [15 mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, NNT = 4; 30 mg vs. placebo difference=31%, (95% CI 22 to 30), p<0.0001, NNT=4].[11] Similarly, more patients met the co-primary endpoint of DAS28-CRP less than or equal to 3.2 at week 12 in the upadacitinib 15 mg (48%) and 30 mg (48%) groups compared with 17% of patients in the placebo group [15 mg vs. placebo difference=29%, (95% CI 19 to 38), P<0.0001, NNT=4; 30 mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, NNT=4, moderate quality evidence].[11] The short duration of the placebo-controlled phase in this trial limits the efficacy assessment to 12 weeks of therapy. Data from the 5-year extension trial has not yet been published.

The SELECT-BEYOND trial used a similar study design as the SELECT-NEXT trial. The efficacy and safety of upadacitinib were evaluated in 499 RA patients who had inadequate response to at least one bDMARD.[12] The placebo-controlled period of 12 weeks was followed by an ongoing double-blind extension study of up to 5 years. More patients in the upadacitinib 15 mg (65%) and 30 mg (56%) treatment groups met the primary endpoint of ACR20 at week 12 compared with 28% in the placebo group [15 mg vs. placebo difference=37%, (95% CI 26 to 46), P<0.0001, NNT=3; 30 mg vs. placebo difference=28%, (95% CI 18 to 38), P<0.0001, NNT=4].[12] More patients met the co-primary endpoint of DAS28-CRP less than or equal to 3.2 at week 12 in the upadacitinib 15 mg (43%) and 30 mg (42%) groups compared with 14% in the placebo group [15 mg vs. placebo difference=29%, (95% CI 20 to 30), P<0.0001, NNT=4; 30 mg vs. placebo difference=28%, (95% CI 19 to 37), P<0.0001, NNT=4].[12] Study limitations included the short study duration, relatively small number of patients, lack of geographic diversity in the patient population, and inadequate assessment of the effect of upadacitinib on progressive structural joint damage.[12]

The SELECT-COMPARE trial evaluated the efficacy and safety of upadacitinib compared to placebo and adalimumab in 1,629 patients with active RA and an inadequate response to MTX.[13] Patients were randomized (2:2:1) to receive upadacitinib (15 mg once daily), placebo, or adalimumab (40 mg every other week) while continuing to take a stable dose of MTX. The primary end points were achievement of ACR20 and a DAS28-CRP less than 2.6 at week 12. Inhibition of radiographic progression was evaluated at week 26. At weeks 14, 18, and 22, if patients did not achieve 20% or greater improvement in the tender joint count (TJC) and swollen joint count (SJC) from baseline, treatment was changed as follows: adalimumab was switched to upadacitinib, upadacitinib was switched to adalimumab, and placebo was switched to upadacitinib.[13] At week 26, all placebo patients were switched to upadacitinib regardless of their response to placebo therapy. Patients remained on treatment through week 48. The study was also designed to test for the noninferiority and superiority of upadacitinib compared to adalimumab over 48 weeks.

Moderate quality evidence showed more patients in the upadacitinib group (71%) met the co-primary endpoint of ACR20 at week 12 compared with 36% in the placebo group [difference= 34%, (95% CI 29 to 39), P≤0.001, NNT=3].[13] More patients also met the co-primary endpoint of DAS28-CRP less than 2.6 at week 12 in the upadacitinib group (29%) compared with 6% in the placebo group [difference=23%, (95% CI 19 to 27), P≤0.001, NNT=5, moderate quality evidence].[13] Moderate quality evidence demonstrated more patients receiving upadacitinib achieved ACR20 (79%) and DAS28-CRP less than 2.6 (29%) compared with 63% of patients who achieved ACR 20 with adalimumab and 11% who achieved DAS28-CRP less than 2.6 with adalimumab [ACR 20 upadacitinib vs. adalimumab difference=8%, (95% CI 1 to 14), P≤0.05, NNT=13 and DAS28-CRP upadacitinib vs. adalimumab difference=11%, (95% CI 5 to 16), P≤0.001, NNT=10).[13] At 48 weeks, patients in the upadacitinib group had a greater response rate for both ACR20 (65%) and DAS28-CRP less than 2.6 (38%) compared with adalimumab (64%, P<0.01 and 28%, P<0.01, respectively).[13] The percentage of patients with no radiographic progression at week 26 was higher with upadacitinib (87%) compared to placebo (74%); P≤0.001). Lack of radiographic progression with adalimumab was noted in 88% of patients, but was not statistically significant compared to upadacitinib (P=0.448).[13] Study limitations include the shortened placebo-controlled period, which was permitted only until week 26 for ethical reasons). In addition, the rescue arms were not powered or designed to enable a valid statistical comparison for efficacy between patients who switched

treatment groups. Furthermore, only adalimumab was used as a comparator so it is unknown how upadacitinib compares with other bDMARDs or JAK inhibitors used for this indication.

The SELECT-MONOTHERAPY trial evaluated the efficacy and safety of switching to upadacitinib monotherapy compared with continuing MTX in 648 patients with an inadequate response to MTX.[14] Eligible patients must have shown active disease despite treatment with MTX, defined as at least six swollen joints out of 66, at least six tender joints out of 68, and more than 3 mg/L C-reactive protein (upper limit of normal 2.87 mg/L).[14] Patients were randomly assigned in a 1:1:1 ratio to receive upadacitinib 15 mg, upadacitinib 30 mg or MTX for 14 weeks. Patients randomized to MTX at week 0 were switched to receive either upadacitinib 15 mg or upadacitinib 30 mg at week 14 for up to 5 years, whereas patients randomized to upadacitinib at week 0 continued to receive their assigned dose from week 14 for up to 5 years.[14] Moderate quality evidence showed both upadacitinib treatment groups resulted in higher proportion of ACR20 responders at week 14 [15 mg (68%) and 30 mg (71%)] compared with the MTX group (41%) [15 mg vs. MTX difference=27%, (95% CI 18 to 36), P<0.0001, NNT=4; 30 mg vs. MTX difference=30% (95% CI 21 to 30), p<0.0001, NNT=4].[14] For the co-primary endpoint of DAS28-CRP less than or equal to 3.2, similar results were observed [15 mg (45%) and 30 mg (53%)] compared to the MTX cohort (19%) [15 mg vs. MTX difference=26%, (95% CI 16 to 33); P<0.001, NNT=4; 30mg vs. MTX difference=33%, (95% CI 25 to 42), P<0.001, NNT=3 moderate quality evidence).[14] Results of the 5-year extension trial have not yet been published. One of the limitations of the study was a relatively short MTX-controlled period (14 weeks); however, this was done to avoid undertreating patients in the continued MTX arm for an extended period (average previous duration of 3.6 years).[14] The trial design did not include radiographic assessments, and the trial was not designed to assess combination therapy with upadacitinib and MTX compared with monotherapy with upadacitinib.[14]

Current ongoing phase 3 trials are investigating the efficacy of upadacitinib in patients with moderate to-severe atopic dermatitis, CD, UC, PsA, and giant cell arteritis.

Clinical Safety:
Reported safety data from these Phase 3 trials showed upadacitinib 15 mg-treated subjects experienced a greater frequency of adverse events compared to placebo, including upper respiratory infection, nausea, cough pyrexia, pneumonia, herpes zoster, herpes simplex, and oral candidiasis.[15] Based on findings in animal studies, upadacitinib may cause fetal harm when administered to a pregnant woman.[15] **Table 5** describes the most prevalent adverse reactions reported with upadacitinib 15 mg compared to placebo during clinical trials.

Table 5. Adverse reactions reported with upadacitinib compared to placebo in clinical trials[15]

Adverse Reaction	Upadacitinib 15 mg N = 1035	Placebo N = 1042
Upper respiratory tract infection	13.5%	9.5%
Nausea	3.5%	2.2%
Cough	2.2%	1.0%
Pyrexia	1.2%	0%

In clinical trials, patients treated with upadacitinib 30 mg had a higher exposure adjusted event rates of adverse effects leading to discontinuation than patients treated with upadacitinib 15 mg. The most common adverse effect leading to discontinuation of upadacitinib was pneumonia (15 mg: 0.5 events/100 patient years, 30 mg 0.9 event/100 patient years).[10] There was a dose-dependent effect observed with higher rates of herpes zoster infections in patients treated with

upadacitinib 30 mg compared to upadacitinib 15 mg patients in the controlled and long- term periods.[10] In the placebo controlled trials, upadacitinib 15 mg and 30 mg event rates of herpes zoster infections were 2.3 events/100 patient years and 8.2 events/100 patient years, respectively.[10]

Upadacitinib prescribing information contains black box warnings for serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections.[15] In addition, lymphoma and other malignancies have been observed in patients treated with upadacitinib.[15] Finally, thrombosis, including DVT, PE, and arterial thrombosis, have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions.[15] Data have been presented for upadacitinib only up to 24 weeks, and show a numeric increase in malignancies and cardiovascular events versus placebo.[15]

Look-alike / Sound-alike Error Risk Potential: No other drugs identified

Table 6. Pharmacology and Pharmacokinetic Properties.[15]

Parameter	
Mechanism of Action	Janus kinase inhibitor
Oral Bioavailability	Maximum absorption occurs within 2-3 hours after a single dose.
Distribution and Protein Binding	Upadacitinib is 52% bound to plasma proteins. Volume of distribution is estimated as 224 liters.
Elimination	53% of drug is excreted unchanged in urine (24%) and in feces (38%) - 34% of upadacitinib excreted as inactive metabolites.
Half-Life	8 to 14 hours
Metabolism	Metabolism is mediated primarily by CYP3A4 and to a minor extent by CYP2D6 hepatic enzymes.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptomatic improvement (ACR 50, ACR 70)
2) Clinical remission
3) Disease progression
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:

1) Proportion of patients achieving ACR20 at 12 to 14 weeks
2) Proportion of patients with DAS28-CRP score of 3.2 or less at 12 to 14 weeks

Table 7. Comparative Evidence Table: Upadacitinib

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Burmester GR, et al.[11] SELECT-NEXT DB, PC, MC, Phase 3 RCT 150 sites in 35 countries N=661 12 weeks	1. UPA 15 mg po QDay 2. UPA 30 mg po QDay 3. Placebo po QDay All administered in combination with csDMARDs (MTX, chloroquine, sulfasalazine, hydroxychloroquine and/or leflunomide). Trial followed by ongoing DB extension study up to 5 yrs. Patients on placebo were randomized to UPA 15 mg or 30 mg.	Demographics: -Mean age: 56 yrs -Female: 79% -Mean time since RA diagnosis: 7.3 yrs -Previous bDMARD exposure: 13% -MTX monotherapy at baseline: 60% -Mean DAS28-CRP score: 5.6 Key Inclusion Criteria: -Adults ≥18 yrs -Active RA ≥ 3 mos -2 concomitant csDMARDs ≥ 3 mos -Stable csDMARD dose for ≥ 4 weeks at baseline -Inadequate response to MTX, sulfasalazine, or leflunomide Key Exclusion Criteria: -Inadequate response to bDMARDs -Previous exposure to a JAK inhibitor -History of inflammatory joint disease other than RA -Hepatic or renal impairment	ITT: 1. 221 2. 219 3. 221 PP: 1. 210 2. 201 3. 207 Attrition: 1. 11 (5%) 2. 18 (8%) 3. 14 (6%)	Co-Primary Endpoints: 1. ACR20 at week 12: 1. 141 (64%) 2. 145 (66%) 3. 79 (36%) 1 vs. 3 Difference: 28% (95% CI 19 to 37); p<0.0001 2 vs.3 Difference: 31% (95% CI 22 to 39); p<0.0001 2. DAS28-CRP score ≤ 3.2 at week 12: 1. 107 (48%) 2. 105 (48%) 3. 38 (17%) 1 vs. 3 Difference: 29% (95% CI 19 to 38) p<0.0001 2 vs. 3 Difference: 28% (95% CI 19 to 37) P<0.0001 Secondary Endpoints: 1. ACR50 at week 12: 1. 83 (38%) 2. 95 (43%) 3. 33 (15%) 1 vs. 2 Difference: 23% 95% CI NR; p<0.0001 2 vs. 3 Difference: 28% 95% CI NR; p<0.0001 2. Mean change in HAQ-DI at week 12: 1. -0.61 2. -0.55 3. -0.26 1 vs. 3 Difference: -0.35 (95% CI -0.4 to -0.3) p<0.0001 2 vs. 3 Difference: -0.28 (95% CI -0.4 to -0.2) p<0.0001	28/4 31/4 29/4 28/4 23/5 28/4 NA NA	AEs: 1. 125 (57%) 2. 118 (54%) 3. 108 (49%) SAEs: 1. 9 (4%) 2. 6 (3%) 3. 5 (2%) AEs leading to discontinuation of drug: 1. 7 (3%) 2. 13 (6%) 3. 7 (3%) 95% CI and p value NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 via IRT and stratified by bDMARD exposure and geographic region. Baseline demographics and disease activity balanced between 3 groups. Performance Bias: Low. Patients, investigators, and AbbVie personnel were blinded to allocation. Placebo and study drug were identical in appearance Detection Bias: Low. Investigators blinded to interventions. Attrition Bias: Low. More subjects receiving UPA 30 mg withdrew due to AE while more subjects receiving placebo withdrew due to lack of efficacy. Did not impact overall rates of attrition. Reporting Bias: Low. Protocol available online. Authors reported endpoints clearly and as outlined in methods Reasons for protocol deviations and percent of patients with deviations included in supplementary appendix. Other Bias: Unclear. Funded by AbbVie. AbbVie had a role in study design, data collection, data analysis, data interpretation and writing of report. Authors had received grants from manufacturers. **Applicability**: Patient: Adults with moderate to severe RA and inadequate response to csDMARDs. Intervention: 15 mg dose is FDA-approved but 30 mg dose is not. All subjects continued csDMARD therapy. Comparator: Placebo is appropriate to evaluate safety and efficacy. Would be helpful to compare to another JAK-I (tofacitinib or baricitinib) Outcomes: ACR 50 and 70 considered more clinically significant than ACR 20. Short duration of treatment (12 weeks).

								Setting: 150 sites in 35 countries: North America (40%); Eastern Europe (34%); Western Europe (10%); Asia (7%); Latin and South America (4%); Australia, New Zealand, & South Africa (4%)
2. Fleischmann R, et al.[13] SELECT-COMPARE MC, DB, PC, AC, Phase 3 RCT N=1629 12 weeks	1. UPA 15 mg po QDay 2. Placebo po QDay 3. Adalimumab 40 mg SC every other week All subjects continued stable background dose of MTX 12 week efficacy assessment. At 26 weeks all placebo patients switched to UPA for an additional 22 week study period. Total study period: 48 weeks	Demographics: -Mean age: 54 yrs -Female: 79% -Mean time since RA diagnosis: 8 yrs -Mean DAS28-CRP score: 5.8 -Average MTX dose: 17 mg/week -Prior bDMARD exposure: 9% Key Inclusion Criteria: -Adults ≥18 yrs -Moderate to severe RA ≥3 mos -Stable MTX therapy ≥3 mos with stable dose of 15 to 25 mg per week ≥4 wks., but w/ inadequate response to therapy - < 3-mos exposure to bDMARDs Key Exclusion Criteria: -Prior exposure to JAK inhibitor -Intolerance or inadequate response to bDMARD (except for adalimumab) -Hepatic or renal impairment -History of inflammatory joint disease other than RA	ITT: 1. 651 2. 651 3. 327 PP: 1. 620 2. 620 3. 300 Attrition: 1. 31 (5%) 2. 31 (5%) 3. 27 (8%)	Co-Primary Endpoints: 1. ACR20 response at week 12: 1. 456 (71%) 2. 237 (36%) 3. 206 (63%) 1 vs. 2: Difference: 34% (95% CI, 29 to 39); p≤0.001 1 vs. 3: Difference: 8% (95% CI, 1 to 14); p≤0.05 2. DAS28-CRP < 2.6 at week 12: 1. 189 (29%) 2. 20 (6%) 3. 118 (18%) 1 vs. 2: Difference: 23% (95% CI, 19 to 27); p≤0.001 1 vs. 3: Difference: 11% (95% CI, 5 to 16); p<0.001 Secondary Endpoints: 1. ACR50 response at week 12: 1. 292 (45%) 2. 98 (15%) 3. 95 (29%) 1 vs. 2 Difference: 30% (95% CI 25.6 to 35.0); P<0.001 2 vs. 3 Difference: 16% (95% CI 9.0 to 22.3); P<0.001 2.Mean change in HAQ-DI at week 12: 1. -0.60 2. -0.28 3. -0.49 1 vs. 2 Difference: -0.32 (95% CI NR); p<0.001 1 vs. 3 Difference: -0.11	34/3 8/13 23/5 11/10 30/4 16/7 NA NA	AEs: 1. 417 (64%) 2. 347 (53%) 3. 197 (60%) SAEs: 1. 24 (4%) 2. 19 (3%) 3. 14 (4%) AEs leading to discontinuation of drug: 1. 23 (3.5%) 2. 15 (2%) 3. 20 (6%) 95% CI and p value NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:2:1 using IRT and stratified by bDMARD exposure and geographic region. Baseline demographics and disease activity balanced between 3 groups. Performance Bias: Low. Patients, investigators, caregivers, and funding personnel all blinded to treatment arm through week 48. Detection Bias: Unclear. Not clear how blinding was maintained for therapy re-assignment during rescue period after 12 weeks. Attrition Bias: Low. More subjects in the adalimumab arm withdrew due to adverse effects, but not concerning enough to increase risk of attrition bias. Withdrawal rates even between UPA and placebo. Reporting Bias: Low. Protocol available online. Authors reported endpoints clearly and as outlined in methods. Other Bias: Unclear. AbbVie funded the trial, contributed to the design of the study, and was involved in data collection and analysis, interpretation of the results, and preparation, review, and approval of the final version. **Applicability**: Patient: Patients with an inadequate response to MTX. Intervention: UPA 15 mg po once daily is an FDA approved dose with background MTX therapy. Comparators: Placebo and adalimumab (non-inferiority and superiority). Would be informative to compare UPA to another JAK inhibitor (baricitinib or tofacitinib). Outcomes: ACR 20 response and DAS28-CRP used in previous UPA trials. ACR 50 and 70

				(95% CI NR); p<0.01				considered more clinically significant than ACR 20. Setting: 286 sites in 46 countries: Eastern Europe (40%); South/Central America (27%); North America (19%); Western Europe (6%); Asia (3%); Other regions (6%)
3. Smolen JS, et al.[14] SELECT-MONO-THERAPY MC, DB, AC RCT N=648 14 weeks	1. UPA 15 mg po QDay 2. UPA 30 mg po Qday 3. Maintenance MTX dose (15 to 25 mg per week).	Demographics: -Mean age: 54 yrs -Female: 79% -Mean time since RA diagnosis: 7 yrs -MTX monotherapy: 60% -Mean DAS28-CRP score: 5.6 Key Inclusion Criteria: -Adults ≥18 yrs -Moderate to severe RA -Stable MTX therapy ≥ 3 mos (15 to 25 mg/week ≥ 4 weeks) -Only using MTX as csDMARD therapy Key Exclusion Criteria: -Prior exposure to JAK inhibitor or bDMARD therapy -History of inflammatory joint disease other than RA -Hepatic or renal impairment	ITT: 1. 217 2. 215 3. 216 PP: 1. 199 2. 202 3. 197 Attrition: 1. 18 (8%) 2. 13 (6%) 3. 19 (9%)	Primary Endpoints: 1. ACR20 response at week 14: 1. 147 (68%) 2. 153 (71%) 3. 89 (41%) 1 vs. 3 Difference: 27% (95% CI 18 to 36); p≤0.0001 2 vs. 3 Difference: 30% (95% CI 21 to 39); p≤0.0001 2. DAS28-CRP ≤ 3.2 at week 14: 1. 97 (45%) 2. 114 (53%) 3. 42 (19%) 1 vs. 3 Difference: 26% (95% CI 16 to 33); p≤0.0001 2 vs. 3 Difference: 34% (95% CI 25 to 42); p≤0.0001 Secondary Endpoints: 1. ACR50 response at week 14: 1. 91 (42%) 2. 112 (52%) 3. 33 (15%) 1 vs. 3 Difference: 27% (95% CI 19 to 35) P<0.0001 2 vs. 3 Difference: 37% (95% CI 29 to 45) P<0.0001 1. Least square mean change in HAQ-DI at week 14: 1. -0.65 2. -0.73 3. -0.32 (95% CI NR) P<0.001	27/4 30/4 26/4 34/3 27/4 37/3 NA	AEs: 1. 103 (47%) 2. 105 (49%) 3. 102 (47%) SAEs: 1. 11 (5%) 2. 6 (3%) 3. 6 (3%) AEs leading to discontinuation of drug: 1. 8 (4%) 2. 6 (3%) 3. 6 (3%) 95% CI and p value NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 via IRT and stratified by geographical region. Patient demographics and disease activity were balanced across the treatment arms. Performance Bias: Low. Patients, investigators, and funding personnel all blinded to study drug allocation. Detection Bias: Unclear. Method of blinding study drug from placebo not described. Attrition Bias: Low. Similar proportions of patients withdrew from each arm. Reporting Bias: Low. Protocol available online. Authors reported endpoints clearly and as outlined in methods. Other Bias: Unclear. Funded by AbbVie. AbbVie was involved in data analysis, the interpretation of results and the preparation, review and approval of the final version of this report. **Applicability**: Patient: Patients with inadequate response to MTX. Intervention: UPA 15 or 30mg once daily. Comparator: UPA monotherapy compared to MTX monotherapy. Outcomes: ACR20 and DAS28-CRP<3.2 at 14 weeks. ACR 50 and 70 considered more clinically significant than ACR 20. Setting: 138 sites in 24 countries: Eastern Europe (37%); North America (30%); South/Central America (14%); Japan (10%); Western Europe (4%); South Africa/Tukey/Israel (6%).

4. Genovese MC, et al.[12] SELECT-BEYOND MC, DB, PC N=499 12 weeks	1. UPA 15 mg po QDay 2. UPA 30 mg po QDay 3. Placebo po QDay All continued background csDMARDs	Demographics: -Mean age: 57 yrs -Female: 84% -Mean time since RA diagnosis: 13 yrs -Failed ≥ 1 TNF-I: 91% -Mean DAS28-CRP score: 5.8 Key Inclusion Criteria: -Adults ≥18 yrs -Active RA ≥ 3 mos -bDMARD ≥ 3 mos or intolerance or toxicity to ≥1 bDMARD -csDMARD ≥3 mos and on stable dose for ≥4 weeks Key Exclusion Criteria: -H/o inflammatory joint diseases other than RA -Any previous exposure to a JAK inhibitor - Impaired renal or hepatic function	ITT: 1. 164 2. 165 3. 169 PP: 1. 148 2. 156 3. 147 Attrition: 1. 17 (10%) 2. 8 (5%) 3. 22 (13%)	Primary Endpoint: 1. ACR20 response at week 12: 1. 106 (65%) 2. 93 (56%) 3. 48 (28%) 1 vs. 3 Difference: 37% (95% CI 26 to 46); P<0.0001 2 vs. 3 Difference 28% (95% CI 18 to 38); P<0.0001 2. DAS28-CRP < 3.2 at week 12: 1. 71 (43%) 2. 70 (42%) 3. 24 (14%) 1 vs. 2 Difference: 29% (95% CI 20 to 38); p<0.0001 2 vs. 3 Difference: 28% (95% CI 19 to 37); p<0.0001 Secondary Endpoints: 1. ACR50 response at week 12: 1. 56 (34%) 2. 59 (36%) 3. 20 (12%) 1 vs. 2 Difference: 2% 2 vs. 3 Difference: 24% (95% CI NR); P<0.0001 for both doses 1. Least square mean change in HAQ-DI at week 12 1. -0.41 2. -0.44 3. -0.16 (95% CI NR); P<0.0001 for both doses	37/3 28/4 29/4 28/4 2/50 24/5 NA	AEs at week 12: 1. 91 (55%) 2. 111 (67%) 3. 95 (56%) SAEs at week 12 1. 8 (5%) 2. 12 (7%) 3. 0 AEs leading to discontinuation of drug at week 12 1. 4 (2%) 2. 15 (9%) 3. 9 (5%) 95% CI and p value NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 via IRT and stratified by the number of previous bDMARDs used and geographic region. At baseline, demographic and disease characteristics were balanced across the treatment groups. Performance Bias: Low. Patients, investigators, and funding personnel blinded to study drug allocation Placebo and study drug identical in appearance. Detection Bias: Low. Investigators blinded to interventions. Attrition Bias: Unclear. Proportion of patients who discontinued the study drug because of adverse events was higher in the UPA 30 mg group than in the UPA 15 mg and placebo groups. Proportion of patients who discontinued the study drug because of lack of efficacy was higher in the placebo group than in the UPA groups. Reporting Bias: Low. Protocol available as well as description of protocol deviations on line. Authors reported endpoints clearly and as outlined in methods. Other Bias: Unclear. Funded by AbbVie, which also had a role in study design, data collection, data analysis, data interpretation, and writing of the report. Authors report grants from several manufacturers including AbbVie. **Applicability**: Patient: More difficult to treat cohort given stipulation of failure to ≥ 1 bDMARD Intervention: Only UPA 15 mg dose is approved by FDA. Comparator: Placebo is appropriate to evaluate safety and efficacy. Would be helpful to compare to another JAK-I (tofacitinib or baricitinib) Outcomes: ACR20 and DAS28-CRP<3.2 at 12 weeks. ACR 50 and 70 considered more clinically significant than ACR 20. Setting: 153 sites in 26 countries. Most of the sites were located in North America (66%).

Abbreviations: AC=active comparator; ACR20=American College of Rheumatology 20% response rate; ACR50=American College of Rheumatology 50% response rate; AE=adverse events; ARR=absolute risk reduction; bDMARDs=biologic Disease-Modifying Antirheumatic Drugs; CI=confidence interval; csDMARDs=conventional synthetic Disease-Modifying Antirheumatic Drugs; DAS28-CRP=28-joint disease activity score based on C-reactive protein; DB=double blind; HAQ-DI=health assessment questionnaire-disability index; ITT=intention to treat; IRT=interactive response technology; JAK=Janus kinase; MTX=methotrexate; MC=multi-center; mos=months; N=number of subjects; NA=not applicable; NNH=number needed to harm; NNT=number needed to treat; NR=not reported; PC=placebo control; PO=oral; PP=per protocol; RA=rheumatoid arthritis; RCT=randomized clinical trial; SAE=serious adverse events; SC=subcutaneous; TNF-I=tumor necrosis factor inhibitor; UPA =upadacitinib; yrs=years

NEW DRUG EVALUATION: Risankizumab-rzaa (Skyrizi™)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Risankizumab-rzaa is an IL-23 antagonist indicated for the treatment of moderate-to-severe PsO in adults who are candidates for systemic therapy or phototherapy.[18] The FDA-approved dose is 150 mg administered via subcutaneous injection at week 0, week 4 and every 12 weeks thereafter.[18] The drug is supplied as a 75 mg/0.83 mL single-dose prefilled syringe. For each dose, the 2 injections should be administered at different anatomic locations such as thighs or abdomen.[18]

The efficacy and safety of risankizumab in patients with moderate-to-severe PsO was evaluated in 2 similar double-blind, randomized, placebo-controlled and ustekinumab-controlled phase 3 trials (UltIMMa-1 and UltIMMa-2).[16] The primary objective of the studies was to demonstrate superiority of risankizumab over placebo and ustekinumab. The ustekinumab used in these trials was the European Union (EU)-approved product, which is distinct from the product that is FDA-approved. One hundred thirty-nine sites in Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Mexico, Japan, Poland, Portugal, Republic of Korea, Spain, and United States participated in the 2 trials.[16] The sites included hospitals, academic medical centers, clinical research units, and private practices.[16] Five hundred six patients were enrolled in UltIMMa-1 and 491 patients were enrolled in UltIMMa-2.[16]

The UltIMMa studies consisted of two parts: Part A and Part B. In Part A, during the 16 week double blind phase, patients received either 150 mg risankizumab, ustekinumab based on weight per label (45 mg for patients with body weight less than or equal to 100 kg or 90 mg for patients with body weight greater than 100 kg), or placebo at week 0 and 4.[16] In Part B (double-blind, weeks 16 through 52), patients initially randomized to placebo switched to 150 mg risankizumab at week 16; other patients continued their originally randomized treatment.[16] During Part B, patients received study drug at weeks 16, 28, and 40. Co-primary endpoints were proportions of patients who achieved 90% improvement in the PASI (PASI-90) and a sPGA score of 0 or 1 at week 16. Secondary endpoints included proportion of patients who achieved 100% improvement in the PASI (PASI-100) and a score of 0 or 1 on the DLQI at week 16.

In both studies, more patients who received risankizumab, compared with those who received placebo or ustekinumab, achieved the co-primary endpoints of PASI-90 and sPGA score of 0 or 1 at week 16. At week 16, moderate quality evidence showed PASI-90 was achieved by 75.3% risankizumab-treated patients compared with 4.9% placebo-treated patients and 42% ustekinumab-treated patients in UltIMMa-1 [risankizumab vs. placebo difference=70%, (95% CI 64 to 76), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=33%, (95% CI 22 to 44), p<0.0001, NNT=3].[16] In UltIMMa-2, 74.8% risankizumab-treated patients compared with 2% placebo-treated patients and 47.5% ustekinumab-treated patients achieved PASI-90 [risankizumab vs. placebo difference=72%, (95% CI 66 to 78), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=27%, (95% CI 16 to 38), p<0.0001, NNT=4, moderate quality evidence].[16] In UltIMMA-1,

moderate quality evidence showed sPGA score of 0 or 1 was achieved by 87.5% of patients who received risankizumab versus 7.8% who received placebo and 63% who received ustekinumab [risankizumab vs. placebo difference=79%, (95% CI 73 to 86), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=25%, (95% CI 15 to 35), p<0.0001, NNT=4].[16] Similar results were observed in UltIMMA-2 for sPGA 0 or 1 at week 16 [risankizumab vs. placebo difference=78%%, (95% CI 72 to 84), p<0.0001, NNT=2; risankizumab vs. ustekinumab difference=22%, (95% CI 12 to 32), p<0.0001, NNT=5, moderate quality evidence].[16] Additional details about these 2 trials are included in **Table 10**.

This trial had some limitations. Since psoriasis is a chronic disease, further studies are needed to evaluate longer-term outcomes. Additionally, as has been typical of studies in moderate-to-severe plaque PsO, patients in both trials were predominantly white and male. The applicant did not provide an adequate comparison between the US-licensed and the EU-approved ustekinumab.[18] Thus, the EU-approved ustekinumab may be considered distinct from the US-licensed ustekinumab.[18]

In the randomized, double-blind, phase 3 IMMVent trial, risankizumab was compared with adalimumab in patients with moderate-to-severe chronic PsO through week 16 (Part A).[17] In Part B, the efficacy and safety of switching to risankizumab through week 44, compared with continued adalimumab, was further evaluated in patients who achieved PASI-50 to less than PASI-90 (intermediate responders) with adalimumab at week 16.[17] Blinding for patients, investigators, and other study personnel was maintained in Phase B. The primary objective was to demonstrate superiority of risankizumab over adalimumab in both Parts A and B.[17] Sixty-six sites in Canada, Czech Republic, Finland, France, Germany, Mexico, Poland, Portugal, Sweden, Taiwan, and the United States participated in the study.

Patients were randomly assigned 1:1 to receive 150 mg risankizumab subcutaneously at weeks 0 and 4 or 80 mg adalimumab subcutaneously at randomization, then 40 mg at weeks 1, 3, 5, and every other week thereafter during Part A. For Part B, adalimumab intermediate responders were re-randomized 1:1 to continue 40 mg adalimumab or switch to 150 mg risankizumab. Co-primary endpoints in part A were proportion of patients who achieved PASI-90 and a sPGA score of 0 or 1 at week 16; for part B, the primary endpoint was PASI-90 at week 44. Moderate quality evidence showed at week 16, PASI-90 was achieved in 72% patients given risankizumab and 47% of patients given adalimumab [adjusted absolute difference 24.9% (95% CI 17.5 to 32.4); p<0.0001, NNT=5], and sPGA scores of 0 or 1 were achieved in 84% of patients given risankizumab and 60% patients given adalimumab [adjusted absolute difference 23.3% (95% CI 16.6 to 30.1); p<0.0001, NNT=5].[17] In part B, among adalimumab intermediate responders, PASI-90 was achieved by 66% of patients switched to risankizumab and 21% of patients continuing adalimumab (adjusted absolute difference 45.0%, (95% CI28.9 to 61.1%); p<0.0001 at week 44.[17]

There is no direct evidence comparing risankizumab with IL-17 inhibitors (brodalumab, secukinumab, ixekizumab) or the IL-23 inhibitors (guselkumab or tildrakizumab), which are also FDA-approved to treat PsO. There is also uncertainty of the efficacy and safety benefit that long-term treatment with risankizumab may have over these other biologic treatments.

Clinical Safety:
Analyses of the reported safety data from Phase 3 trials demonstrates that risankizumab-treated subjects experienced a greater frequency of adverse events, compared to placebo including upper respiratory infections, headache, fatigue, injection site reactions and tinea infections.[18] **Table 8** describes the most prevalent adverse reactions reported with risankizumab compared to placebo during clinical trials. No reports of tuberculosis, opportunistic infections, adjudicated major adverse cardiac events (MACE) or serious hypersensitivity were reported during clinical trials.

Table 8. Adverse Reactions Occurring in > 1% of Subjects on risankizumab-rzaa through week 16[18]

Adverse Reactions	Risankizumab-rzaa 150 mg (n=1306) N (%)	Placebo (n=300) N (%)
Upper Respiratory Infections	170 (13)	29 (9.7)
Headache	46 (3.5)	6 (2)
Fatigue	33 (2.5)	3 (1)
Injection Site Reactions	19 (1.5)	3 (1)
Tinea Infections	14 (1.1)	1 (0.3)

Look-alike / Sound-alike Error Risk Potential: No drugs have been identified

Table 9. Pharmacology and Pharmacokinetic Properties[18]

Parameter	
Mechanism of Action	IL-23 antagonist
Bioavailability	After subcutaneous injection: 89%
Distribution and Protein Binding	Volume of distribution: 11.2 L
Elimination	Estimated clearance: 0.31 L/day
Half-Life	28 days
Metabolism	Not characterized. As a humanized IgG1 monoclonal antibody, risankizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Abbreviations: IgG=immune globulin G; IL=interleukin; L=liters

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptomatic improvement (e.g., PASI-100)
2) Functional status
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:

1) PASI-90 at 16 weeks
2) sPGA 0/1 at 16 weeks

Table 10. Comparative Evidence Table: Risankizumab

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Gordon, et al[16] UltIMMa-1 DB, PC, AC, Phase 3 RCT N=506 16 weeks	1. Risankizumab 150 mg at week 0, 4, 16, 28 and 40 2. Ustekinumab 45 or 90 mg (weight-based) at week 0, 4, 16, 28, and 40 3. Placebo at weeks 0 and 4 followed by risankizumab 150 mg at week 16, 28 and 40 Part A: Weeks 0 to 16. Part B: Weeks 17 to 52. Patients assigned to placebo in Part A were switched to risankizumab 150 mg every 12 weeks x 3 doses. This phase was double blinded.	Demographics: -Male 70% -Mean Wt.: 88 kg -Mean BSA involvement: 26% -White 70% -Asian: 26% -Mean age: 48 yo -Prior TNF use: 21% Key Inclusion Criteria: -Adults ≥ 18 yo -Chronic PsO ≥6 mos -Stable moderate-to-severe chronic PsO with baseline metrics: a. ≥10% BSA involvement b. PASI ≥12 c. sPGA ≥3 -Candidate for systemic therapy or phototherapy -Candidate for treatment with ustekinumab Key Exclusion Criteria: -Non-plaque forms of PsO -Current drug-induced PsO -Active ongoing inflammatory diseases other than Ps and PsA -Prior exposure to	ITT: 1. 304 2. 100 3. 102 PP: 1. 299 2. 99 3. 98 Attrition at 16 weeks: 1. 5 (1.6%) 2. 1 (1.0%) 3. 4 (3.9%)	Co-Primary Endpoints: 1. PASI-90 at week 16: 1. 229 (75.3%) 2. 42 (42.0%) 3. 5 (4.9%) 1 vs. 2 AD = 33.5% (95% CI 22.7 to 44.3%) p<0.0001 1 vs. 3 AD = 70.3% (95% CI 64.0 to 76.7%) p<0.0001 2. sPGA 0/1 at week 16: 1. 267 (87.8%) 2. 63 (63.0%) 3. 8 (7.8%) 1 vs. 2 AD 25.1% (95% CI = 15.2 to 35.0%) P<0.0001 1 vs. 3 AD 79.9% (95% CI 73.5to 86.3%) P<0.0001 Secondary Endpoints: 1. PASI-100 at week 16: 1. 109 (35.9%) 2. 12 (12.0%) 3. 0 1 vs. 2 AD 23.8% (95% CI 15.5 to 32.1%) P<0.001 1 vs. 3 AD 35.5% (95% CI 30.0 to 41.0%) P<0.001 2. DLQI 0/1 at week 16:	33.5/3 70.3/2 25.1/4 79.9/2 23.8/5 35.5/3	1.AE 1. 151 (49.7%) 2. 50 (50.0%) 3. 52 (51.0%) 2.SAE 1. 7 (2.3%) 2. 8 (8.0%) 3. 3 (2.9%) AE leading to discontinuation of drug 1. 2 (0.7%) 2. 2 (2.0%) 3. 4 (3.9%) p-value and 95% CI NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Subjects randomized 3:1:1 to risankizumab, ustekinumab, or placebo via IRT and stratified by weight (≤ 100kg or > 100 kg) and previous TNFI exposure (yes or no). Baseline patient demographics generally balanced between treatment groups. Performance Bias: Low. Double blinding achieved through IRT. To maintain blinding, the studies utilized a double-dummy strategy wherein risankizumab and its matching placebo or ustekinumab and its matching placebo were identical in appearance. Detection Bias: Low. Patients, investigators, and study personnel involved in the trial conduct or analyses remained masked to treatment assignments until study completion. Attrition Bias: Low. Rates of discontinuation with similar patient loss across all 3 arms. Reporting Bias: Low. Protocol is available online. Other Bias: Unclear. Funded by AbbVie and Boehringer Ingelheim. Boehringer Ingelheim contributed to study design and participated in data collection. AbbVie did the data analysis, and participated in data interpretation. AbbVie and Boehringer Ingelheim participated in writing, review, and approval of the manuscript. All authors had full access to the data from both studies, reviewed and approved the final version, and were responsible for the decision to submit for publication. A medical writer, employed by AbbVie, assisted with manuscript preparation under the authors' direction. **Applicability**: Patient: Patient population primarily male, white participants with stable moderate-to-severe PsO. Intervention: Risankizumab dosing is the FDA approved dose. Comparator: Ustekinumab is an Il-12/23 antagonist, with similar mechanism of activity to study drug.

		ustekinumab or risankizumab -History of allergy or hypersensitivity biologic agent or its excipients		1. 200 (65.8%) 2. 43 (43.0%) 3. 8 (7.8%) <u>1 vs. 2</u> AD 23.0% (95% CI 11.9 to 34.0) P<0.001 <u>1 vs. 3</u> AD 57.9% (95% CI 50.4 to 65.3) P<0.001	23/5 57.9/2			<u>Outcomes</u>: PASI-90 and sPGA 0/1 are validated indicators of efficacy. <u>Setting</u>: 79 sites across 8 countries: Australia, Canada, Czech Republic, France, Germany, Japan, Republic of Korea, and the United States.
2. Gordon, et al[16] UltIMMa-2 DB, PC, AC, Phase 3 RCT N=491 16 weeks	1. Risankizumab 150 mg at week 0, 4, 16, 28 and 40 2. Ustekinumab 45 or 90 mg (weight-based) at week 0, 4, 16, 28, and 40 3. Placebo at weeks 0 and 4 followed by risankizumab 150 mg at week 16, 28 and 40 Part A: Weeks 0 to 16. Part B: Weeks 17 to 52. Patients assigned to placebo in Part A were switched to risankizumab 150 mg every 12 weeks x 3 doses. Double blinding maintained in this phase.	<u>Demographics:</u> -Male 68% -Mean Wt.: 92 kg -Mean BSA Involvement: 25% -White: 89% -Asian: 7% -Mean age: 47 yo -Prior TNF use: 25% <u>Inclusion Criteria:</u> See above <u>Exclusion Criteria:</u> See above	<u>ITT</u>: 1. 294 2. 99 3. 98 <u>PP</u>: 1. 292 2. 96 3. 94 <u>Attrition</u>: 1. 2 (0.6%) 2. 3 (3.0%) 3. 4 (4.3%)	<u>Co-Primary Endpoints</u>: 1. PASI-90 at week 16: 1. 220 (74.8%) 2. 47 (47.5%) 3. 2 (2.0%) <u>1 vs. 2</u> AD = 27.6% (95% CI 16.7 to 38.5%) p<0.0001 <u>1 vs. 3</u> AD = 72.5% (95% CI 66.8 to 78.2%) p<0.0001 2. sPGA 0/1 at week 16: 1. 246 (83.7%) 2. 61 (61.6%) 3. 5 (5.1%) <u>1 vs. 2</u> AD 22.3% (95% CI = 12.0 to 32.5%) P<0.0001 <u>1 vs. 3</u> AD 78.5% (95% CI 72.4 to 84.5%) P<0.0001 <u>Secondary Endpoints</u>: 1. PASI-100 at week 16: 1. 149 (50.7%) 2. 24 (24.2%) 3. 2 (2.0%) <u>1 vs. 2</u> AD 27% (95% CI 17.0 to 37.0%)	 27.6/4 72.5/2 22.3/5 78.5/2	<u>1.AE</u> 1. 134 (45.6%) 2. 53 (53.5%) 3. 45 (45.9%) <u>2.SAE</u> 1. 6 (2.0%) 2. 3 (3.0%) 3. 1 (1.0%) <u>AE leading to discontinuation of drug:</u> 1. 1 (0.3%) 2. 0 3. 1 (1.0% p-value and 95% CI NR for all	NA for all	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: See above <u>Performance Bias</u>: See above <u>Detection Bias</u>: See above <u>Attrition Bias</u>: Low. Rates of discontinuation with similar patient loss across all 3 arms. <u>Reporting Bias</u>: See above <u>Other Bias:</u> See above **Applicability**: <u>Patient</u>: See above <u>Intervention</u>: See above <u>Comparator</u>: See above <u>Outcomes</u>: See above <u>Setting</u>: 64 sites across 10 countries: Austria, Belgium, Canada, Germany, Mexico, Poland, Portugal, Spain, and the United States

				P<0.001 <u>1 vs. 3</u> AD 48.2% (95% CI 41.9 to 54.6%) P<0.001 2. DLQI 0/1 at week 16: 1. 196 (66.7%) 2. 46 (46.5%) 3. 4 (4.1%) <u>1 vs. 2</u> AD 20.2% (95% CI 9.1 to 31.4%) P<0.004 <u>1 vs. 3</u> AD 62.2% (95% CI 55.5 to 68.9%) P<0.001	27/4 48.2/3 20.2/5 62.2/2			
3. Reich, et al.[17] IMMVENT DB, AC, Phase 3 RCT N=605 16 weeks	1. Risankizumab 150 mg at week 0, 4, 16, 28 2. Adalimumab 80 mg at week 0, 40 mg at week 1 then every 2 weeks Part A: Weeks 0-16 Part B: Weeks 17-44. Adalimumab intermediate responders (PASI≥50 to <90) re-randomized 1:1 to continue adalimumab 40 mg or switch to risankizumab 150 mg	<u>Demographics</u>: -Male 70% -Mean Wt.: 90 kg -Mean BSA Involvement: 17% -White 80% -Mean Age: 48 yo -Prior TNF use: 30% <u>Key Inclusion Criteria</u>: -Age ≥18 yrs -Chronic mod-severe plaque PsO ≥6 mos with: ≥10% BSA involvement; PASI ≥12; and sPGA ≥3 <u>Key Exclusion Criteria</u>: -Non-plaque PsO -Drug-induced PsO -Active ongoing inflammatory diseases other than PsO and PsA	**Part A** <u>ITT</u>: 1. 301 2. 304 <u>PP</u>: 1. 294 2. 291 <u>Attrition</u>: 1. 7 (2.3%) 2. 13 (4.2%) **Part B** <u>ITT</u>: 1. 53 2. 56 <u>PP</u>: 1. 51 2. 51 <u>Attrition</u>: 1. 2 (3.7%) 2. 5 (8.9%)	<u>Co-Primary Endpoint</u>: 1. PASI 90 at week 16: 1. 218 (72.4%) 2. 144 (47.4%) AD 24.9% (95% CI 17.5 to 32.4%) P<0.001 2. SPGA 0/1 at week 16: 1. 252 (83.7%) 2. 183 (60.2%) AD 23.3% (95% CI 16.6 to 30.1%) P<0.001 <u>Secondary Endpoints</u>: 1. PASI 100 at week 16: 1. 120 (40%) 2. 70 (23%) AD 16.7% (95% CI 9.5 to 23.9%) P<0.0001 2. PASI 90 at week 44 1. 35 (66%) 2. 12 (21%) AD 45%	24.9/5 23.3/5 16.7/6	<u>1.AE</u> 1. 168 (56%) 2. 173 (57%) <u>2.SAE</u> 1. 10 (3%) 2. 9 (3%) <u>AE leading to discontinuation of drug:</u> 1. 4 (1%) 2. 6 (2%)	NA for all	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: See above <u>Performance Bias</u>: See above <u>Detection Bias</u>: See above <u>Attrition Bias</u>: See above <u>Reporting Bias</u>: See above <u>Other Bias</u>: See above **Applicability**: <u>Patient</u>: See above <u>Intervention</u>: See above <u>Comparator</u>: Adalimumab is a TNFI, with different mechanism of activity than an IL-23 antagonist. <u>Outcomes</u>: See above <u>Setting</u>: 66 sites in 11 countries: Canada, Czech Republic, Finland, France, Germany, Mexico, Poland, Portugal, Sweden, Taiwan, and the United States

		-Prior exposure to risankizumab or adalimumab -History of allergy or hypersensitivity to biologic agent or its excipients		(95% CI 28.9 to 61.1%) P<0.0001	45/3			

Abbreviations: AC=active comparator; AD=adjusted difference; AE=adverse effects; BSA body surface area; CI = confidence interval; DB = double blind; DLQI = Dermatology Life Quality Index; IL=interleukin; IRT=interactive response technology; ITT=intention to treat; kg=kilogram; N=number of subjects; NA=not applicable; NNH=number needed to harm; NNT=number needed to treat; PASI= Psoriasis Area Severity Index; PC=placebo controlled; PP=per protocol; PsA=psoriatic arthritis; P=psoriasis; PsO=plaque psoriasis; RCT=randomized clinical trial; SAE=serious adverse effects; sPGA=static Physician's Global Assessment; TEAE=treatment-emergent adverse event ; TNFI=tumor necrosis factor inhibitor; yo=years old

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
adalimumab	HUMIRA PEN	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA PEN CROHN'S-UC-HS	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA PEN PSOR-UVEITS-ADOL HS	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA(CF) PEN	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA(CF) PEN CROHN'S-UC-HS	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA(CF) PEN PSOR-UV-ADOL HS	PEN IJ KIT	SQ	Y
adalimumab	HUMIRA	SYRINGEKIT	SQ	Y
adalimumab	HUMIRA PEDIATRIC CROHN'S	SYRINGEKIT	SQ	Y
adalimumab	HUMIRA(CF)	SYRINGEKIT	SQ	Y
adalimumab	HUMIRA(CF) PEDIATRIC CROHN'S	SYRINGEKIT	SQ	Y
etanercept	ENBREL MINI	CARTRIDGE	SQ	Y
etanercept	ENBREL SURECLICK	PEN INJCTR	SQ	Y
etanercept	ENBREL	SYRINGE	SQ	Y
etanercept	ENBREL	VIAL	SQ	Y
abatacept	ORENCIA CLICKJECT	AUTO INJCT	SQ	N
abatacept	ORENCIA	SYRINGE	SQ	N
abatacept/maltose	ORENCIA	VIAL	IV	N
anakinra	KINERET	SYRINGE	SQ	N
apremilast	OTEZLA	TAB DS PK	PO	N
apremilast	OTEZLA	TABLET	PO	N
baricitinib	OLUMIANT	TABLET	PO	N
belimumab	BENLYSTA	AUTO INJCT	SQ	N
belimumab	BENLYSTA	SYRINGE	SQ	N
belimumab	BENLYSTA	VIAL	IV	N
brodalumab	SILIQ	SYRINGE	SQ	N
canakinumab/PF	ILARIS	VIAL	SQ	N
certolizumab pegol	CIMZIA	KIT	SQ	N
certolizumab pegol	CIMZIA	SYRINGEKIT	SQ	N
golimumab	SIMPONI	PEN INJCTR	SQ	N
golimumab	SIMPONI	SYRINGE	SQ	N
golimumab	SIMPONI ARIA	VIAL	IV	N
guselkumab	TREMFYA	AUTO INJCT	SQ	N
guselkumab	TREMFYA	SYRINGE	SQ	N
infliximab	REMICADE	VIAL	IV	N
infliximab-abda	RENFLEXIS	VIAL	IV	N
infliximab-dyyb	INFLECTRA	VIAL	IV	N
ixekizumab	TALTZ AUTOINJECTOR	AUTO INJCT	SQ	N

ixekizumab	TALTZ AUTOINJECTOR (2 PACK)	AUTO INJCT	SQ	N
ixekizumab	TALTZ AUTOINJECTOR (3 PACK)	AUTO INJCT	SQ	N
ixekizumab	TALTZ SYRINGE	SYRINGE	SQ	N
natalizumab	TYSABRI	VIAL	IV	N
risankizumab-rzaa	SKYRIZI	SYRINGE	SQ	N
risankizumab-rzaa	SKYRIZI (2 SYRINGES) KIT	SYRINGEKIT	SQ	N
rituximab	RITUXAN	VIAL	IV	N
sarilumab	KEVZARA	PEN INJCTR	SQ	N
sarilumab	KEVZARA	SYRINGE	SQ	N
secukinumab	COSENTYX PEN	PEN INJCTR	SQ	N
secukinumab	COSENTYX PEN (2 PENS)	PEN INJCTR	SQ	N
secukinumab	COSENTYX (2 SYRINGES)	SYRINGE	SQ	N
secukinumab	COSENTYX SYRINGE	SYRINGE	SQ	N
tildrakizumab-asmn	ILUMYA	SYRINGE	SQ	N
tocilizumab	ACTEMRA ACTPEN	PEN INJCTR	SQ	N
tocilizumab	ACTEMRA	SYRINGE	SQ	N
tocilizumab	ACTEMRA	VIAL	IV	N
tofacitinib citrate	XELJANZ XR	TAB ER 24H	PO	N
tofacitinib citrate	XELJANZ	TABLET	PO	N
ustekinumab	STELARA	SYRINGE	SQ	N
ustekinumab	STELARA	VIAL	IV	N
vedolizumab	ENTYVIO	VIAL	IV	N

Appendix 2: Abstracts of Comparative Clinical Trials

Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: Results from IXORA-S, a phase 3 study[59]

BACKGROUND: Biologics targeting interleukin 17A (IL-17A) allow for rapid clearance of psoriatic plaques, with a clinically favorable safety profile.
OBJECTIVES: To compare the safety and efficacy of ixekizumab, an IL-17A antagonist, with the safety and efficacy of the IL-12/23 inhibitor ustekinumab through 52 weeks of treatment in the head-to-head trial IXORA-S.
METHODS: Patients were randomized to ixekizumab (n = 136) or ustekinumab (n = 166) and dosed per the approved labels. After 1 year, efficacy was assessed via improvements in Psoriasis Area and Severity Index (PASI) score (with PASI 90 indicating a 90% or greater improvement from baseline PASI score) and a static Physician's Global Assessment (sPGA) response of either 0 or 0 or 1, with dropouts counted as non-responders. Safety analyses included treatment-emergent adverse events (AEs).
RESULTS: At week 52, significantly more ixekizumab-treated patients (P < .01) reported PASI 90 (104 [76.5%]), an sPGA response of 0 (72 [52.9%]), or an sPGA response of 0 or 1 (110 [82.1%]) responses than did ustekinumab-treated patients (PASI 90, 98 [59.0%]; sPGA response of 0, 60 [36.1%]; and sPGA response of 0 or 1, 108 [65.1%]). Treatment-emergent AEs, serious AEs, and discontinuation rates were not different between the treatment groups. Injection site reactions occurred more frequently in the ixekizumab-treated group (ixekizumab, 22 [16.3%]; ustekinumab, 2 [1.2%]) (P < .001).
LIMITATIONS: This study was not designed to compare safety end points related to rare events.
CONCLUSIONS: Compared with ustekinumab, ixekizumab showed superior efficacy and comparable safety outcomes through 52 weeks of treatment.

Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial.[60]

BACKGROUND: Antibodies targeting interleukin (IL)-23 and IL-17A effectively treat moderate-to-severe psoriasis. ECLIPSE is the first comparator study of an IL-23p19 inhibitor, guselkumab, versus an IL-17A inhibitor, secukinumab. The primary objective of this study was to show superiority of clinical response at week 48 for guselkumab versus secukinumab.
METHODS: In this phase 3, multicenter, double-blind, randomised, comparator-controlled trial at 142 outpatient clinical sites in nine countries (Australia, Canada, Czech Republic, France, Germany, Hungary, Poland, Spain, and the USA), eligible patients were aged 18 years or older, had moderate-to-severe plaque-type psoriasis, and were candidates for phototherapy or systemic therapy. Eligible patients were randomly assigned with permuted block randomization using an interactive web response system to receive either guselkumab (100 mg at weeks 0 and 4 then every 8 weeks) or secukinumab (300 mg at weeks 0, 1, 2, 3, and 4, and then every 4 weeks). The primary endpoint, the proportion of patients in the intention-to-treat population who achieved 90% reduction or more from baseline of Psoriasis Area and Severity Index (PASI 90 response) at week 48, and major secondary endpoints (the proportions of patients in the guselkumab group and in the secukinumab group who achieved a PASI 75 response at both weeks 12 and 48, a PASI 90 response at week 12, a PASI 75 response at week 12, a PASI 100 response at week 48, an Investigator's Global Assessment [IGA] score of 0 [cleared] at week 48, and an IGA score of 0 or 1 [minimal] at week 48) were to be tested in a fixed sequence to control type I error rate. Safety was evaluated in patients who received one or more doses of study drug from week 0 to 56.
FINDINGS: This study was done between April 27, 2017, and Sept 20, 2018. 1048 eligible patients were enrolled and, of these, 534 were assigned to receive guselkumab and 514 to receive secukinumab. The proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group (451 [84%]) than in the secukinumab group (360 [70%]; p<0·0001). Although non-inferiority (margin of 10 percentage points) was established for the first major secondary endpoint (452 [85%] of patients in the guselkumab group vs. 412 [80%] of patients in the secukinumab group achieving a PASI 75 response at both weeks 12 and 48), superiority was not established (p=0·0616). Consequently, formal statistical testing was not done for subsequent major secondary endpoints. Proportions of patients with adverse events, infections, and serious adverse events were similar between the two treatments and, in general, safety findings were consistent with registrational trial observations.

INTERPRETATION: Guselkumab showed superior long-term efficacy based on PASI 90 at week 48 when compared with secukinumab for treating moderate-to-severe psoriasis. This finding could assist health-care providers in their decision making process when selecting a biologic for treating moderate-to-severe psoriasis.

Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis[61]

BACKGROUND: Biologic therapies are widely used in patients with ulcerative colitis. Head-to-head trials of these therapies in patients with inflammatory bowel disease are lacking.

METHODS: In a phase 3b, double-blind, double-dummy, randomized trial conducted at 245 centers in 34 countries, we compared vedolizumab with adalimumab in adults with moderately to severely active ulcerative colitis to determine whether vedolizumab was superior. Previous exposure to a tumor necrosis factor inhibitor other than adalimumab was allowed in up to 25% of patients. The patients were assigned to receive infusions of 300 mg of vedolizumab on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (plus injections of placebo) or subcutaneous injections of 40 mg of adalimumab, with a total dose of 160 mg at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter until week 50 (plus infusions of placebo). Dose escalation was not permitted in either group. The primary outcome was clinical remission at week 52 (defined as a total score of ≤2 on the Mayo scale [range, 0 to 12, with higher scores indicating more severe disease] and no sub score >1 [range, 0 to 3] on any of the four Mayo scale components). To control for type I error, efficacy outcomes were analyzed with a hierarchical testing procedure, with the variables in the following order: clinical remission, endoscopic improvement (sub score of 0 to 1 on the Mayo endoscopic component), and corticosteroid-free remission at week 52.

RESULTS**:** A total of 769 patients underwent randomization and received at least one dose of vedolizumab (383 patients) or adalimumab (386 patients). At week 52, clinical remission was observed in a higher percentage of patients in the vedolizumab group than in the adalimumab group (31.3% vs.. 22.5%; difference, 8.8 percentage points; 95% confidence interval [CI], 2.5 to 15.0; P = 0.006), as was endoscopic improvement (39.7% vs.. 27.7%; difference, 11.9 percentage points; 95% CI, 5.3 to 18.5; P<0.001). Corticosteroid-free clinical remission occurred in 12.6% of the patients in the vedolizumab group and in 21.8% in the adalimumab group (difference, -9.3 percentage points; 95% CI, -18.9 to 0.4). Exposure-adjusted incidence rates of infection were 23.4 and 34.6 events per 100 patient-years with vedolizumab and adalimumab, respectively, and the corresponding rates for serious infection were 1.6 and 2.2 events per 100 patient-years.

CONCLUSIONS: In this trial involving patients with moderately to severely active ulcerative colitis, vedolizumab was superior to adalimumab with respect to achievement of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission.

Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial.[62]

OBJECTIVE: To examine the efficacy of methotrexate monotherapy relative to etanercept monotherapy and the value of combining methotrexate and etanercept for the treatment of patients with psoriatic arthritis (PsA).

METHODS: In this double-blind study, 851 patients with PsA were randomized to 1 of 3 treatment arms, as follows: oral methotrexate (20 mg) plus subcutaneous placebo given weekly (n = 284), subcutaneous etanercept (50 mg) plus oral placebo given weekly (n = 284), or subcutaneous etanercept (50 mg) plus oral methotrexate (20 mg) given weekly (combination therapy; n = 283). The American College of Rheumatology 20% improvement (ACR20) response and Minimal Disease Activity (MDA) response at week 24 were the primary end point and key secondary end point, respectively. Other measures of inflammatory arthritis, radiographic progression, and nonarticular disease manifestations were also assessed.

RESULTS: Patients with PsA had a mean ± SD age of 48.4 ± 13.1 years, and the mean ± SD duration of PsA was 3.2 ± 6.3 years (median 0.6 years). ACR20 and MDA response rates at week 24 were significantly greater in patients who received etanercept monotherapy compared with those who received methotrexate monotherapy (ACR20, 60.9% versus 50.7% of patients [P = 0.029]; MDA, 35.9% versus 22.9% of patients [P = 0.005]), and both were significantly greater in the combination therapy group compared with the methotrexate monotherapy group at week 24 (ACR20, 65.0% versus 50.7% of patients [P = 0.005]; MDA, 35.7% versus 22.9% of patients [P = 0.005]). Other secondary outcomes (ACR50 and ACR70 response rates, proportions of patients achieving a Very Low Disease

Activity score, and PsA disease activity scores) showed between-group differences that were consistent with the primary and key secondary end point results. Furthermore, patients in both etanercept treatment arms showed less radiographic progression at week 48 compared with patients who received methotrexate monotherapy. Outcomes were similar in the combination therapy and etanercept monotherapy groups, except for some skin end points. No new safety signals were seen.
CONCLUSION: Etanercept monotherapy and combination therapy with etanercept and methotrexate showed greater efficacy than methotrexate monotherapy in patients with PsA, according to the ACR and MDA response rates and extent of radiographic progression at follow-up. Overall, combining methotrexate and etanercept did not improve the efficacy of etanercept.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to October Week 3 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to October 23, 2019

1 Adalimumab/	4685
2 Etanercept/	5199
3 tocilizumab.mp.	2504
4 Abatacept/	1847
5 Infliximab/	8777
6 Rituximab/	11624
7 golimumab.mp.	1014
8 apremilast.mp.	456
9 tofacitinib.mp.	1010
10 certolizumab.mp.	1074
11 Certolizumab Pegol/	515
12 secukinumab.mp.	750
13 Abatacept/	1847
14 ixekizumab.mp.	357
15 Ustekinumab/	837
16 Natalizumab/	1378
17 vedolizumab.mp.	683
18 brodalumab.mp.	219
19 guselkumab.mp.	120
20 anakinra.mp.	1462
21 canakinumab.mp.	570
22 sarilumab.mp.	71
23 baricitinib.mp	188
24 guselkumab.mp	120
25 ixekizumab	357
26 risankizumab.mp	40
27 tildrakizumab.mp	64
23 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	36181
24 Arthritis, Psoriatic/or Arthritis, Rheumatoid/or Arthritis/ or Arthritis, Juvenile	61751
25 PSORIASIS/	17093
27 Spondylitis, Ankylosing/	6564
28 Crohn Disease/	20265
29 Colitis, Ulcerative/	15589
30 Arthritis, Juvenile/	5065
31 24 or 25 or 26 or 27 or 28 or 29 or 30	111992
32 23 and 31	14302

33 limit 32 to (yr="2018-current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 396

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RINVOQ safely and effectively. See full prescribing information for RINVOQ.

RINVOQ™ (upadacitinib) extended-release tablets, for oral use
Initial U.S. Approval: 2019

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving RINVOQ. (5.1)**
- **If a serious infection develops, interrupt RINVOQ until the infection is controlled. (5.1)**
- **Prior to starting RINVOQ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting RINVOQ. (5.1)**
- **Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)**
- **Lymphoma and other malignancies have been observed in patients treated with RINVOQ. (5.2)**
- **Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions. (5.3)**

INDICATIONS AND USAGE

RINVOQ is a Janus kinase (JAK) inhibitor indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. (1)
Limitation of Use: Use of RINVOQ in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of RINVOQ is 15 mg once daily. (2.1)
- RINVOQ may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs. (2.1)
- Avoid initiation or interrupt RINVOQ if absolute lymphocyte count is less than 500 cells/mm^3, absolute neutrophil count is less than 1000 cells/mm^3, or hemoglobin level is less than 8 g/dL. (2.2, 2.3, 5.4)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 15 mg (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid use of RINVOQ in patients with active, serious infection, including localized infections. (5.1)
- Malignancy: Consider the risks and benefits of RINVOQ treatment prior to initiating therapy in patients with a known malignancy. (5.2)
- Thrombosis: Consider the risks and benefits prior to treating patients who may be at increased risk of thrombosis. Promptly evaluate patients with symptoms of thrombosis and treat appropriately. (5.3)
- Gastrointestinal Perforations: Use with caution in patients who may be at increased risk. (5.4)
- Laboratory Monitoring: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.5)
- Embryo-Fetal Toxicity: RINVOQ may cause fetal harm based on animal studies. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.6, 8.1, 8.3)
- Vaccinations: Avoid use of RINVOQ with live vaccines. (5.7)

ADVERSE REACTIONS

Adverse reactions (greater than or equal to 1%) are: upper respiratory tract infections, nausea, cough, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- RINVOQ should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors (e.g., ketoconazole). (7.1)
- Coadministration of RINVOQ with strong CYP3A4 inducers (e.g., rifampin) is not recommended. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Hepatic Impairment: RINVOQ is not recommended in patients with severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SKYRIZI safely and effectively. See full prescribing information for SKYRIZI.

SKYRIZI™ (risankizumab-rzaa) injection, for subcutaneous use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

SKYRIZI is an interleukin-23 antagonist indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. (1)

DOSAGE AND ADMINISTRATION

- 150 mg (two 75 mg injections) administered by subcutaneous injection at Week 0, Week 4 and every 12 weeks thereafter. (2.1)

DOSAGE FORMS AND STRENGTHS

- Injection: 75 mg/0.83 mL in each single-dose prefilled syringe. (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Infections: SKYRIZI may increase the risk of infection. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If such an infection develops, do not administer SKYRIZI until the infection resolves. (5.1)
- Tuberculosis (TB): Evaluate for TB prior to initiating treatment with SKYRIZI. (5.1)

ADVERSE REACTIONS

Most common adverse reactions (≥ 1%) are upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Avoid use of live vaccines in patients treated with SKYRIZI. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2019

Biologics for Autoimmune Diseases

Goal(s):

- Restrict use of biologics to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of high value products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All biologics for autoimmune diseases (both pharmacy and physician-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. Approved and Funded Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo		
Adalimumab (HUMIRA) and biosimilars	≥18 y	≥6 yo(Humira) ≥18 yo(biosimilars)	≥2 yo (Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥2 yo (Humira) HS ≥ 12 yo
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			Oral Ulcers associated with BD ≥ 18 yo
Baricitinib (OLUMIANT)						≥18 yo		
Broadalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo

								TRAPS ≥ 4 yo HIDS ≥ 4 yo MKD ≥ 4 yo FMF ≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo		Nr-axSpA ≥ 18 yo
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥18 yo (biosimilars)	≥18 yo	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo				≥18 yo	≥18 yo	≥18 yo (Simponi)	
Guselkumab (TREMFYA)				≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo	
Ixekizumab (TALTZ)	≥ 18 yo			≥18 yo	≥18 yo			
Risankizumab-rzaa (SKYRIZI)				≥18 yo				
Rituximab (RITUXAN)						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥2yo MPA ≥ 2 yoPemphigus Vulgaris ≥18 yo
Sarilumab (KEVZARA)						≥18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			
Tildrakizumab-asmn (ILUMYA)				≥18 yo				
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo
Tofacitinib (XELJANZ)					≥18 yo	≥18 yo	≥18 yo	
Upadacitinib (RINVOQ)						≥18 yo		
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo		≥18 yo	
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: BD = Behcet's Disease; CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; HS: Hidradenitis Suppurativa; MKD = Mevalonate Kinase Deficiency; MPA = microscopic polyangiitis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; nr-axSpA = non-radiographic axial spondyloarthritis; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #5
5. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. May approve for up to 3 months to allow time for screening.

Approval Criteria		
6. Is the diagnosis Juvenile Idiopathic Arthritis, non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Non-infectious Posterior Uveitis, or one of the following syndromes: • Familial Cold Autoinflammatory Syndrome • Muckel-Wells Syndrome • Neonatal Onset Multi-Systemic Inflammatory Disease • Tumor Necrosis Factor Receptor Associated Periodic Syndrome • Hyperimmunoglobulin D Syndrome • Mevalonate Kinase Deficiency • Familial Mediterranean Fever • Giant Cell Arteritis • Cytokine Release Syndrome • Non-radiographic axial spondyloarthritis • Oral ulcers associated with Behcet's Disease AND Is the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #7
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to #8	**No:** Go to #9
8. If the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® product or an Enbrel® product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to #10	**No**: Go to #12
10. Is the plaque psoriasis severe in nature, which has resulted in functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.
11. Has the patient failed to respond or had inadequate response to each of the following first-line treatments: • 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%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; and • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
12. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #13	**No:** Go to #17
13. Has the patient failed to respond or had inadequate response to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; or • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira® product or an Enbrel® product for at least 3 months? • AND • Is the patient on concurrent DMARD therapy with plans to continue concomitant use?	**Yes:** Go to #14 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.
14. Is the request for tofacitinib, baricitinib, or upadacitinib?	**Yes:** Go to #16	**No:** Go to #15

Approval Criteria		
15. 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
16. Is the request for adalimumab in an adult with moderate-to-severe Hidradenitis Suppurativa (HS)?	**Yes:** Go to # 17	**No:** Go to # 18
17. Has the patient failed to respond, had inadequate response, or do they have an intolerance or contraindication to a 90 day trial of conventional HS therapy (e.g. oral antibiotics)? Note: Treatment of moderate-to-severe HS with adalimumab is funded on the Prioritized List of Health Services per Guideline Note 198	**Yes:** Approve for up to 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness**.**
18. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 19	**No:** Go to # 20

Approval Criteria		
19. Has the patient failed to respond or had inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? AND • Has the patient tried and failed a 3 month trial of a Humira® product?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
20. Is the diagnosis for an FDA approved diagnosis and age as outlined in Table 1, and is the requested drug rituximab for *induction or maintenance* of remission?	**Yes:** Approve for length of treatment.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for treatment of psoriatic arthritis or rheumatoid arthritis?	**Yes:** Go to # 4	**No:** Go to # 2
2. Is the request for continuation of adalimumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to # 3	**No:** Go to # 5

Renewal Criteria		
3. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: A) a reduction of 25% or more in the total abscess and inflammatory nodule count, AND B) no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
4. 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 #4	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *2/20 (DM); 5/19; 1/19; 1/18; 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *TBD; 7/1/2019; 3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/2*

Belimumab (Benlysta®)

Goal(s):
- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:
- 6 months

Requires PA:
- Benlysta® (belimumab)

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/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the patient have severe active lupus nephritis or severe active central nervous system lupus?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient aged 5 years or older?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the patient currently on other biologic therapy or intravenous cyclophosphamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.	**No:** Go to # 7
7. Is the drug being prescribed by or in consultation with a rheumatologist or a provider with experience treating SLE?	**Yes:** Go to # 8	**No:** Pass to RPh. Deny; medical appropriateness
8.Does the patient have active autoantibody-positive SLE and is a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index	**Yes:** Go to # 9. Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient currently receiving standard of care treatment for Systemic Lupus Erythematosus (SLE) e.g., hydroxychloroquine, systemic corticosteroids, non-steroidal anti-inflammatory drugs, azathioprine, mycophenolate, or methotrexate?	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied as monotherapy in patients with SLE.

Renewal Criteria		
1. Is the patient currently on other biologic therapy or intravenous cyclophosphamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.	**No:** Go to #2
2. Has the patient's SLE disease activity improved as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index	**Yes:** Approve for 6 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *2/2020 DM, 5/18 (DM)*
Implementation: *3/1/2020; 7/1/18*