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Drug Class Update: Biologics for Autoimmune Conditions

Date of Review: January 2018

Date of Last Review: July 2017
End Date of Literature Search: 10/30/2017

Generic Name: sarilumab **Brand Name (Manufacturer)/Dossier Received:** Kevzara® (Sanofi and Regeneron Pharmaceuticals, Inc.)/Yes
Generic Name: guselkumab **Brand Name (Manufacturer)/Dossier Received:** Tremfya® (Janssen)/Yes

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

Purpose for Class Update:
To define place in therapy and review comparative biologic response modifier evidence for 2 new biologic response modifiers recently approved by the United States (U.S.) Food and Drug Administration (FDA): sarilumab for the treatment of moderate to severe rheumatoid arthritis and guselkumab for the treatment of moderate to severe plaque psoriasis. In addition, new comparative evidence between biologics for autoimmune conditions will be reviewed.

Research Questions:
1. Is there new comparative evidence that biologics for autoimmune conditions differ in efficacy or effectiveness for alleviating symptoms and stabilizing disease in adults or children with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), or plaque psoriasis (PsO)?
2. Is there new comparative evidence that biologics for autoimmune conditions differ in serious adverse events or tolerability when used to manage adults or children with RA, JIA, AS, PsA, CD, UC, or PsO?
3. Are there specific subpopulations based on age, gender, race, disease severity, or concomitant therapies for which one biologic is better tolerated or more effective than other available biologics for specific autoimmune conditions?

Conclusions:
CLASS UPDATE
- One systematic review (Cochrane Collaboration on RA)[1], 5 new clinical practice guidelines from the National Institute for Health and Care Excellence (NICE) and the European League Against Rheumatism (EULAR) [2-6], 8 new indications approved by the FDA[7-12], and one new formulation approved by the FDA[13] were identified which provide clinically meaningful new evidence for these drugs. The evidence is applicable to Medicaid patients; however, no subgroup analyses specific to Medicaid patients were provided in any of the studies reviewed. Several systematic reviews and meta-analyses were excluded from this review due to poor quality.[14-17]

- There is insufficient new evidence to determine if biologics differ in effectiveness for alleviating symptoms and stabilizing patients with JIA, AS, PsA, CD, UC, or PsO. There is moderate quality evidence that compares sarilumab and adalimumab in RA as discussed below.[18]
- Compared with placebo, there is high quality evidence from one systematic review that American College of Rheumatology (ACR) 50% improvement criteria (ACR50) is improved with certolizumab pegol 200 mg every other week in RA (relative risk [RR] 3.80; 95% confidence interval [CI] 2.42-5.95; absolute risk reduction [ARR] 25%; number needed to treat [NNT] 4 at 24 weeks).[1] There is insufficient new evidence to determine comparative efficacy of certolizumab pegol versus other biologic modifiers.
- There is insufficient new comparative evidence to determine if biologics differ in harms except for the comparison of sarilumab and adalimumab which is discussed below.[18]
- There is insufficient new comparative evidence to determine if there are specific subpopulations for which one biologic agent is better tolerated or more effective than other available agents.
- New high quality guidelines identified for CD, PsO, PsA, and RA support the current PDL and PA criteria.[2-6]

SARILUMAB

- There is moderate quality evidence that treatment with sarilumab 150 mg subcutaneously (SC) every 2 weeks and sarilumab 200 mg SC every 2 weeks results in a statistically significant improvement in symptoms compared to placebo as evaluated by ACR 20% improvement criteria (ACR20) at 24 weeks in patients with RA (ARR 22.1-35.6% and 27.2-44.0%, respectively; NNT 3-5 and 3-4, respectively; studies = 2).[19,20] There is also moderate quality evidence that treatment with sarilumab 200 mg SC every 2 weeks results in a statistically significant change from baseline in Disease Activity Score-28 (DAS-28)-Erythrocyte Sedimentation Rate (ESR) at week 24 (-3.28 vs. -2.20; 95% CI -1.36 to -0.79; p<0.0001) as well as achievement of ACR20/50/70 at week 24 (71.7% vs. 58.4%/45.7% vs. 29.7%/23.4% vs. 11.9%, respectively) compared to adalimumab 40 mg SC every 2 weeks in patients with RA.[18] A significant difference also was found in the secondary endpoint of mean improvement in HAQ-DI score from baseline to week 24 for sarilumab compared to adalimumab (-0.61 vs. -0.43; 95% CI -0.31 to -0.06; p=0.0037).[18] There is insufficient comparative evidence for RA radiographic progression for sarilumab and adalimumab as this was not studied in the trial.[18]
- There is moderate quality evidence that adalimumab 40 mg every 2 weeks and sarilumab 200 mg every 2 weeks have similar risk of infections (27.7% vs. 28.8%) and serious adverse events (6.5% vs. 4.9%) but that sarilumab has a higher risk of neutropenia (13.6% vs. 0.5%) based on data from a 24 week study which was not powered to determine differences in adverse effects.[18] There is insufficient evidence to determine long-term safety of sarilumab compared to other treatments for moderate-to-severe RA.
- There is insufficient evidence to determine differences in efficacy or safety of sarilumab compared to other biologic agents for specific subpopulations.

GUSELKUMAB

- Moderate quality evidence from 2 Phase 3 trials (VOYAGE 1 and VOYAGE 2) demonstrated comparative efficacy of guselkumab with adalimumab in treating PsO.[21, 22] At week 16 in the VOYAGE 1 trial, patients who received guselkumab demonstrated higher achievement in the Psoriasis Area and Severity Index (PASI) 90 (73.3% vs. 49.7%; ARR = 23.6%, NNT = 5; p <0.001), and Investigator's Global Assessment (IGA) 0/1 (85.1% vs. 65.9%; ARR = 19.2%; NNT =6; p< 0.001) scores than patients treated with adalimumab.[21] Similar results were observed at week 16 when guselkumab was compared to adalimumab during the VOYAGE 2 trial. During the withdrawal and retreatment phase of VOYAGE 2, adalimumab non-responders started on guselkumab had PASI 90 response rates of 66% at week 48.[22] Both Phase 3 trials demonstrated the effectiveness of guselkumab 100mg in treating patients with moderate to severe PsO when compared to placebo and the active comparator, adalimumab.
- The most common adverse events for guselkumab observed during clinical trials were upper respiratory tract infections, injection-site reactions, and headaches. Rates of adverse events and serious adverse events observed with guselkumab were comparable to placebo and adalimumab. In the Voyage

1 trial, discontinuation rates through 48 weeks due to adverse effects with guselkumab were 2.7% compared to 3.6% with adalimumab.[21] A higher proportion of adalimumab patients had injection site reactions (6.9% vs 4.5%) compared to guselkumab.[23] Pooled data from VOYAGE 1 and VOYAGE 2 did not demonstrate an increased risk of suicidal ideation or adverse cardiovascular events with guselkumab.[23]

- There is insufficient evidence to determine long term safety with guselkumab due to limited duration of published clinical trials. VOYAGE 1 and 2 have extended open-label treatment arms that are currently investigating treatment with guselkumab through 252 weeks.

Recommendations:

- Modify PA criteria as follows:
  - Add new and updated indications for previously approved drugs to the approved indications table
  - Add guselkumab to the PA criteria for use in moderate-to-severe plaque psoriasis for ages ≥18 years
  - Add sarilumab to the PA criteria for use in moderate-to-severe rheumatoid arthritis for ages ≥18 years
  - Remove natalizumab (Tysabri) from biologic PA criteria as separate natalizumab criteria were approved at the November 2017 P and T meeting
- After evaluating comparative costs in executive session, the PA criteria was modified to require trial and failure of preferred Humira® or Enbrel® products instead of adalimumab or etanercept.

Previous Conclusions:

- For the treatment of RA, four systematic reviews provide moderate quality evidence to support the efficacy of abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib in improving disease activity and function compared to conventional disease modifying antirheumatic drug (DMARD) therapy. In head-to-head trials of biologic therapy combined with a DMARD versus adalimumab monotherapy, adalimumab was similar to abatacept, tofacitinib, and certolizumab pegol in rates of remission achieved, American College of Rheumatology (ACR) response, and improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI).
- Compared with placebo, there is high quality evidence that patients on a tumor necrosis factor (TNF) inhibitor are 3 to 4 times more likely to achieve an improvement in ankylosing spondylitis (AS) clinical symptoms as measured by Assessment of Spondyloarthritis (ASAS) 40 response within 6 months (adalimumab: RR 3.53, 95% CI 2.49 to 4.91; etanercept: RR 3.31, 95% CI 2.38 to 4.53; golimumab: RR 2.90, 95% CI 1.90 to 4.23; infliximab: RR 4.07, 95% CI 2.80 to 5.74, with a 25% to 40% absolute difference between treatment and placebo groups. There is a lack of head to head trials to define superiority of one agent over another for the treatment of AS.
- In 6 direct comparative trials evaluating treatment of adults with PsO ustekinumab, secukinumab, and ixekizumab were superior to etanercept for disease severity, measured by the Psoriasis Area Severity Index (PASI) 90 and 100. Secukinumab and brodalumab were superior to ustekinumab in PASI 90 and 100. Refer to Table 6 for specific results of the six different head-to-head trials. One-year follow-up of pivotal trials demonstrate that etanercept, ustekinumab, secukinumab, and brodalumab have comparable safety profiles when used for the treatment of psoriasis. There is limited comparative data in pediatric patients.
- There is moderate to high quality evidence of no increase in the risks of breast cancer, lymphoma, or non-melanoma skin cancer (NMSC) with TNF inhibitors compared to placebo in RA studies. There is insufficient evidence on total malignancy risk. In IBD, PsA, and PsO patients, TNF inhibitors were not associated with elevated cancer risk compared to control groups.
- Evidence is inconclusive for withdrawals due to adverse events, rates of cancer occurrence, and rates of serious adverse events with biological response modifiers compared to conventional therapy.

- There is moderate quality evidence that treatment with brodalumab 210 mg every 2 weeks results in a statistically significant improvement in symptoms compared to placebo (as evaluated by PASI75) in patients with moderate to severe PsO (absolute risk reduction [ARR] of 79 to 81%, number-needed-to-treat [NNT] 2). Evaluation of symptoms using a static physician's global assessment (sPGA) score of 0 or 1 corresponding to clear or almost clear skin, resulted in similar improvements.
- There is moderate quality evidence that compared to ustekinumab, more patients with PsO treated with brodalumab achieved complete disease clearance (PASI100 or sPGA of 0) at 12 weeks (37-44% vs. 19-22%; ARR 18-22%, NNT 5-6). The proportion of PsO patients with 75% improvement in PASI score was also improved with brodalumab treatment compared to ustekinumab (low quality evidence).
- There is insufficient evidence to determine differences in long-term efficacy, remission rates, health-related quality of life, or functional improvement with brodalumab compared to other treatments for moderate to severe PsO.
- There is insufficient evidence to determine long-term safety of brodalumab or differences in safety compared to currently available treatments for moderate to severe plaque psoriasis. During the clinical trial program, 10 patients treated with brodalumab attempted suicide, and 6 patients had completed suicides. In order to mitigate and further monitor these safety concerns including increased risk for suicidality, brodalumab is only available through a Risk Evaluation and Mitigation Strategy (REMS) program. Furthermore, due to significant safety concerns associated with long-term treatment, discontinuation of brodalumab is recommended if adequate response is not achieved within 12 to 16 weeks.
- There is insufficient evidence to determine differences in efficacy or safety of brodalumab compared to other biologic agents for specific demographics or populations including subgroups based on age, gender, ethnicity, prior treatment or concurrent psoriasis treatments, disease duration or severity, or concomitant psoriatic arthritis.
- There is no evidence regarding the efficacy or safety of brodalumab for conditions other than moderate to severe plaque psoriasis. It has also been evaluated in clinical trials for the treatment of psoriatic arthritis and axial spondyloarthritis though trials were discontinued with due to safety concerns associated with brodalumab use.

Previous Recommendations:

- Modify PA criteria to reflect updated indications and age ranges for specific biologic response modifiers as follows:
    - Decrease age for abatacept to ≥ 2 years old for juvenile idiopathic arthritis
    - Decrease age for etanercept to ≥ 4 years old for plaque psoriasis
    - Add Crohn's Disease indication for ustekinumab for patients ≥ 18 years
- Remove alefacept from PA criteria as it is no longer marketed in the United States.
- Require trial and failure of adalimumab or enteracept for arthritic or psoriatic conditions or ankylosing spondylitis before advancing to another biologic agent. Require trial and failure of adalimumab before advancing to another biologic for Crohn's Disease.
- Modify the PA criteria to required TB screening prior to initial approval and renewal criteria to ascertain patient response to therapy.
- Because brodalumab is associated with significant safety concerns including suicidal ideation and behavior, add brodalumab as a non-preferred drug to the PDL. Modify PA criteria to include brodalumab for use in moderate to severe plaque psoriasis.
- After evaluation of comparative costs in executive session, no PDL changes were recommended.

Background:

Rheumatoid Arthritis

RA is an autoimmune inflammatory disease that causes cartilage damage, bone erosions, and eventually joint deformity. Other tissues and organs, including the heart, kidney, and lungs, may also be affected. Inflammation in RA is mediated by activation of T-cells, B-cells, and macrophages which leads to expression of cytokines such as tumor necrosis factor and interleukins. In 2005, the prevalence of RA in the U.S. was estimated to be 0.6% of the adult population.[24] The diagnosis of RA increases after the fourth decade of life and is 3 times more likely in women than men.[25] According to the ACR, first-line treatment of early RA is an oral nonbiologic disease-modifying antirheumatic drug (DMARD) such as methotrexate (MTX), leflunomide, sulfasalazine, or hydroxychloroquine.[26] Monotherapy with MTX is the preferred therapy.[26] This recommendation is based on low quality evidence, but has strong support from the ACR panel due to ease of patient access and relatively low cost of therapy.[26] For patients with established RA with continued disease activity despite DMARD therapy, biologics are recommended to improve function and control RA symptoms.[26] The TNF inhibitors adalimumab, certolizumab, etanercept, golimumab, and infliximab are approved by FDA to manage RA. Other injectable biologics approved to manage RA are abatacept, anakinra, rituximab, sarilumab, and tocilizumab. One oral agent, tofacitinib, a janus kinase inhibitor, was approved by FDA for RA in 2012. No head-to-head comparative effectiveness trials have been conducted in this drug class with the exception of one trial that compared adalimumab with sarilumab.[18] This trial is discussed in the drug evaluation for sarilumab.[18,27]

Primary endpoints used in RA clinical trials are ACR response, the Health Assessment Questionnaire Disability Index (HAQ-DI), and the DAS-28. The ACR response is considered a measure of efficacy and evaluates tender joint count, swollen joint count, patient's assessment of pain, patient's and physician's global assessments of disease activity, patient's assessment of physical function, and laboratory evaluation of an acute-phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein level [CRP]).[28] ACR20 criteria is met when patients have at least 20% improvement in tender and swollen joint counts and at least 20% improvement in at least 3 of the 7 domains.[27] ACR50 and ACR70 criteria correspond to improvement of at least 50% and 70%, respectively, in tender and swollen joints and at least 50% and 70% improvement, respectively, at least 3 of the 7 domains.[27] The HAQ-DI is a self-reported measure of functional capacity (total score 0 to 3).[27] Scores of 0 to 1 are generally considered mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[27] A decreases 0.22-0.25 is generally considered the minimum clinically important difference for this scale.[29] However, one study has also indicated that a greater decrease of -0.375 may be needed to be clinically significant.[30] The DAS-28 is another index of disease activity (similar to the ACR response) which assesses 28 joints in swelling, tenderness, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP, and patient global assessment of health.[27,31] A DAS-28 score greater than 5.1 corresponds to high disease activity and less than 3.2 corresponds to low disease activity.[27] A DAS-28 score of 2.6 is considered to correspond to remission.[27]

Juvenile Idiopathic Arthritis

JIA is diagnosed in children under the age of 16 years who present with joint inflammation of unknown etiology lasting longer than 6 weeks.[32] In 2001, the International League of Associations of Rheumatology (ILAR) proposed classification criteria for chronic childhood arthritis to enhance diagnosis and optimize treatment.[32] The umbrella term "juvenile idiopathic arthritis" was chosen and the disease was subdivided into 7 categories according to clinical presentation and disease course.[32] The 7 categories are: systemic arthritis, oligoarthritis, rheumatoid factor (RF) negative polyarthritis, RF positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis.[32] The oligoarticular subtype is the most common.[33] JIA is the most common pediatric rheumatic disease and prevalence rates have been reported as 1.6 to 86.0 cases per 100,000 children.[33] JIA treatment goals include: suppression of inflammation, achievement of remission, relief of pain, maintenance of function and minimizing toxicity.[34] Nonsteroidal anti-inflammatory drugs (NSAIDs) have a role in treating pain associated with mild disease.[34] Intra-articular steroid injections are most commonly used in patients with oligoarticular JIA.[34] Disease-modifying agents such as MTX have demonstrated efficacy and safety; however some patients do not respond to DMARD therapy and progress to treatment with biologic

agents.[34] Biologic agents are selected according to the presenting symptoms such as active joint counts and JIA stratification by presence of active systemic features such as fever, evanescent rash, lymphadenopathy, hepatomegaly, splenomegaly, or serositis.[35] Effective therapies include TNF inhibitors (adalimumab, etanercept and infliximab) and abatacept (a T-cell inhibitor).[35] Interleukin inhibitors such as canakinumab and tocilizumab are two additional agents used to manage the systemic form of JIA.[35]

Ankylosing Spondylitis

AS is a chronic rheumatic disorder that primarily affects the sacroiliac joints and spine.[36] Bone inflammation results in inflammation of entheses, or attachment points between tendon, ligament, and bone.[36] Cytokine production released during inflammation affects osteoclast and osteoblast activity which can lead to paradoxical systemic bone loss, despite new bone formation which causes fusion of joints or the spine.[37] Prevalence estimates in the US are between 0.9 to 1.4% of the adult population.[38] AS is more common in males than females by 5 to 1, with a peak age of onset between 15 to 35 years of age.[36] Diagnosis is based on radiologic confirmation of sacroiliitis and the presence of at least one clinical symptom: low back pain for at least 3 months, limited lumbar spine motion, or decreased chest expansion for age and sex.[39] Patients who have chronic pain and other features suggestive of spondyloarthritis (SpA) without radiologic changes are classified as having nonradiographic axial SpA.[40] Organ involvement can result in uveitis, psoriasis, and inflammatory bowel disease (IBD).[38] Guidelines for management of AS were updated in 2010 by the Assessments in Ankylosing Spondylitis International Society (ASA) and the European League against Rheumatism (EULAR).[41] NSAIDs and exercise are recommended as first-line therapies to alleviate pain and stiffness.[38,41] TNF inhibitors are recommended for patients with persistent disease activity despite conventional treatment.[41] Five TNF inhibitors including infliximab, etanercept, adalimumab, certolizumab, and golimumab are proven to provide sustained improvement in disease activity and patient functioning as assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDI) and Functional Index (BASFI) scores.[38] The anti–interleukin monoclonal antibody secukinumab has also demonstrated efficacy in treating AS.[38] There is no evidence for the efficacy of systemic glucocorticoids or disease-modifying antirheumatic drugs (DMARDs) in the treatment of AS, although sulfasalazine may be considered for patients with peripheral arthritis.[41]

Plaque Psoriasis

PsO is a chronic, inflammatory, immune-mediated skin disorder resulting in formation of erythematous, scaly papules or plaques on the skin.[42] Psoriasis affects men and women equally, with the onset peaking between the ages 30 and 50 years, and affects about 2% of the U.S. population.[43,44] The disease often has a negative impact on quality of life and is estimated to account for more than $5 billion in total direct medical expenses.[45] People with psoriasis, especially those with severe disease, are also at increased risk of cardiovascular disease, diabetes, and depression.[42] The cause of psoriasis is not yet fully understood, but several risk factors have been identified, including a family history of psoriasis, smoking, infections, drugs, obesity, stress, and alcohol consumption.[46] Typically, PsO is classified as mild, moderate or severe. Mild disease involves less than 5% of the body surface area involved and has little to no impact on quality of life or function. Per NICE guidance, topical medications including corticosteriods and vitamin D analogs, such as calcipotriene, or coal tar are first-line agents for PsO.[47] Phototherapy is an option for moderate-to-severe plaque psoriasis that has not responded to topical therapy. Systemic nonbiologic treatments are recommended for moderate-to-severe PSO unresponsive to topical or phototherapy and include MTX, cyclosporine, or acitretin. Biologics such as apremilast, etanercept, adalimumab, infliximab, secukinumab, ixekizumab, brodalumab or ustekinumab are added for moderate-to-severe PsO not controlled by other therapies. A new biologic agent, guselkumab, was approved by the FDA in 2017 for the treatment of adult patients with moderate-to-severe PsO who are candidates for systemic therapy or phototherapy.[23]

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.[48,49] 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 and extremities, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[48,49] 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.[42] 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.[49] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, 100% improvement indicating complete disease clearance, is considered more clinically significant.[50] In 2013, a 5-point Investigator's Global Assessment (IGA) was developed to assist in overcoming the limitations of disease severity assessment of the PASI scoring tool.[51] In clinical trials that assessed secukinumab, the IGA was utilized as an outcome measure in responder analyses by determining the proportion of patients with scores ranging from 0 (clear), 1 (minimal), 2 (mild), 3 (moderate) or 4 (severe).[51] At a given point in time, psoriatic lesions are graded by the investigator for induration, erythema, and scaling on the 5-point scale.[51] The IGA does not measure the extent of psoriasis and small changes in symptom severity may not be distinguishable.[51]

Psoriatic Arthritis

PsA is a spondyloarthropathy characterized by synovitis, enthesitis, dactylitis, and skin and nail psoriasis.[52] PsA most commonly appears between the ages of 30 and 50 years but it can develop at any time including childhood.[44] Men and women are affected equally and PsA symptoms include stiffness, pain, swelling, and tenderness of the joints and surrounding ligaments and tendons.[44] Common locations include the insertion sites of the plantar fascia, the Achilles' tendons, and ligamentous attachments to the ribs, spine, and pelvis.[44] Dactylitis is a combination of enthesitis of the tendons and ligaments and synovitis involving a whole digit.[44] The prevalence of PsA in the U.S. population ranges from 6 to 25 cases per 10,000 people.[53] Approximately 30% of patients with psoriasis with have symptoms of PsA.[53] Initially, management of PsA was extrapolated from experiences in managing RA.[54] The European League against Rheumatism (EULAR) developed PsA management recommendations in 2011 to improve management of this disease.[55] First-line treatment recommendations include NSAID therapy to alleviate joint pain, but it is recognized that NSAIDs cannot improve skin lesions.[55] DMARD therapy (MTX, sulfasalazine or leflunomide) should be initiated in patients with active disease (one or more inflamed joints) and poor prognosis (>5 actively inflamed joints).[55] If DMARD therapy is not effective, TNF inhibitors (adalimumab, etanercept, golimumab, or infliximab) should be added to improve skin and joint symptoms and to prevent radiographic damage.[55] More recent guidelines advocate for the use of secukinumab, ustekinumab, and apremilast for PsA in patients who do not respond to TNF inhibitors.[54,56]

Crohn's Disease

CD is characterized by transmural inflammation of any part of the gastrointestinal tract, but most often affects the small bowel and colon.[57] Symptoms of CD include abdominal pain, chronic diarrhea, and gastrointestinal bleeding.[58] The prevalence of CD in the U.S. is estimated at 50 cases per 100,000 persons.[59] CD is incurable; it begins in young people between the ages of 10 and 30 years and continues throughout life.[59] Among patients with CD, surgery is required for the majority and some require multiple operations.[57] Approved biologics to manage CD are adalimumab, certolizumab, infliximab, natalizumab, ustekinumab, and vedolizumab. AHRQ clinical practice guidelines for CD recommend taking into account the disease location, severity, complications, and extraintestinal manifestations when choosing a treatment strategy.[58] Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission).[58] There is controversy between two treatment strategies: "top-down therapy," when biologics are used early in therapy, versus "step-up therapy," when biologics are taken after prolonged corticosteroid.[58] There is insufficient evidence to guide which strategy is most appropriate but currently the "step-up" strategy is standard of care.[58] A recent randomized controlled trial compared conventional "step-up" therapy to early combined immunosuppression therapy with a TNF inhibitor ("top-down" therapy) and found no statistically significant difference in remission rates between the two strategies. The "step-up" strategy was associated with a lower rate of major adverse outcomes for the

combined therapy.[60] The American Gastroenterological Association (AGA) strongly recommends induction with an anti-TNF drug in patients who have moderately severe CD despite standard therapies, and to maintain remission.[61] NICE guidelines recommend TNF inhibitors for induction, but only after failure of conventional therapy with corticosteroids, azathioprine or mercaptopurine, and should only be used for maintenance if there is clear evidence of active disease.[62]

Ulcerative Colitis

UC is a relapsing and remitting form of IBD, with inflammation typically restricted to the colon and rectum.[63,64] Symptoms include bloody diarrhea with or without mucus, abdominal pain, weight loss, fatigue, rectal urgency and tenesmus.[65] Unlike CD, UC is limited to the colon and does not usually present with fistulas or strictures.[65] The onset of symptoms and diagnosis of UC usually occurs in young to middle-aged adults. The peak age of onset is between 15 and 30 years of age.[64] The prevalence in the U.S. is approximately 205 to 240 cases per 100,000 people.[64] Smoking is protective for UC but it is a risk factor for CD.[64] Colectomy rates range from 5% to 20% of patients.[65] Acute severe ulcerative colitis (ASUC) is a potentially life-threatening condition.[66] The lifetime risk of a severe exacerbation requiring hospitalization is around 25%.[66] Severe flares of UC are associated with considerable morbidity and a mortality rate of approximately 1%.[67] Treatment for UC aims to relieve symptoms during a flare-up and then to maintain remission.[68] The American College of Gastroenterology (ACG) and the NICE Guidelines recommend the use of biologic agents (infliximab, adalimumab, vedolizumab, golimumab) for treating moderately to severely active UC in adults whose disease has responded inadequately to, or have intolerance or contraindications to conventional therapy including mesalamine, corticosteroids, mercaptopurine, or azathioprine.[63,69,70] Continuation of these agents is only recommended if there is clear evidence of response.[63,70] As placebo-controlled trials are common, a 2017 Cochrane Collaboration systematic review evaluated placebo responses for various treatments for ulcerative colitis in adults and found that trials of biologics had the highest placebo response rate (35%; 95% confidence interval [CI] 31-38%; trials = 29; I^2 = 52%; I^2 p value <0.001).[71]

Fee-for-Service Utilization July 1, 2017 to September 30, 2017

In the third quarter of 2017 there were approximately 148 pharmacy claims for biologic agents in the fee-for-service (FFS) population. Seventy-two percent of the claims were for the preferred agents of etanercept or adalimumab. For the non-preferred agents, there were 1-2 claims for tocilizumab, abatacept, golimumab, anakinra, natalizumab and 4-10 claims for certolizumab, apremilast, ustekinumab, tofacitinib, and secukinumab. There were no pharmacy claims for brodalumab, canakinumab, infliximab, ixekizumab, rituximab, tocilizumab, or vedolizumab. Seventy-one percent of the submitted prior authorization (PA) requests were approved. No PA request was submitted for 16% of the claims that were not paid.

Table 1. Approved Indications of Biologics for Autoimmune Conditions.[72]

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 yo	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo(Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥18 yo (Humira) HS ≥18 yo (Humira)
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			
Broadalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo			≥18 yo	≥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 (Remicade) ≥18 yo (biosimilars)	
Ixekizumab (TALTZ)				≥18 yo	≥18 yo			
Natalizumab (TYSABRI)		≥18 yo						MS ≥18 yo
Rituximab (RITUXAN)						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Sarilumab (KEVZARA)						≥18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo
Tofacitinib (XELJANZ)					≥18 yo	≥18 yo		
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo			
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: 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; MS =

Multiple Sclerosis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; SLE = Systemic Lupus Erythematosus; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Table 2. Mechanisms of Action, Dosing and Formulations of Biologics for Autoimmune Conditions.[72]

Generic Name	Maintenance Dosing	How Supplied
CD-20 Inhibitor		
Rituximab	1000 mg IV every 2 weeks x 2 doses (one course) repeated every 24 weeks	100 and 500 mg IV vials
Integrin Receptor Antagonist		
Natalizumab	300 mg IV every 4 weeks	300 mg IV vial
Vedolizumab	300 mg IV every 8 weeks	300 mg IV vial
IL-1 Receptor Antagonist		
Anakinra	100 mg SC once daily	100 mg SC Injection
Canakinumab	4 mg/kg SC every 4 weeks	150 mg SC Injection
IL-6 Receptor Antagonist		
Tocilizumab	**Adults:** 4 to 8 mg/kg IV every 4 weeks OR 162 mg SC every week or every other week based on clinical response **Pediatrics**: 8-12 mg IV Infusion depending on indication and weight Cytokine Release Syndrome: IV dose varies by weight (12 mg/kg for <30 kg; 8 mg/kg for ≥30 kg)	80, 200 and 400 mg IV vials and 162 mg SC Injection
Sarilumab	200 mg SC every 2 weeks	150 mg and 200 mg prefilled syringes
IL-12 and IL-23 Inhibitor		
Ustekinumab	Psoriasis: SC dosing varies by weight for adolescents (0.75 mg/kg if <60 kg; 45 mg if 60-100 kg; 90 mg if >100 kg) and adults (45 mg if ≤100 kg; 90 mg if >100 kg) every 12 weeks Psoriatic Arthritis: 45 mg SC every 12 weeks; if co-existent moderate-to-severe plaque psoriasis and weight of >100 kg, 90 mg every 12 weeks Crohn's Disease: Initial weight-based IV infusion x1 followed by 90 mg SC every 8 weeks	45 and 90 mg SC pre-filled syringe, 45 mg SC vial, and 130 mg IV vial
IL-17 Receptor Antagonist		
Brodalumab	210 mg SC every 2 weeks	210 mg SC Injection
Ixekizumab	80 mg SC every 4 weeks	80 mg SC Injection
Secukinumab	SC dosing varies by indication	150 mg SC Injection
IL-23 Inhibitor		
Guselkumab	100 mg SC every 8 weeks	100 mg prefilled syringe
Janus Kinase Inhibitor		
Tofacitinib	5 mg po twice daily OR 11 mg XR po once daily	5 mg oral immediate release and 11 mg XR
PDE-4 Inhibitor		
Apremilast	30 mg orally twice daily	10, 20 and 30 mg tablets
T Lymphocyte Inhibitor		
Abatacept	**Adults:** 500 mg to 1000 mg (dose varies by weight) IV every 4 weeks OR 125 mg SC once weekly **Pediatrics**: 10 mg/kg IV every 4 weeks (≥6 yo) OR 50 -125 mg (weight based) SC once weekly (≥2 yo)	250 mg IV vial and 125 mg SC Injection
TNF inhibitor		
Adalimumab	SC dosing varies by indication	10, 20, 40 and 80 mg SC Injection

Certolizumab	SC dosing varies by indication	200 mg SC Injection
Etanercept	50 mg SC once weekly	50 mg SC Injection
Golimumab	SC dosing varies by indication IV: 2 mg/kg via IV infusion every 8 weeks	50 and 100 mg SC Injection, 50 mg/4 mL IV vial
Infliximab	3-10 mg/kg via IV infusion – dose and interval varies by indication	100 mg IV vial

Abbreviations: IL = interleukin; IM= intramuscular; IV = intravenous; kg = kilogram; mg = milligram; PDE = phosphodiesterase; po = oral; SC = subcutaneous; TNF = tumor necrosis factor; XR = extended release

Table 3. Selected Outcomes Used for Assessment of Disease Progression in Clinical Trials[73,74]

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

Ankylosing Spondylitis Disease Activity Score (ASDAS) ASDAS Calculator: http://www.asas-group.org/clinical-instruments/asdas_calculator/asdas.html	Measures severity of symptoms and signs of inflammation including: 1. Back pain 2. Patient global assessment of spondylitis 3. Peripheral pain and swelling (BASDAI score) 4. Duration of morning stiffness (BASDI score) 5. CRP or ESR	Scale of 0-10: 0 is no symptoms, 10 is very severe ASDAS scores: < 1.3 – Inactive Disease 1.4 to 2.1 – Moderate Disease Activity 2.2 to 3.4 – High Disease Activity >3.5 – Very High Disease Activity Improvement Criteria: Change ≥ 1.1 – Clinically Important Improvement Change ≥ 2.0 – Major Improvement
Psoriasis		
Outcome Measure	**Domains**	**Scale and Scoring**
Static Physician's Global Assessment Scale (sPGA)	The static PGA is a 0-5 ordinal rating ranging from "clear" to "very severe psoriasis" as evaluated by the provider	Scale of 0 – 5: 0 = clear; scores 1–5 = increasing severity Response to therapy indicated by a score of 0 or 1
Psoriasis Symptom Inventory (PSI)	Patient reported outcome in 8 areas: 1. Itch 2. Redness 3. Scaling 4. Burning 5. Cracking 6. Stinging 7. Flaking 8. Pain of Lesions	Scale of 0-4: 0 = not at all severe, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe Score ranges from 0 – 32 Response to therapy indicated by scores < 8 with no single item rated higher than 1
Psoriasis Area and Severity Index (PASI) PASI-75	Measure of overall psoriasis severity and coverage on Head, Upper Extremities, Trunk and Lower Extremities • Erythema • Induration • Scaling 75% Improvement in PASI score	Scale of 0-4: 0 is clear, 1-4 increasing severity PASI score: 1. Sum rows 1, 2, and 3 for each area of the body using 0-4 scale 2. Add an area score based on percentage involvement from 0 (clear) to 6 (≥90% coverage) 3. Multiply score as rated for each body area (0.1, 0.2, 0.3, 0.4 for head, arms, trunk, and legs, respectively) 4. Add all the scores together Composite score ranges from 0 -72: 0 = normal 72 = maximal disease
PsA Response Criteria (PsARC)	Used by the National Institute of Health Care Excellence (NICE) to continue TNF inhibitor therapy with an assessment at baseline and 12 weeks 1. 66 swollen joint score 2. 68 tender joint score 3. Patient global assessment 4. Physician global assessment	**Response** = improvement in ≥ 2 of the 4 tests: -One of which must be the joint tenderness or swelling score -No worsening in any of the four measures • **Improvement** is defined as a decrease ≥ 30% in the swollen or tender joint score and ≥1 in either of the global assessments

Dermatology Quality of Life (DQLI)	10 question patient self-reported assessment 1. How itchy has your skin been? 2. How embarrassed are because of your skin? 3. Has your skin interfered with activities? 4. Has your skin influenced the clothes you wear/ 5. Has your skin affected social activities? 6. How your skin impacted your ability to participate in a sport? 7. Has your skin prevented you from working? 8. Has your skin caused any problems with friends? 9. Has your skin impacted sexual activities? 10. How much has the treatment for your skin affected your daily activities?	Scale of 0-3: 0 not at all, 1 a little, 2 a lot, and 3 very much Interpretation of DQLI score: 0 – 1 no effect at all on patient's life 2 – 5 small effect on patient's life 6 – 10 moderate effect on patient's life 11 – 20 very large effect on patient's life 21 – 30 extremely large effect on patient's life
Rheumatoid Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**
Disease Activity Score(DAS)-28 DAS-28 calculator https://www.das-score.nl/das28/DAScalculators/dasculators.html	Clinical assessment of disease activity in combination with an acute phase reactant level 1. Assessment of 28 joints for swelling and tenderness - swollen joint count (SJC) - tender joint count (TJC) 2. General health (GH) - patient assessment of disease on a 0-100 scale where 100 means maximal disease activity 3. Either ESR or CRP adjusted with SJC and TJC scores	DAS-28 scoring ranges from 0 to 9.4: <2.6: Remission ≥2.6 and ≤3.2: Low Disease Activity >3.2 and ≤5.1: Moderate Disease Activity >5.1: High disease activity • DAS-28 reduction by 0.6 represents a moderate improvement. • DAS-28 reduction more than 1.2 represents a major improvement.
Health Assessment Questionnaire Disability Index (HAQ-DI)	Assess 8 domains of daily activity – patient self-reported 1. Dressing and Grooming 2. Arising 3. Eating 4. Walking 5. Hygiene 6. Reach 7. Grip 8. Chores or Activities	Scored 0 to 3: 0 - no difficulty 1 - with some difficulty 2- with much difficulty 3 - unable to do HAQ-DI calculation: Sum of all domains then divided by 8 to give total score ranging from 0 (best) to 3 (worst)

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

Crohn's Disease		
Outcome Measure	**Domains**	**Scale and Scoring**
Crohn's Disease Activity Score (CDAI)	Evaluation of 8 clinical factors (each weighted and summed to reach a total score) 1. Number of liquid or soft stools each day for 1 week (weight x2) 2. Abdominal pain (graded on a severity scale of 0-3) for 1 week (weight x5) 3. General Well-being (subjective score of 0-4) for 1 week (weight x7) 4. Presence of complications (weight x20) 5. Use of Lomotil or opiates for diarrhea (weight x30) 6. Presence of abdominal mass (graded as 0 [none], 2 [questionable] or 5 [definite]) (weight x10) 7. Absolute deviation of Hematocrit from 47% (men) or 42% (women) (weight x6) 8. Percentage deviation from standard weight (weight x1)	Each factor is weighted and summed to achieve a total score • Scores ≤150 indicate minimal disease • Scores >150 indicate active disease • Scores >450 indicate extremely severe disease

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analog scale

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 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

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

New Systematic Reviews:

Rheumatoid Arthritis

Cochrane Collaboration

A 2017 update of a 2014 Cochrane Review assessed the efficacy and safety of certolizumab pegol (with or without MTX) compared to placebo (with or without MTX) in RA for adult patients who had not responded to conventional DMARDs.[1] This review included 14 trials (12 for efficacy, n=5422; 13 for safety, n=5273) with at least 3 months of follow-up.[1] The major outcomes investigated included ACR50, HAQ or Short Form Health Survey (SF-36), DAS28, radiological changes, serious adverse events (SAEs), early study withdrawals, and early study withdrawals due to adverse events.[1] Both the 200 mg and 400 mg doses were investigated, but 200 mg every other week dose will be focused on as that is the usual dose for RA maintenance therapy.[1,75] ACR50 was achieved in a significantly higher proportion of certolizumab-treated patients compared to placebo-treated patients based on high quality evidence (RR 3.80; 95% CI 2.42-5.95; ARR 25%; NNT 4).[1] A significant benefit in change in HAQ from baseline was also found with certolizumab based on moderate quality evidence (mean difference [MD] -0.35; 95% CI -0.43 to -0.26).[1] High quality evidence showed a statistically significant benefit in DAS28 with certolizumab and moderate quality evidence showed a statistically significant benefit in radiological changes with certolizumab.[1] An increase in SAE (ARR 3%; NNH 33) as well as an increase in withdrawals due to adverse events (ARR 2%; NNH 58) was found with certolizumab based on high quality evidence.[1] Additionally, a higher number of withdrawals was seen with certolizumab (RR 0.47; 95% CI 0.39-0.56; ARR -29%; NNH 3) based on moderate quality evidence.[1] The authors concluded that these findings confirm that certolizumab is clinically beneficial based on greater efficacy outweighing greater risk of harms in management of RA compared to placebo.[1] There were no head-to-head comparator trials between certolizumab pegol and other anti-TNFs to evaluate.[1]

New Guidelines:

Crohn's Disease

National Institute for Health and Care Excellence

NICE guidance for treating adults with moderate to severe CD after previous treatment with ustekinumab was updated July 2017.[5] Recommendations based on clinical and cost effectiveness which take into consideration evidence and expert opinion are as follows:

- Ustekinumab is recommended as an option for treating moderate to severe active CD for adults who have had an inadequate response with, lost response to, have a contraindication to, or were intolerant of, conventional therapy or a TNF-alpha inhibitor.[5]
- The choice of treatment with ustekinumab or another biologic should be individualized based on a discussion between the patient and provider after weighing risks and benefits.[5] The least expensive option should be chosen if more than one option is acceptable.[5]
- Ustekinumab should be given until treatment failure (including necessity of surgery) or until 12 months after treatment initiation, whichever is shorter.[5] The disease severity should be reassessed at that time to determine if treatment should continue.[5]

Plaque Psoriasis

National Institute for Health and Care Excellence

NICE guidance for treating plaque psoriasis in children and young people with adalimumab, etanercept, and ustekinumab was also updated in July 2017.[6] Recommendations based on clinical and cost effectiveness which take into consideration evidence and expert opinion are as follows:

- Adalimumab is recommended as an option for plaque psoriasis in children and young people age 4 and older if the disease is severe (defined by PASI of 10 or more) and has not responded to standard systemic therapy (cyclosporine, methotrexate, or phototherapy) or if those options are contraindicated or not tolerated.[6]

- Etanercept is recommended as an option for plaque psoriasis in children and young people age 6 and older if the disease is severe (defined by PASI of 10 or more) and has not responded to standard systemic therapy (cyclosporine, methotrexate, or phototherapy) or if those options are contraindicated or not tolerated.[6]
- Ustekinumab is recommended as an option for plaque psoriasis in children and young people age 12 and older if the disease is severe (defined by PASI of 10 or more) and has not responded to standard systemic therapy (cyclosporine, methotrexate, or phototherapy) or if those options are contraindicated or not tolerated.[6]
- Treatment should be discontinued for etanercept at 12 weeks, and adalimumab and ustekinumab at 16 weeks if the psoriasis has not responded adequately (defined as 75% reduction in PASI score from treatment initiation).[6]
- The choice of treatment should be made on an individual patient basis after discussion of advantages and disadvantages of treatments available. The lowest cost option, including the consideration of biosimilars, should be started first after taking administration cost, dose, and product cost per dose into consideration.[6]

Psoriatic Arthritis

National Institute for Health and Care Excellence

NICE guidance for treating adults with active PsA after inadequate response to DMARDs with certolizumab pegol and secukinumab was updated May 2017.[4] Recommendations based on clinical and cost effectiveness which take into consideration evidence and expert opinion are as follows:

- Certolizumab pegol monotherapy or in combination with MTX is recommended for treating active PsA if:
    - It is used as described in the NICE technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of PsA;[76] or
    - The patient has a history of TNF-alpha inhibitor treatment but they no longer had a response to the treatment after the first 12 weeks.[4]
- Secukinumab monotherapy or in combination with MTX is recommended for treating active PsA if:
    - It is used as described in the NICE technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of PsA;[76] or
    - The patient has a history of TNF-alpha inhibitor treatment but they no longer had a response to the treatment after the first 12 weeks; or
    - TNF-alpha inhibitors are contraindicated but would otherwise be considered as described in the NICE technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of PsA.[4,76]
- Assessment of response to certolizumab pegol and secukinumab should be completed after 12 weeks and 16 weeks, respectively.[4] Treatment should only be continued if there is clear evidence of response.[4]

Rheumatoid Arthritis

National Institute for Health and Care Excellence

NICE guidance for treating adults with moderate to severe RA with tofacitinib was updated October 2017.[3] Recommendations based on clinical and cost effectiveness which take into consideration evidence and expert opinion are as follows:

- Tofacitinib in combination with MTX is recommended as an option to treat active RA in adults who have not adequately responded to a combination of conventional DMARDs if the disease is severe (DAS28 >5.1).[3]
- Tofacitinib in combination with MTX is recommended as option to treat active RA in adults who have not adequately responded to other DMARDs, including at least 1 biologic DMARD if the disease is severe (DAS28 >5.1) and the patient cannot have rituximab.[3]
- Tofacitinib monotherapy may be used in adults when MTX is contraindicated or not tolerated when the two criteria above are met.[3]

- Treatment should be continued only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after initiation.[3] After an initial response, discontinue treatment if at least a moderate EULAR response is not maintained.[3]

European League Against Rheumatism (EULAR)
A 2016 update of the 2013 EULAR recommendations for the management of RA was published in 2017.[2] Recommendations regarding biologics will be the focus of this summary and are as follows:

- If the treatment target is not achieved with the first conventional DMARD, and when poor prognostic factors are present, addition of a biologic or targeted synthetic DMARD (tsDMARD; defined by the guidelines as tofacitinib or baricitinib) should be considered (Level A Strength of Evidence indicating evidence from RCTs or meta-analyses of RCTs); current practice would be to start a biologic (Level D Strength of Evidence indicating expert opinion or extrapolated recommendation from evidence from nonrandomized trials or descriptive studies).[2]
    - This recommendation was expanded to include tsDMARDs such as tofacitinib and baricitinib (which is not currently approved in the U.S.[72]).[2]
- Biologics or tsDMARDs should be combined with a DMARD. In patients who cannot use a concomitant DMARD, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other biologics (Level A Strength of Evidence).[2]
    - This recommendation was updated to include tsDMARDs similarly to above as increasing evidence has been published supporting combination therapy.[2]
- If a biologic (Level A Strength of Evidence) or tsDMARD (Level D Strength of Evidence) has failed, treatment with another biologic or tsDMARD should be considered. If one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action.[2]
- If a patient is in persistent remission after having tapered corticosteriods, tapering the biologic may be considered (Level B Strength of evidence indicating either evidence from nonrandomized studies or quasi-experimental studies or recommendations extrapolated from RCTs or meta-analyses of RCTs).[2]

This guideline was rated as high quality using the AGREE II Global Rating Scale. A systematic review process for new literature was performed, recommendations were organized, and there was complete information to inform decision making. However, conflict of interest statements were documented for each member contributing to the guideline and a large majority of the members' document personal remuneration from pharmaceutical companies within the last two years.[2]

New Formulations or Indications:
Actemra (tocilizumab) (May 2017): A new indication was approved for the treatment of adult patients with giant cell arteritis (GCA) for the subcutaneous injection formulation.[7] This approval was based on a randomized, double-blind, multicenter study in which patients with active GCA were randomized to either tocilizumab 162 mg every week or every other week in combination with a 26 week prednisone taper, or two different placebo groups (pre-specified prednisone-taper regimen over 26 weeks and 52 weeks).[77] Enrolled patients were 50 years of age or older with active GCA within 6 weeks before baseline.[77] The proportion of patients achieving the primary efficacy endpoint of sustained remission from week 12 through week 52 was 56% (n=56), 53% (n=26), 14% (n=7), and 18% (n=9), respectively ($p<0.001$ for comparisons of either active treatment with placebo).[77]

Orencia (abatacept) (June 2017): A new indication was approved for the treatment of active psoriatic arthritis in adults.[11] This approval was based on two randomized, double-blind, placebo-controlled studies (n=594) in adult patients with active psoriatic arthritis despite prior DMARD treatment.[78,79] Prior TNF-inhibitor treatment was noted for 37% and 61% of patients in trial 1 and trial 2, respectively.[78,79] The primary efficacy endpoint for both trials was the proportion of patients achieving an ACR20 response at week 24.[78,79] In the first trial (n=170), which was a dose-ranging study, patients received IV study drug at days 1, 15,

29, and every 28 days after for 24 weeks.[79] Patients were randomized to placebo, abatacept 3 mg/kg, abatacept 10 mg/kg (weight range-based dosing: 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1000 mg for patients weighing greater than 100 kg), or two doses of abatacept 30 mg/kg followed by weight range-based dosing of 10 mg/kg for 24 weeks.[79] In the second trial (n=424), patients were randomized to either weekly SC placebo or abatacept 125 mg without a loading dose for 24 weeks, followed by open-label abatacept 125 mg SC weekly.[78] A higher proportion of patients achieved an ACR20 response at week 24 in both the abatacept 10 mg/kg IV (trial 1) and abatacept 125 mg SC (trial 2) groups compared to placebo (47.5% vs. 19.0%, respectively, p=0.006 vs. placebo in trial 1; 39.4% vs. 22.3%, respectively, p<0.001 vs. placebo in trial 2).[78,79]

Actemra (tocilizumab) (August 2017): A new indication was approved for the IV treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and pediatric patients 2 years of age and older.[7] The efficacy for this indication was assessed in a retrospective analysis of pooled outcome data from clinical trials of CAR T-cell therapies for hematological malignancies.[7] A total of 45 patients treated with tocilizumab 8 mg/kg (12 mg/kg for patients <30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS.[7] 31 patients (n=69%; 95% CI 53%-82%) had a response defined as CRS resolved within 14 days of first dose of tocilizumab, no more than 2 doses needed, and no drugs other than tocilizumab or corticosteroids used for treatment.[7] A second independent cohort study of 15 patients confirmed achievement of resolution within 14 days.[7]

Enbrel (etanercept) (September 2017): A new 50 mg/mL Enbrel Mini prefilled cartridge formulation was approved for use with the AutoTouch reusable autoinjector only.[13]

Simponi Aria (intravenous golimumab) (October 2017): Two new indications were approved for the treatment of adult patients with active psoriatic arthritis and adults patients with active ankylosing spondylitis.[10]

- The efficacy for psoriatic arthritis was assessed in a multicenter, randomized, double-blind, placebo-controlled trial (n=480) of adult patients with active psoriatic arthritis despite NSAID or DMARD therapy who were biologic-naïve.[80] Patients were randomized to golimumab 2 mg/kg or placebo IV infusions at weeks 0, 4, 12, and 20.[80] Patients randomized to placebo then received golimumab at week 24, 28 and every 8 weeks after through week 52 while patients randomized to golimumab continued to receive golimumab at week 28 and every 8 weeks after through week 52.[10] A greater proportion of patients achieved the primary efficacy endpoint of an ACR20 response at week 14 in the golimumab group compared to the placebo group (75.1% vs. 21.8%; p<0.001).[80]
- The efficacy for ankylosing spondylitis was assessed in a multicenter, randomized, double-blind, placebo-controlled phase 3 trial (n=208) of adult patients with active ankylosing spondylitis and inadequate response or intolerance to NSAIDs.[81] Patients were randomized to golimumab 2 mg/kg or placebo IV infusions at weeks 0, 4, and 12.[81] Patients randomized to placebo then received golimumab at weeks 16, 20, and every 8 weeks after through week 52 while patients randomized to golimumab continued golimumab at week 20 and every 8 weeks through week 52.[81] A greater proportion of patients achieved the primary efficacy endpoint of an Assessment in Ankylosing Spondylitis (ASAS) 20 response at week 16 in the golimumab group compared to the placebo group (73.3% vs. 26.2%; p<0.001).[81]

Stelara (ustekinumab) (October 2017): An extended indication was approved for moderate to severe plaque psoriasis to include treatment of adolescent patients ages 12-17 years who are candidates for phototherapy or systemic therapy.[8] This approval was based on a multicenter, randomized, double-blind, placebo-controlled phase 3 study of adolescent patients age 12-17 years (n=110) randomized to either placebo or weight-based ustekinumab with a minimum BSA involvement of 10%, PASI score $\geq$12, and a PGA score $\geq$3 whose disease was inadequately controlled by topical therapy.[82] Standard weight-based dosing for ustekinumab was 0.75 mg/kg for patients less than or equal to 60 kg, 45 mg for patients greater than 60 kg and less than or equal to 100 kg, and 90 kg for

patients over 100 kg.[82] A greater proportion of standard weight-based ustekinumab-treated patients compared to placebo-treated patients achieved a PGA score of cleared or minimal (69.4% vs. 5.4%; p<0.001), PASI 75 (80.6% vs. 10.8%; p<0.001), and PASI 90 (61.6% vs. 5.4%; p<0.001) at week 12.[82]

Taltz (ixekizumab) (December 2017): A new indication was approved for the treatment of adults with active psoriatic arthritis.[9] The efficacy for this indication was assessed in 2 randomized, double-blind, placebo-controlled studies in adults with active psoriatic arthritis despite NSAID, corticosteroid, or DMARD treatment.[9] In one trial, only biologic-naïve patients (n=417) were included and 57.9% of the patients in the ixekizumab 80 mg every 4 weeks (Q4W) group achieved the primary efficacy endpoint of an ACR20 response at week 24 compared to 30.2% of placebo-treated patients ($p \leq 0.001$).[83] In the second trial, patients were TNF-alpha inhibitor experienced (n=363) and 53% of the patients in the ixekizumab 80 mg Q4W achieved an ACR20 response at week 24 compared to 20% of placebo-treated patients (p<0.0001).[84]

Xeljanz (tofacitinib) (December 2017): A new indication was approved for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other DMARDs.[12] The efficacy for this indication was assessed in two multicenter, randomized, double-blind, placebo-controlled trials in adults with active psoriatic arthritis (n=816).[12] The first study randomized patients who had inadequate response with a DMARD to either tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg SC every 2 weeks, placebo with a switch to tofacitinib 5 mg twice daily at 3 months, or placebo with a switch to tofacitinib 10 mg twice daily at 3 months.[85] The second study randomized patients who had an inadequate response with at least one TNF inhibitor to either tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo with a switch to tofacitinib 5 mg twice daily at 3 months, or placebo with a switch to tofacitinib 10 mg twice daily at 3 months.[86] The primary endpoints in both trials were the proportion of patients with an ACR20 response and change from baseline in HAQ-DI at month 3.[85,86] In the first trial of patients with a prior inadequate response to a DMARD, a higher proportion of patients treated with tofacitinib 5 mg twice daily (50%) and 10 mg twice daily (61%) achieved an ACR20 response at month 3 compared to placebo (33%; p=0.01 for comparison of 5 mg dose with placebo; p<0.001 for comparison of 10 mg dose with placebo).[85] For the co-primary endpoint of least squares mean change from baseline in HAQ-DI at month 3, patients treated with tofacitinib 5 mg twice daily and 10 mg twice daily demonstrated greater improvement (-0.35 and -0.40, respectively), compared to placebo (-0.18; p=0.006 for comparison of 5 mg dose with placebo; p<0.001 for comparison of 10 mg dose with placebo).[85] In the second trial of patients with a previous inadequate response to at least one TNF inhibitor, a higher proportion of patients treated with tofacitinib 5 mg twice daily (50%) and 10 mg twice daily (47%) achieved an ACR20 response at month 3 compared to placebo (24%; p<0.001 for both doses compared to placebo).[86] For the co-primary endpoint of least squares mean change from baseline in HAQ-DI at month 3, patients treated with tofacitinib 5 mg twice daily and 10 mg twice daily demonstrated greater improvement (-0.39 and -0.35, respectively), compared to placebo (-0.14; p<0.001 for both doses compared to placebo).[86]

New FDA Safety Alerts:

Otezla (apremilast) (June 2017): A new subsection under the Warnings and Precautions in the prescribing information was added regarding post-marketing reports of severe diarrhea, nausea, and vomiting.[87] Most of the events occurred within the first few weeks of treatment and some patients were hospitalized.[87] Dose reduction or suspension should be considered if severe diarrhea, nausea, or vomiting develops.[87]

Taltz (ixekizumab) (July 2017): An update to the hypersensitivity warning in the prescribing information was added documenting anaphylaxis, including cases leading to hospitalization, has been reported in post-marketing use.[88]

Tysabri (natalizumab) (August 2017): An addition to the warnings documented the higher risk of acute retinal necrosis (ARN) caused by herpes viruses in patients being administered Tysabri.[89] Patients with eye symptoms such as decreased visual acuity, redness, or eye pain should be referred for retinal screening for ARN.[89]

Xeljanz and Xeljanz XR (tofacitinib citrate) (August 2017): An addition to the malignancy and lymphoproliferative disorders warning in the prescribing information documented that other malignancies observed in clinical studies and post-marketing settings include, but are not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.[90]

Remicade (infliximab) (October 2017): Two new subsections were added to the Warnings and Precautions in the prescribing information.[91] The first regards cervical cancer based on a population-based retrospective cohort study using Swedish registries.[91] The data found a 2- to 3-fold increase in the incidence of invasive cervical cancer in women with RA treated with infliximab compared to biologic-naïve patients or the general population.[91] Periodic screening is recommended.[91] The second subsection, "Cardiovascular and Cerebrovascular Reactions During and After Infusion" documents serious cerebrovascular accidents, myocardial ischemia/infarction (some fatal), hypotension, and arrhythmias have been reported during and within 24 hours of infliximab infusion.[91] It is recommended to monitor patients during infusion and discontinue if serious reaction occurs.[91] Further management of reactions should be dictated by signs and symptoms.[91]

Xeljanz and Xeljanz XR (tofacitinib) (December 2017): An addition to the boxed warning was added to include herpes zoster to the list of reported infections.[12] Additionally, information regarding 3 malignancies in patients treated with tofacitinib in the clinical trials for active psoriatic arthritis.[12]

Randomized Controlled Trials:
A total of 252 citations were manually reviewed from the initial literature search. After further review, all 252 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), outcome studied (eg, non-clinical), or published prior to dates of interest.

NEW DRUG EVALUATION: Sarilumab (Kevzara®)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The approval of sarilumab was based on two randomized, double-blind, placebo-controlled multicenter trials that assessed the safety and efficacy of the drug (the MOBILITY Part B and TARGET studies).[19,20,92] One active comparator study, MONARCH, was published since the approval of sarilumab and several other unpublished studies were also reviewed by the FDA.[18,93]

The MOBILITY Part B study was a randomized, multicenter, double-blind, placebo-controlled phase 3 study comparing sarilumab and placebo over 52 weeks.[19] This study followed MOBILITY Part A which was a dose-ranging phase 2 study.[19] MOBILITY Part B had two cohorts.[19] The first cohort was an extension of a previous phase 2 dose-ranging study used only for the safety analysis.[19] The second cohort included patients randomized after identification of the optimal dose and data from this population was used both for safety and efficacy analyses.[19] The patients in the efficacy cohort (Cohort 2) were randomized to sarilumab 150 mg every 2 weeks, sarilumab 200 mg every 2 weeks, or placebo, in combination with weekly MTX.[19] Patients enrolled in the study had a mean age of 50 years, mean duration of RA for 9 years, and a mean HAQ-DI score of 1.6 (indicating moderate to severe functional disability).[19] Most subjects (80.7%) had no prior biologic DMARD exposure.[19] Three primary efficacy endpoints were investigated: the proportion of patients achieving an ACR20 at week 24, change from physical function baseline to week 16 as assessed by HAQ-DI, and change from baseline to week 52 in the modified Sharp/van der Heijde (SHS) score which assesses radiographic progression of structural damage.[19] A change of around 5 units or more in the SHS score is considered clinically significant.[27] A significant benefit in each of these primary efficacy endpoints was seen with both doses of sarilumab in combination with MTX compared to placebo in combination with MTX.[19] An ACR20 response was seen in 58.0% and 66.4% of patients within the sarilumab 150 mg and 200 mg groups, respectively, compared to 22.4% in the placebo group (150 mg vs. placebo: ARR 35.6%, NNT 3; 200 mg vs. placebo: ARR 44.0%, NNT 3; p<0.0001 for both doses of sarilumab vs. placebo).[19] Changes from baseline in HAQ-DI at week 16 for the sarilumab 150 mg, sarilumab 200 mg, and placebo groups were -0.53 $\pm$0.03, -0.55 $\pm$0.03, and -0.29 $\pm$0.03, respectively (p<0.0001 for both doses of sarilumab vs. placebo) which are clinically significant differences.[19] Changes from baseline in the SHS at week 52 were statistically but not clinically significant at 0.90 $\pm$4.66, 0.25 $\pm$4.61, and 2.78 $\pm$7.73, respectively, for sarilumab 150 mg, sarilumab 200 mg, and placebo (p<0.0001 for both doses of sarilumab vs. placebo).[19] Overall, this manufacturer-funded study was graded as poor quality with significant limitations from unclear methods of blinding for the primary endpoint and high overall attrition (38.5%).[19] Since approximately 80% of patients included in the study were biologic-naive, applicability to patients who have previously tried and failed other biologics is limited.

The TARGET study was a multicenter, randomized, double-blind, placebo-controlled, phase 3 study in which patients were randomized to sarilumab 150 mg, sarilumab 200 mg, or placebo every 2 weeks in combination with background oral DMARD therapy for 24 weeks.[20] Patients enrolled in the study had a mean age of 52 years, mean duration of RA for 28 years, and mean HAQ-DI of 1.77.[20] Approximately 77% of patients had prior exposure to one anti-TNF agent and 23% had prior exposure to more than one anti-TNF agent.[20] The two primary efficacy endpoints studied were the proportion of patients with an ACR20 at week 24 and change from baseline to week 12 in physical function assessed by HAQ-DI.[20] A statistically significant response in ACR20 at week 24 was seen for the sarilumab 150 mg group (55.8% vs. 33.7%; ARR 22.1%; NNT 5; p<0.0001) and the sarilumab 200 mg group (60.9% vs. 33.7%; ARR 27.2%; NNT 4; p<0.0001) versus placebo.[20] A statistically significant improvement was also seen in change in HAQ-DI score from baseline to week 12 for both the sarilumab 150 mg group (-0.46 $\pm$0.04;

p<0.001) and 200 mg group (-0.47 ±0.04; p<0.001) versus placebo (-0.26 ±0.04), though these results may not be clinically significant.[20] Overall, this manufacturer-funded study was graded as fair quality with adequate randomization, double-dummy blinding, but high overall attrition.

The MONARCH study was a multicenter, randomized, active-controlled, double-blind, double-dummy, phase 3 superiority trial in which patients were randomized to sarilumab 200 mg or adalimumab 40 mg every 2 weeks for 24 weeks.[18] This study was not published at the time of the FDA review and was only highlighted in their report.[93] Patients enrolled in the study were a mean age of 52 years with a mean duration of RA for 7 years, and a mean HAQ-DI of 1.6.[18] Patients included were inappropriate candidates for continued MTX therapy due to intolerance or inadequate response, and patients with prior biologic use were excluded.[18] The primary efficacy endpoint was change from baseline in DAS28-ESR (which evaluates DAS28 with the erythrocyte sedimentation rate as opposed to the C reactive protein in DAS28-CRP) at week 24, in which a statistically significant benefit was seen with sarilumab compared to adalimumab (-3.28 vs. -2.20; difference: -1.08; 95% CI -1.36 to -0.79; p<0.0001).[18] A statistically significant difference was also seen in the secondary endpoints of ACR20 at week 24 (71.7% vs. 58.4%; ARR 13.3%; NNT 8; p=0.0074), ACR50 at week 24 (45.7% vs. 29.7%; ARR 16.0%; NNT 7; p=0.0017), and ACR70 at week 24 (23.4% vs. 11.9%; ARR 11.5%; NNT 9; p=0.0036) for sarilumab versus adalimumab.[18] A statistically significant difference was also found in mean change in HAQ-DI score from baseline to week 24 for sarilumab compared to adalimumab (-0.61 vs. -0.43; 95% CI -0.31 to -0.06; p=0.0037).[18] There is insufficient comparative evidence for RA radiographic progression for sarilumab and adalimumab as this was not studied in the trial.[18] Overall, this was a good quality manufacturer-funded trial with adequate allocation concealment, double-dummy blinding, and low attrition.

Other studies reviewed to support efficacy of sarilumab in the FDA clinical review include MOBILITY Part A, SARIL-RA-ASCERTAIN, SARIL-RA-ONE, SARIL-RA-COMPARE, SARIL-RA-EASY, ACT11575, and SARIL-RA-EXTEND.[93] The phase 2 MOBILITY Part A study showed numerically higher proportion of responders who achieved ACR20 at 12 weeks with sarilumab 150 mg and 200 mg every 2 weeks versus placebo (66.7% and 65.4% vs. 46.2%; p=0.0426 and 0.0363, respectively).[93] A significantly higher proportion of ACR50 responders was also seen for the sarilumab 200 mg every 2 weeks group compared to placebo (40.4% vs. 15.4%; p<0.01).[93] SARIL-RA-ASCERTAIN was an active comparator study of sarilumab and tocilizumab, the only other approved IL-6 receptor blocking agent.[93] Exploratory efficacy endpoints found generally similar efficacy although they were not powered to make comparative efficacy assessments.[93] SARIL-RA-ONE, SARIL-RA-COMPARE, SARIL-RA-EASY, ACT11575, and SARIL-RA-EXTEND were excluded from this review due to early study discontinuation and lack of efficacy analyses, a focus on usability or immunogenicity, or wrong comparator (no control).

Clinical Safety:
The FDA safety analysis of sarilumab included a total of 7875 patients treated with sarilumab in combination with a DMARD, 264 patients treated with sarilumab monotherapy, and 1240 patients treated with placebo in combination with a DMARD.[93] Most of the FDA clinical review safety analysis focused on the phase 3 placebo-controlled population in the pre-rescue period.[93] This group included 579 patients treated with sarilumab 150 mg every 2 weeks plus a DMARD, 582 patients treated with sarilumab 200 mg every 2 weeks plus a DMARD, and 579 patients treated with placebo plus a DMARD from the MOBILITY Part B and TARGET studies.[93]

In the phase 3 placebo-controlled population, there were more serious adverse events (SAEs) in the sarilumab arms compared to placebo (2.1% in placebo vs. 3.3% in sarilumab 150 mg every 2 weeks and 5.8% in sarilumab 200 mg every 2 weeks).[93] The most common SAE were infections and infestations (0.7% vs. 1.0% vs. 1.0%).[93] There were also more SAE rates of neutropenia in the sarilumab 150 mg (1/579; 0.2%) and 200 mg (4/582; 0.7%) arms compared to placebo (0/579; 0%).[93] Adverse events leading to discontinuation for this population was also higher in the sarilumab 150 mg and 200 mg groups (6.4% and 7.6%, respectively)

compared to placebo (3.1%).[93] A summary of the common treatment-emergent adverse events (TEAEs) is in **Table 4.** The TEAEs are consistent with the expected effects of IL-6 inhibition in the RA population.[93] Statistical differences between groups were not reported.[93]

Table 4. Treatment-Emergent Adverse Events (≥0.5% Higher Incidence in Subjects in ≥1 of the Sarilumab Groups) in the Phase 3 Placebo-Controlled Population.[93]

	Placebo + DMARD	Sarilumab 150 mg every 2 weeks + DMARD	Sarilumab 200 mg every 2 weeks + DMARD
Neutropenia	1/579 (0.2%)	40/579 (6.9%)	59/582 (10.1%)
Increased alanine aminotransferase	10/579 (1.7%)	27/579 (4.7%)	28/582 (4.8%)
Injection site erythema	5/579 (0.9%)	26/579 (4.5%)	23/582 (4.0%)
Upper respiratory tract infection	14/579 (2.4%)	21/579 (3.6%)	20/582 (3.4%)
Urinary tract infection	11/579 (1.9%)	18/579 (3.1%)	17/582 (2.9%)
Nasopharyngitis	14/579 (2.4%)	18/579 (3.1%)	14/582 (2.4%)
Hypertension	8/579 (1.4%)	7/579 (1.2%)	13/582 (2.2%)
Leukopenia	0/579 (0%)	5/579 (0.9%)	13/582 (2.2%)
Bronchitis	9/579 (1.6%)	5/579 (0.9%)	12/582 (2.1%)
Sinusitis	5/579 (0.9%)	6/579 (1.0%)	12/582 (2.1%)
Injection site pruritus	1/579 (0.2%)	13/579 (2.2%)	11/582 (1.9%)
Hypertriglyceridemia	3/579 (0.5%)	16/579 (2.8%)	8/582 (1.4%)

The common TEAEs for placebo, sarilumab 150 mg, and sarilumab 200 mg were similar in the entire double-blind population as well: infections and infestations were the most common (28.6%, 34.2%, and 35.2%, respectively); neutropenia (0.5%, 9.8%, and 14.2%, respectively), upper respiratory infections (4.8%, 6.4%, and 7.1%, respectively), and increased alanine aminotransferase (2.6%, 6.7%, and 6.8%, respectively) were also common.[93] Of note, neutropenia appeared to be dose-dependent.[93] Overall, there were a total of 26 deaths from the safety analysis.[93] This rate does not exceed that of the general RA population and the majority of causes (i.e., infection, cardiovascular event, or malignancy) are consistent with that of the general RA population.[93]

The MONARCH study's comparative safety data between adalimumab 40 mg every 2 weeks and sarilumab 200 mg every 2 weeks was not included in the main FDA safety analysis. In this study, the proportion of patients with any adverse event were similar between adalimumab (63.6%) and sarilumab (64.1%).[18] The number of SAEs (6.5% vs. 4.9%), adverse events leading to treatment discontinuation (7.1% vs. 6.0%), infections (27.7% vs. 28.8%), and serious infections (1.1% vs. 1.1%) were similar for adalimumab and sarilumab, respecitvely.[18] However, risk of neutropenia was higher in the sarilumab group (13.6%) compared to the adalimumab group (0.5%).[18] Injection site reactions were also more common in sarilumab-treated patients (9.2%) compared to adalimumab-treated patients (4.3%).[18] The study was not powered to detect differences in adverse events.[18]

Similar to other biologic treatments for RA, labeling for sarilumab includes a boxed warning for risk of serious infections.[92,93] In the phase 3 placebo-controlled population, the incidence rates for infections (17.3% vs. 21.1% vs. 22.3%) and serious infections (0.7% vs. 1.0% vs. 1.0%) were lower with placebo compared to

sarilumab 150 mg and sarilumab 200 mg, respectively.[93] Opportunistic infections were similar with placebo and sarilumab 150 mg but higher with sarilumab 200 mg (0.3% vs. 0.3% vs. 0.7%, respectively).[93]

Labeling for sarilumab also has warnings for neutropenia, thrombocytopenia, elevated liver enzymes, lipid abnormalities, gastrointestinal perforation, hypersensitivity, and avoiding use with live vaccines.[92] These warning labels are similar to tocilizumab, another IL-6 antagonist treatment.[94]

Look-alike / Sound-alike Error Risk Potential: None identified.

Table 5. Pharmacology and Pharmacokinetic Properties of Sarilumab.[92]

Parameter	
Mechanism of Action	Binds to soluble and membrane-bound IL-6 receptors to inhibit IL-6-mediated signaling
Oral Bioavailability	N/A – administered via subcutaneous injection
Distribution and Protein Binding	Apparent volume of distribution of 7.3 L at steady state
Elimination	Not via renal or hepatic pathways; eliminated by parallel linear, non-saturable proteolytic and non-linear saturable target-mediated elimination pathways
Half-Life	Concentration dependent. 200 mg q2w: up to 10 days; 150 mg q2w: up to 8 days
Metabolism	Has not been characterized; expected to be degraded into small peptides and amino acids via catabolic pathways

Abbreviations: IL-6 = interleukin-6; L= liter; N/A = not applicable; q2w = every two weeks

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Symptomatic improvement (ACR20/50/70, DAS28)
2) Functional status (HAQ-DI)
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:
1) ACR20 at week 24
2) Change from baseline in HAQ-DI at weeks 12 and 16
3) Change from baseline in SHS at week 52
4) Change from baseline in DAS28-ESR at week 24

Table 6. Comparative Evidence Table for Sarilumab.

Ref./Study Design	Drug Regimens Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Genovese MC, et al.[19]	Cohort 1 (Safety outcomes) 1. Sarilumab 150 mg q2w	Demographics: • Mean age: 50 yr • 82% Female • 86% White • Mean duration of RA: 9 yr	Efficacy Analysis Group (Cohort 2):	Primary Endpoints: ACR20 at week 24 1. 232/400 (58.0%) 2. 265/399 (66.4%) 3. 133/398 (33.4%)	35.6%/3 44.0%/3	Serious AEs 1. 38 (8.8%) 2. 48 (11.3%) 3. 23 (5.4%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomization was performed centrally and patients were randomized 1:1:1 for cohort 2 (those randomized after dose selection). Allocation

MOBILITY Part B (Phase 3) MC, DB, PC, RCT	2. Sarilumab 200 mg q2w 3. Placebo <u>Cohort 2 (Efficacy and safety outcomes)</u> 1. Sarilumab 150 mg q2w + weekly MTX 2. Sarilumab 200 mg q2w + weekly MTX 3. Placebo + weekly MTX 52 weeks Randomized 1:1:1	• Mean MTX dosage: 15.4 mg/week • Prior biologic DMARD exposure: 20.2% • Concomitant corticosteroids: 64.9% • Mean SHS: 49.7 • Mean HAQ DI: 1.6 <u>Key Inclusion Criteria</u>: • Age 18-75 years • Active RA ≥3 months despite tx with MTX for ≥12 weeks at a stable dosage at ≥6 weeks prior to screening • ≥1 documented bone erosion OR positive for anti-CCP antibodies OR seropositive for rheumatoid factor on screening lab tests at baseline <u>Key Exclusion Criteria</u>: • Uncontrolled concomitant diseases • Significant extra-articular manifestations of RA • Functional class IV RA (indicating severe disease) • Other inflammatory joint diseases • Current/recurrent infections • Prior nonresponse to a biologic DMARD	<u>ITT</u>: Total: 1197 1. 400 2. 399 3. 398 <u>Attrition</u>: Total: 461 (38.5%) 1. 130 (32.5%) 2. 129 (32.4%) 3. 202 (50.8%) <u>Safety Analysis Group (Cohorts 1 & 2)</u> Total: 1282 1. 431 2. 424 3. 427	p<0.0001 for both strengths of sarilumab + MTX vs. placebo + MTX (RR & CI NR) Change from baseline in HAQ DI at week 16 (± SEM) 1. -0.53 ± 0.03 2. -0.55 ± 0.03 3. -0.29 ± 0.03 p<0.0001 for both strengths of sarilumab + MTX vs. placebo + MTX (CI NR) Change from baseline in the SHS at week 52 (± SEM) 1. 0.90 ± 4.66 2. 0.25 ± 4.61 3. 2.78 ± 7.73 p<0.0001 for both strengths of sarilumab + MTX vs. placebo + MTX (CI NR) <u>Key Secondary Endpoint</u>: ACR70 maintained x24w 1. 51/400 (12.8%) 2. 59/399 (14.8%) 3. 12/398 (3.0%) p<0.0001 for both strengths of sarilumab + MTX vs. placebo + MTX (RR & CI NR)	 NA NA 9.8%/11 11.8%/9	<u>AEs Leading to DC</u> 1. 54 (12.5%) 2. 59 (13.9%) 3. 20 (4.7%) <u>Infections and Infestations</u> 1. 173 (40.1%) 2. 168 (39.6%) 3. 133 (31.1%) <u>Injection Site Reactions</u> 1. 9% 2. 10.1% 3. 1.2% <u>Neoplasms</u> 1. 4 (0.9%) 2. 3 (0.7%) 3. 1 (0.2%) <u>AEs Leading to Death</u> 1. 2 (0.5%) 2. 1 (0.2%) 3. 2 (0.5) p-values, RR, 95% CI were NR	NA NA NA NA	stratified by region and prior use of biologic agents. Baseline characteristics similar among treatment groups. <u>Performance Bias</u>: Unclear. Noted double-blinded but did not specify who was blinded or how. Noted a protocol was approved but did not specify that it was standardized across all sites and followed consistently. Use of subjective outcomes may increase bias. <u>Detection Bias</u>: Unclear. Investigators were blinded to CRP and IL-6 levels. Radiograph readers were blinded to treatment assignment, chronologic order of the radiographs, and patient's clinical status. However, method for blinding primary endpoint of ACR20 assessment not mentioned. <u>Attrition Bias</u>: High. Overall high attrition of 38.5%. Attrition similar between sarilumab groups and significantly higher in placebo group. ITT used for efficacy analysis. Missing data for ACR20 classified as nonresponse giving a conservative estimate of effect. Radiographic progression data were imputed using linear extrapolation for missing or post-rescue therapy data. Data before the rescue therapy period were included as observed <u>Reporting Bias</u>: High. Funded by the manufacturer who had a role in the study design, data collection, data analysis, data interpretation, and writing of the manuscript. Study protocol not available. Not all secondary endpoints reported. Confidence intervals not reported. **Applicability**: <u>Patient</u>: The mean age 50 years. Broad exclusion criteria limits applicability to patients with other uncontrolled comorbid condition(s). ~80% of patients did not have prior exposure to a biologic DMARD, which affects applicability. <u>Intervention</u>: Weekly MTX was given in combination with all treatments, which reflects clinical practice with other biologics.

								Comparator: Placebo appropriate to determine efficacy, though a comparative efficacy study would have provided more information regarding place in therapy. Outcomes: Primary outcomes were an appropriate assessment for the treatment of RA, although ACR50 or ACR70 might be considered more clinically important. Setting: The study was conducted at 199 centers across 36 countries. 18.7% of the patients were from either Austria, Australia, Belgium, Canada, Finland, Germany, Greece, Hungary, New Zealand, Portugal, Spain, or the U.S. Proportion of patients from the US not specified.
2. Fleischmann R, et al.[20] TARGET 3-arm, MC, DB, PC, RCT	1. Sarilumab 150 mg q2w+ background conventional synthetic DMARD(s) 2. Sarilumab 200 mg q2w + background conventional synthetic DMARD(s) 3. Placebo q2w + background conventional synthetic DMARD(s) 24 weeks Randomized 1:1:1	Demographics: • Mean age: 52 yr • 82% Female • 71% White • Mean duration of RA: 12.1 yr • Background MTX: 86% • Background leflunomide: 9% • Background sulfasalazine: 6% • Background hydroxychloroquine: 7% • Prior exposure to 1 anti-TNF agent: 77% • Prior exposure to >1 anti-TNF agent: 23% • Mean HAQ DI: 1.77 • Mean DAS28-CRP: 6.2 Key Inclusion Criteria: • Age ≥18 years • Active RA ≥6 months • Inadequate response or intolerance to ≥1 anti-TNF therapy • Continuous tx with background conventional synthetic DMARD(s)	ITT: Total: 546 1. 181 2. 184 3. 181 Attrition: Total: 187 (34%) 1. 56 (31%) 2. 51 (28%) 3. 80 (44%)	Primary Endpoints: ACR20 at week 24 1. 101/181 (55.8%) 2. 112/184 (60.9%) 3. 61/181 (33.7%) p<0.0001 for both strengths of sarilumab + csDMARD(s) vs. placebo + csDMARD(s) (RR & CI NR) Change from baseline in HAQ DI at week 12 (± SEM) 1. -0.46 ± 0.04 2. -0.47 ± 0.04 3. -0.26 ± 0.04 p<0.001 for both strengths of sarilumab + csDMARD(s) vs. placebo + csDMARD(s) (CI NR) Secondary Endpoints: Mean adjusted change in DAS28-CRP (± SEM) 1. -2.4 ± 0.11 2. -2.8 ± 0.11 3. -1.4 ± 0.12 p<0.0001 for both strengths of sarilumab + csDMARD(s) vs. placebo + csDMARD(s) (CI NR)	22.1%/5 27.2%/4 NA NA	Serious AEs 1. 6 (3.3%) 2. 10 (5.4%) 3. 6 (3.3%) AEs leading to DC 1. 14 (7.7%) 2. 17 (9.2%) 3. 8 (4.4%) AEs leading to death 1. 0 (0%) 2. 0 (0%) 3. 1 (0.6%) Infections 1. 40 (22.1%) 2. 56 (30.4%) 3. 48 (26.5%) Injection-site reactions 1. 7.2% 2. 8.2% 3. 1.1% Malignancies 1. 1 2. 1	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized centrally and allocated 1:1:1. Baseline characteristics similar between groups. Patients stratified by number of previous anti-TNF agents. Performance Bias: Unclear. Double-blind but not specified which groups blinded. Double-dummy using matching placebo subcutaneous injections. Protocol was approved by ethics committees/institutional review boards. Use of subjective outcomes increases risk of bias. Detection Bias: Low. Investigators blinded and assessors had no access to patient data. Attrition Bias: High. ITT utilized for efficacy and safety analyses. High total attrition (34%) but lower attrition with sarilumab than placebo. Differential attrition >10% for sarilumab vs. placebo with placebo having greater attrition. LOCF applied to impute missing ACR20 data and HAQ-DI data. Reporting Bias: Low. All primary outcomes reported. Documented end point in predefined hierarchy of secondary endpoints. Study was funded by the manufacturer. Confidence intervals not reported **Applicability:**

		Key Exclusion Criteria: • Uncontrolled concomitant disease • Significant extra-articular manifestations of RA • Functional class IV RA • Other inflammatory diseases • Current/recurrent infections • Receiving prednisone (or equivalent) >10 mg/day		ACR50 at week 24: 1. 67/181 (37.0%) 2. 75/184 (40.8%) 3. 33/181 (18.2%) p<0.0001 for both strengths of sarilumab + csDMARD(s) vs. placebo + csDMARD(s) (RR & CI NR) ACR70 at week 24: 1. 36/181 (19.9%) 2. 30/184 (16.3%) 3. 13/181 (7.2%) p<0.001 for #1 and p<0.01 for #2 vs. placebo + csDMARD(s) (RR & CI NR)	18.8%/6 22.6%/5 12.7%/8 9.1%/11	3. 1 p-values, RR, 95% CI were NR		Patient: Broad exclusion criteria limits applicability to patients with uncontrolled concomitant disease and class IV RA. Intervention: Subcutaneous injections were self-administered or administered by a caregiver. Comparator: A comparative efficacy comparison would have been more meaningful than placebo. Outcomes: Primary outcome was an appropriate assessment for the treatment of rheumatoid arthritis. The short study duration prevents ability to report long-term outcomes data. Setting: The study was conducted at 155 study centers across 27 countries including the U.S.
3. Burmester GR, et al.[18] MONARCH MC, active-controlled, DB, DD, phase 3 superiority RCT	1. Sarilumab 200 mg q2w plus placebo q2w 2. Adalimumab 40 mg q2w plus placebo 24 weeks	Demographics: • Mean age: 52 years • 83.2% Female • 90.8% White • Mean duration of RA: 7 yr • Use of 1 prior csDMARD: 46.4% • Concomitant oral corticosteroids: 54.8% • Mean HAQ-DI: 1.6 • Mean DAS28-CRP: 6.0 Key Inclusion Criteria: • Active RA ≥3 months • Intolerant or inappropriate candidate for continued MTX or MTX inadequate responders Key Exclusion Criteria: • Prior biological disease-modifying antirheumatic drugs (bDMARD) experience	ITT: Total: 369 1. 184 2. 185 Attrition: Total: 45 (12.2%) 1. 19 (10.3%) 2. 26 (15.7%)	Primary Endpoint: Change from baseline in DAS28-ESR at week 24 1. -3.28 2. -2.20 Difference: -1.08 95% CI (-1.36 to -0.79) P<0.0001 Secondary Endpoint: DAS28-ESR remission (<2.6) at week 24 1. 49 (26.6%) 2. 13 (7.0%) OR 4.88 95% CI (2.54 – 9.39) P<0.0001 ACR20 at week 24 1. 132 (71.7%) 2. 108 (58.4%) P=0.0074 (RR & CI NR) ACR50 at week 24 1. 84 (45.7%) 2. 55 (29.7%)	NA 19.6%/6 13.3%/8 16.0%/7	Serious AEs 1. 9 (4.9%) 2. 12 (6.5%) AEs leading to DC 1. 11 (6.0%) 2. 13 (7.1%) Infections 1. 53 (28.8%) 2. 51 (27.7%) Serious infections 1. 2 (1.1%) 2. 2 (1.1%) Neutropenia 1. 25 (13.5) 2. 1 (0.5%) Injection site reactions 1. 17 (9.2%) 2. 8 (4.3%) Deaths 1. 1 (0.5%)* 2. 0 (0%)	NA NA NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Centrally randomized using an interactive voice response system. Baseline characteristics similar between groups. Performance Bias: Low. Double-dummy blinding was used. A protocol was used. Use of subjective outcomes increases risk of bias. Detection Bias: Low. Investigators did not have access to randomization information. Attrition Bias: Low. Low total and differential attrition. ITT was used for efficacy analysis. Patients who discontinued treatment were considered nonresponders. Reporting Bias: Low. Study protocol was approved by ethics committees/institutional review boards. Primary and secondary endpoints were reported per hierarchy. The study was funded by the manufacturer. **Applicability**: Patient: Patients with prior bDMARD experience were excluded, limiting the applicability to bDMARD retreatment. Intervention: Sarilumab dosing appropriate. Comparator: Adalimumab dosing appropriate. Outcomes: Primary outcome was an appropriate assessment for RA.

				P=0.0017 (RR & CI NR) ACR70 at week 24 1. 43 (23.4%) 2. 22 (11.9%) P=0.0036 (RR & CI NR) HAQ-DI LS mean change from baseline at week 24 1. -0.61 2. -0.43 Difference: -0.18 95% CI (-0.31 to -0.06) P=0.0037	11.5%/9 NA	*Acute cardiac failure secondary to aortic dissection and papillary muscle rupture		Setting: Conducted at 86 study centers in Europe, Israel, Russia, South Africa, South America, South Korea, and the USA.

Abbreviations [alphabetical order]: ACR20 = American College of Rheumatology 20% Improvement Criteria; ACR50 = American College of Rheumatology 50% Improvement Criteria; ACR70 = American College of Rheumatology 70% Improvement Criteria; AE = adverse event; ARR = absolute risk reduction; bDMARD = biologic disease-modifying antirheumatic drug; CCP = cyclic citrullinated peptide; CI = confidence interval; CRP = C-reactive protein; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; DAS28-ESR = 28-joint disease activity score using erythrocyte sedimentation rate; DB = double-blinded; DC = discontinuation; DD = double-dummy; DMARD = disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire disability index; IL-6 = interleukin-6; ITT = intention to treat; LOCF = last observation carried forward; LS = least squares; MC = multicenter; mITT = modified intention to treat; MTX = methotrexate; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = odds ratio; PC = placebo-controlled; PP = per protocol; q2w = every 2 weeks; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = relative risk; SEM = standard error of the mean; SHS = Sharp/van der Heijde score; TNF = tumor necrosis factor; tx = treatment; yr = year.

NEW DRUG EVALUATION: Guselkumab (Tremfya®)

See **Appendix 3** for Highlights of Prescribing Information of guselkumab from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Guselkumab, an interleukin (IL)-23 inhibitor, is indicated for treatment of adults with moderate to severe PsO who are candidates for systemic therapy or phototherapy. Two phase 3 trials (VOYGAGE 1 and VOYAGE 2) provide efficacy and safety data for guselkumab in PsO compared to placebo or adalimumab.

In VOYAGE 1, guselkumab was compared to placebo for 16 weeks or adalimumab for 48 weeks in 837 patients with moderate to severe PsO.[21] Patients were randomized in a 2:1:2 ratio to guselkumab 100 mg administered at weeks 0, 4 and 12 and then every 8 weeks; placebo administered at weeks 0, 4, and 12 followed by guselkumab 100 mg at weeks 16 and 20 and every 8 weeks thereafter; or adalimumab 80 mg at week 1 followed by 40 mg every 2 weeks. Co-primary endpoints were the proportion of patients achieving an IGA score of cleared/minimal disease (IGA 0/1) and 90% or greater improvement in PASI score from baseline (PASI 90) at week 16. Secondary endpoints included the proportion of patients who achieved IGA 0/1, PASI 75, and PASI 90 scores at week 16, 24 and 48 in the guselkumab treated group compared to those who received adalimumab. At week 16, the co-primary endpoints of IGA score 0/1 and PASI 90 were achieved by more guselkumab-treated patients compared to placebo patients (85.1% vs. 6.9%; ARR = 78.2%; NNT = 2 and 73.3% vs. 2.9%; ARR = 70.4%; NNT = 2 respectively; p<0.001 for each).[21] At week 16, more guselkumab-treated patients achieved IGA 0/1, PASI 90, and PASI 75 than adalimumab- treated patients (85.1% vs. 65.9%; ARR = 19.2%; NNT =6: 73.3% vs. 49.7%; ARR = 23.6%; NNT = 5: 91.2% vs. 73.1%; ARR = 18.1%; NNT = 6 respectively; p<0.001 for each outcome). A[21] At week 24, IGA score 0/1, and PASI 90 were achieved by significantly more guselkumab-treated patients compared to adalimumab-treated patients (84.2% vs. 61.7% and 80.2% vs. 53.0%, respectively; p<0.001 for each).[21] At week 48, IGA score 0/1, and PASI 90 were achieved by significantly more guselkumab-treated patients than adalimumab-treated patients (80.5% vs. 55.4%, and 76.3% vs. 47.9%, respectively; p<0.001 for each outcome).[21]

VOYAGE 2 consisted of a placebo-controlled phase (weeks 0-16), active comparator-controlled phase (weeks 0-28), and placebo-controlled, randomized withdrawal and retreatment phase (weeks 28-48) in 992 subjects.[22] At baseline patients were randomized 2:1:1 to guselkumab (n=496), placebo (n= 248), or adalimumab (n=248) for the first 28 weeks of the trial.[22] During the subsequent withdrawal/retreatment phase patients were re-randomized to either guselkumab or placebo in the same dosing strategy used for VOYAGE 1. The inclusion and exclusion criteria were similar in both trials. To evaluate maintenance and durability of response, at week 28 subjects with PASI 90 response to guselkumab (n=219) were re-randomized to either continue guselkumab or change to placebo treatment.[22] In addition, patients who were adalimumab non-responders (n=220) were switched to guselkumab or placebo at week 28.[22]

In the VOYAGE 2 trial, the co-primary endpoints of an IGA score 0/1 and PASI 90 were achieved by more guselkumab-treated patients compared to placebo-treated patients at week 16 (84.1% vs. 8.5%; ARR =75.6%; NNT = 2 and 70.0% vs. 2.4%; ARR = 67.6%; NNT = 2 respectively; p<0.001 for both).[22] In addition, more guselkumab-treated patients achieved IGA 0/1, PASI 90 and PASI 75 than adalimumab-treated patients at week 16 (84.1% vs. 67.7%, 70.0% vs. 46.8%, and 86.3% vs. 68.5%, respectively; p<0.001 for each).[22] Similar differences were sustained for another 8 weeks to week 24 (83.5% vs. 64.9% for IGA 0/1; 75.2% vs. 54.8% for PASI 90; and 89.1% vs. 71.0% for PASI 75; p<0.001 for each outcome).[22]

During the re-randomized withdrawal and retreatment period (week 28-48), PASI 90 response was better maintained by the guselkumab week 28 responders who continued guselkumab (maintenance group) compared to those who were re-randomized to placebo (withdrawal group).[22] Through week 48, 88.6% of patients in the maintenance group sustained a PASI 90 response versus 36.8% of those in the withdrawal group (p< 0.001).[22] Guselkumab-treated patients

maintained response whereas psoriasis slowly recurred in patients receiving placebo. Of adalimumab non-responders who switched to guselkumab, 66.1% achieved PASI 90 at week 48.[22] VOYAGE 2 provides data to support the need for continuing therapy with guselkumab to maintain a level of response over 48 weeks and successful transition from adalimumab to guselkumab.[22]

Trial Limitations:
Most of the patients (75%) enrolled in the guselkumab trials had moderate PsO at baseline and a higher percentage of males were enrolled in study. The duration of the VOYAGE 1 trial limited safety assessment to 48 weeks, although open label extension continued to week 160. In VOYAGE 2 the comparison of guselkumab with adalimumab was limited to 24 weeks. Approximately 75% of the VOYAGE trials were conducted outside of the U.S., which limits the applicability of the trial results to U.S. patients.

Comparative Efficacy:
Another Phase 3 trial sponsored by the manufacturer evaluated the efficacy and safety of guselkumab in patients with moderate-to-severe plaque psoriasis who had an inadequate response to 2 doses of open label ustekinumab at weeks 0 and 4.[95] At week 16, patients (n=268) with an inadequate response to ustekinumab (IGA ≥ 2) were randomized (double-blind) to guselkumab 100 mg or to continue ustekinumab; 585 of 871 patients (67%) with IGA 0/1 at week 16 continued open-label ustekinumab.[95] The primary end point was the number of visits at which randomized patients achieved IGA 0/1 and at least a two-grade improvement (from week 16) from week 28 to week 40.[95] The visit interval from week 28 to week 40 included a total of 4 visits; therefore, the possible number of visits for the primary endpoint ranged from 0 to 4. The FDA stated to the manufacturer in advice letters that using the number of visits as a combination of success and duration makes the interpretation of study findings difficult.[96] In their advice letters, the FDA recommended comparing the response rates at a specific time point and comparing the duration of effect for patients who achieved success with treatment.[96] The authors of this trial reported the mean number of visits at which patients achieved IGA 0/1 and at least a two-grade improvement was greater in the guselkumab group compared to the randomized ustekinumab group (1.5 vs. 0.7; P < 0.001, 95% CI not reported).[95] After week 16, 64% of patients in the guselkumab group and 56% in the ustekinumab group had at least one adverse event; infections were the most frequent type of adverse event.[95] Overall, 6.7% (n = 9) of patients in the guselkumab group had at least one serious adverse effect compared with 4.5% (n = 6) for the ustekinumab group.[95] Based on the small number of randomized patients, primary endpoint of limited value, and open label ustekinumab arms, this trial was rated as poor quality and not included in the comparative evidence table.

Clinical Safety:
In VOYAGE 1 through week 16, the proportions of patients with at least one adverse event were comparable across treatment groups (49.4% placebo, 51.7% guselkumab, 51.1% adalimumab).[21] The most commonly reported adverse effects were nasopharyngitis and upper respiratory tract infections. SAEs were reported at similar rates across all 3 treatment arms: 1.7% for placebo, 2.4% for guselkumab, and 1.8% for adalimumab.[21] Through week 48, the proportion of patients with more than one adverse effect were similar in the guselkumab and adalimumab groups (73.9% vs. 74.5%, respectively).[21] SAEs were also reported at a similar rate: 4.9% for the guselkumab group and 4.5% for the adalimumab group.[21] Through week 48, injection site reactions occurred in 2.2% of guselkumab-treated patients and in 9.0% of adalimumab-treated patients.[21] Most injection site reactions were mild. Study discontinuation rates over 48 weeks due to adverse effects with guselkumab were 2.7% compared to 3.6% with adalimumab.[21]

In VOYAGE 2 during the placebo-controlled period (weeks 0-16), at least one adverse effect occurred in 44.8%, 47.6%, and 48.4% of patients in the placebo, guselkumab, and adalimumab groups, respectively.[22] The most commonly reported adverse effects were nasopharyngitis, headache, and upper respiratory tract

infection. SAEs occurred in 1.2%, 1.6%, and 2.4% of patients in the placebo, guselkumab, and adalimumab groups, respectively.[22] Injection-site reactions occurred in 6.9% of adalimumab treated patients compared to 2.6% of guselkumab-treated patients.[22]

Upper respiratory infections, headache and injection site reactions were the most frequent adverse effects observed with guselkumab during clinical trials.[23] Pooled data from VOYAGE 1 and VOYAGE 2 did not demonstrate an increased risk of suicidal ideation or adverse cardiovascular events with guselkumab.[23] A summary of the adverse reactions observed through week 16 in the VOYAGE 1 and 2 trials is presented in **Table 7.**

Table 7: Adverse Reactions Occurring in ≥1% of Subjects through Week 16 in VOYAGE 1 and VOYAGE 2[23]

Adverse Effect	**Guselkumab N=823 n (%)**	**Adalimumab N=196 n (%)**	**Placebo N=422 n (%)**
Upper respiratory infections	118 (14.3)	21 (10.7)	54 (12.8)
Headache	38 (4.6)	2 (1.0)	14 (3.3)
Injection site reactions	37 (4.5)	15 (7.7)	12 (2.8)
Arthralgia	22 (2.7)	4 (2.0)	9 (2.1)
Diarrhea	13 (1.6)	3 (1.5)	4 (0.9)
Gastroenteritis	11 (1.3)	4 (2.0)	4 (0.9)
Tinea infections	9 (1.1)	0	0
Herpes simplex infection	9 (1.1)	0	2 (0.5)

Look-alike / Sound-alike Error Risk Potential: No issues identified.

Table 8. Pharmacology and Pharmacokinetic Properties of Guselkumab

Parameter	
Mechanism of Action	IL-23 inhibition
Distribution	Volume of distribution = 13.5 liters
Elimination	0.516 liters/day
Half-Life	15-18 days
Metabolism	Not characterized

Abbreviations: IL = interleukin

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Symptomatic improvement (PASI 75)
2) Remission
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1)Proportion of patients achieving co-primary endpoint of IGA 0/1 or PASI 90 at week 16 compared to placebo

Table 9. Comparative Evidence Table for Guselkumab

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Blauvelt et al.[21] (VOYAGE 1) Phase 3, DB, MC, RCT 48 weeks N=837	1. Guselkumab 100 mg SC at weeks 0, 4 and 12 and then every 8 weeks through week 48 2. Placebo injections at weeks 0, 4, and 12 followed by guselkumab 100 mg SC at weeks 16 and 20, and every 8 weeks through week 48 3. Adalimumab 80 mg at week 0, 40 mg at week 1, 40 mg every 2 weeks through week 47	Demographics: -Mean age: 44 y -Male: 74% -White: 82% Duration of Psoriasis: 17 years -Median baseline PASI score: 19 -Baseline IGA score = 3 (moderate): 75% Key Inclusion Criteria: ≥18 years with moderate to severe PsO defined as: IGA score ≥3, PASI score ≥12, and ≥10% BSA involvement ≥ 6 mos. Key Exclusion Criteria: -Uncontrolled medical condition -Patients with gutatte, erythrodermic, or pustular psoriasis -Malignancy -History of active TB -Other TNF therapy within 3 months -IL-12/23, IL-17, or IL-23 therapy within 6 months -MTX or phototherapy within 4 weeks	ITT: 1. 329 2. 174 3. 333 PP: 1.301 2.162 3.282 Attrition: 1. 28 (8.5%) 2. 12 (6.9%) 3.52 (15.6%)	Primary Endpoint: Achieved IGA 0/1 or PASI 90 at week 16: IGA 0/1: 1. 280 (85.1%) 2. 12 (6.9%) p < 0.001 (RR and CI NR) PASI 90: 1. 241 (73.3%) 2. 5 (2.9%) p < 0.001 (RR and CI NR) Secondary Endpoints: Achieved PASI 75 at week 16: 1. 300 (91.2%) p < 0.001 vs. 2 (RR and CI NR) 2. 10 (5.7%) 3. 244 (73.1%) p < 0.001 vs. 2 (RR and CI NR) Achieved IGA score 0/1 at week 24 (guselkumab vs. adalimumab) 1. 277 (84.2%) 3. 206 (61.7%) p < 0.001 (RR and CI NR) Achieved PASI 90 at week 24 (guselkumab vs. adalimumab): 1. 264 (80.2%) 3. 177(53%) p < 0.001 (RR and CI NR) Achieved IGA score 0/1 at week 48 (guselkumab vs. adalimumab)	78%/2 70%/2 85%/2 18%/6 23%/5 27%/4	AE through week 16 1. 170 (51.7%) 2. 86 (49.4%) 3. 170 (51.1%) SAE through week 16 1. 8 (2.4%) 2. 3 (1.7%) 3. 6 (1.8%) Discontinued study due to AE through week 16 1. 1.4 (1.2%) 2. 2 (1.1%) 3. 3 (.0.9%)	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomized using IVRS in 2:1:2 ratio. Baseline characteristics balanced between groups. Performance Bias: LOW. Matching placebo used to maintain blinding. Detection Bias: LOW: PASI and IGA are validated instruments to assess PsO. Attrition Bias: UNCLEAR. Higher attrition rate in adalimumab arm vs guselkumab vs placebo. Patients who discontinued study agents or started a protocol-prohibited psoriasis treatment were considered non-responders. Reporting Bias: UNCLEAR. 95% confidence intervals not provided. Protocol available. Supported by Janssen. **Applicability**: Patient: 75% of patients had moderate PsO at baseline, higher percentage of males enrolled in study Intervention: Guselkumab dosing appropriate and is approved by the FDA. Comparator: Placebo and active comparator (adalimumab) used to assess safety and efficacy of guselkumab Outcomes: Validated outcomes: IGA and PASI. Duration of trial may have limited safety assessment to 48 weeks, although OL extension continued to week 160. Setting: 101 clinical sites in 10 countries: Canada (n=11); US (n=27); Hungary (n=6); Poland (n=7); Russia (n=12); Germany (n=14); Spain (n=5); Australia (n=7); Korea (n=6); Taiwan (n=6).

				1. 265 (80.5%) 3. 185 (55.4%) p < 0.001 (RR and CI NR) Achieved PASI 90 at week 48 (guselkumab vs. adalimumab) 1. 251 (76.3%) 3. 160 (47.9%) p < 0.001 (RR and CI NR)	26%/4 28%/4			
2. Reich et al[22] (VOYAGE 2) MC, RCT, DB 48 weeks N=992	1. Guselkumab 100 mg SC at weeks 0, 4, 12 and 20 2. Placebo at week 0, 4, and 12 then guselkumab at week 16 and 20 3.Adalimumab 80mg SC at week 0, 40mg week 1 and then every 2 weeks through week 23 Withdrawal and retreatment period (weeks 28-48) -PASI 90 non-responders continued guselkumab 100 mg SC every 8 weeks. -PASI 90 responders received placebo until loss of ≥50% PASI improvement. Then re-treated with guselkumab 100 mg SC every 8 weeks OR placebo 1.Guselkumab 100 mg SC starting week	Demographics: -Mean age: 43.5 y -Male: 70% -Average duration of psoriasis: 17.8 y -Median baseline PASI score: 19 Baseline IGA score = 3 (moderate): 78% Key Inclusion Criteria: See VOYAGE 1 Key Exclusion Criteria: See VOYAGE 1	Week 0-28 ITT: 1. 496 2. 248 3. 248 PP: 1.470 2.212 3.228 Attrition: 1.26 (5%) 2.21 (8%) 3.20 (8%)	Primary Endpoint: Achieved IGA 0/1 and PASI 90 response at week 16: IGA 0/1 1. 417(84.1%) 2. 21 (8.5%) p < 0.001 (RR and CI NR) PASI 90 1. 347 (70%) 2. 6 (2.4%) p < 0.001 (RR and CI NR) Secondary Endpoints: Proportion of subjects who achieved PASI 75 at week 16: 1. 428 (86.3%) p < 0.001 vs 2 (RR and CI NR) 2. 20 (8.1%) 3. 170 (68.5%) p < 0.001 vs 2 (RR and CI NR) Achieved IGA score 0/1 at week 24 (guselkumab vs. adalimumab) 1. 414 (83.5%) 3. 161 (64.9%) p < 0.001 (RR and CI NR) Achieved PASI 90 at week 24 (guselkumab vs. adalimumab)	75%/2 68%/2 78%/2 19%/6 19%/6	AE: 1. 235 (47.6%) 2. 111 (44.8%) 3. 120 (48.4%) SAE: 1. 8 (1.6%) 2. 3 (1.2%) 3. 6 (2.4%) Discontinued study due to AE: 1. 7 (1.4%) 2. 2 (0.8%) 3. 4 (1.6%) Infections: 1. 106 (21.5%) 2. 46 (18.5%) 3. 58 (23.4%)	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Subjects randomized 2:1:1 ratio using permuted block method via IVRS. Baseline demographics comparable amongst groups. Performance Bias: LOW. Matching placebo used to maintain blinding to active treatment arms. Detection Bias: UNCLEAR. Not described Attrition Bias: LOW. Attrition rates similar between arms. Reporting Bias: UNCLEAR. No 95% confidence intervals provided for results. Protocol available. Supported by Janssen. **Applicability**: Patient: Reasonable patient group identified through inclusion/exclusion criteria Intervention: Guselkumab dosing appropriate Comparator: Placebo and active comparator (adalimumab) used to assess efficacy of drug Outcomes Validated outcomes: IGA and PASI Setting: 115 clinical sites in 9 countries: Canada (n=10); Czech (n=7); US (n=31); Poland (n=18); Russia (n=11); Germany (n=10); Spain (n=9); Australia (n=6); Korea (n=13)

	28 followed by 100mg SC 4 weeks later then every 8 weeks through week 48 2.Placebo			1. 373 (75.2%) 3. 136 (54.8%) p < 0.001 (RR and CI NR)	20%/5			

Abbreviations [alphabetical order]: AE = Adverse Effects; ARR = absolute risk reduction; CI = confidence interval; DB= Double Blind; IGA = Investigator's Global Assessment; IL = interleukin; ITT = intention to treat; IVRS = Interactive Voice Response System; MC = Multi-Center; MTX = methotrexate; N = number of subjects; NA = not applicable; NR=Not Reported; NNH = number needed to harm; NNT = number needed to treat; OL = open label; PASI = Psoriasis Area Severity Index; RR=Relative Risk; SAE = Serious Adverse Effects; SC= Subcutaneous; TB = tuberculosis; PP = per protocol YO=Years Old

References:

1. Ruiz Garcia V, Burls A, Cabello JB, Vela Casasempere P, Bort-Marti S, Bernal JA. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. *Cochrane Database Syst Rev.* 2017;9:CD007649.
2. Smolen JS, Landewe R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Annals of the Rheumatic Diseases.* 2017;76(6):960-977.
3. National Institute for Health and Care Excellence. Tofacitinib for moderate to severe rheumatoid arthritis. Updated October 2017. https://www.nice.org.uk/guidance/ta480. Accessed November 3, 2017.
4. National Institute for Health and Care Excellence. Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs. Updated May 2017. https://www.nice.org.uk/guidance/ta445. Accessed November 3, 2017.
5. National Institute for Health and Care Excellence. Utekinumab for moderately to severely active Crohn's disease after previous treatment. Updated July 2017. https://www.nice.org.uk/guidance/ta456. Accessed November 3, 2017.
6. National Institute for Health and Care Excellence. Adalimumab, etanercept, and ustekinumab for treating plaque psoraisis in children and young people. Updated July 2017.https://www.nice.org.uk/guidance/ta455. Accessed November 3, 2017.
7. Actemra (tocilizumab) [product information]. South San Francisco, CA: Genentech, Inc., Aug 2017.
8. Stelara (ustekinumab) [product information]. Horsham, PA: Janssen Biotech, Inc., Oct 2017.
9. Taltz (ixekizumab) [product information]. Indianapolis, IN: Eli Lilly and Company, Dec 2017.
10. Simponi Aria (golimumab) [product information]. Horsham, PA: Janssen Biotech, Inc., Oct 2017.
11. Orencia (abatacept) [product information]. Princeton, NJ: Bristol-Myers Squibb Company, June 2017.
12. Xeljanz (tofacitinib) [product information]. New York, NY: Pfizer Inc., Dec 2017.
13. Enbrel (etancercept) [product information]. Thousand Oaks, Ca: Immunex Corporation, Inc., Sept 2017.
14. Cholapranee A, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther.* 2017;45(10):1291-1302.
15. Jabbar-Lopez ZK, Yiu ZZN, Ward V, et al. Quantitative Evaluation of Biologic Therapy Options for Psoriasis: A Systematic Review and Network Meta-Analysis. *J Invest Dermatol.* 2017;137(8):1646-1654.
16. Ma Z, Liu X, Xu X, et al. Safety of tumor necrosis factor-alpha inhibitors for treatment of ankylosing spondylitis: A meta-analysis. *Medicine (Baltimore).* 2017;96(25):e7145.
17. Park SK, Lee MY, Jang EJ, Kim HL, Ha DM, Lee EK. A comparison of discontinuation rates of tofacitinib and biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis: a systematic review and Bayesian network meta-analysis. *Clin Exp Rheumatol.* 2017;35(4):689-699.
18. Burmester GR, Lin Y, Patel R, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Annals of the Rheumatic Diseases.*76(5):840-847.
19. Genovese MC, Fleischmann R, Kivitz AJ, et al. Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study. *Arthritis Rheumatol.* 2015;67(6):1424-1437.

20. Fleischmann R AJ, Lin Y, et al. Sarilumab and Nonbiologic Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Tumor Necrosis Factor Inhibitors. *Arthritis & Rheumatology*.69(2):277-290.
21. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol.*76(3):405-417.
22. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol.*76(3):418-431.
23. Tremfya (guselkumab) Product Information. Horsham, PA: Janssen Biotech, Inc. December 2017.
24. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum.* 2008;58(1):15-25.
25. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis.* 2014;73(7):1316-1322.
26. Singh JA, Saag KG, Bridges SL, Jr., et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol.* 2016;68(1):1-26.
27. Donahue KE, Jonas DE, Hansen RA, et al. AHRQ Comparative Effectiveness Reviews. Drug Therapy for Rheumatoid Arthritis in Adults: An Update. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.
28. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology Preliminary Core Set of Disease Activity Measures for Rheumatoid Arthritis Clinical Trials. Arthritis and Rheumatism. 1993(6); 36:729-740.
29. Orbai AM, Bingham CO, 3rd. Patient reported outcomes in rheumatoid arthritis clinical trials. *Curr Rheumatol Rep.* 2015;17(4):28.
30. Ward MM, Guthrie LC, Alba MI. Clinically important changes in individual and composite measures of rheumatoid arthritis activity: thresholds applicable in clinical trials. *Ann Rheum Dis.* 2015;74(9):1691-1696.
31. The DAS28 Score. National Rheumatiod Arthritis Society. April 2017. https://www.nras.org.uk/the-das28-score. Accessed November 8, 2017.
32. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. The Journal of rheumatology. 2004;31(2):390-392.
33. Espinosa M, Gottlieb BS. Juvenile Idiopathic Arthritis. *Pediatrics in Review*. 2012;33(7):303-313.
34. Ruth NM, Passo MH. Juvenile idiopathic arthritis: management and therapeutic options. *Ther Adv Musculoskelet Dis.* 2012;4(2):99-110.
35. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum.* 2013;65(10):2499-2512.
36. McVeigh CM, Cairns AP. Diagnosis and management of ankylosing spondylitis. BMJ (Clinical research ed). 2006;333(7568):581-585.
37. Magrey MN, Khan MA. The Paradox of Bone Formation and Bone Loss in Ankylosing Spondylitis: Evolving New Concepts of Bone Formation and Future Trends in Management. *Curr Rheumatol Rep.* 2017;19(4):17.
38. Taurog JD, Chhabra A, Colbert RA. Ankylosing Spondylitis and Axial Spondyloarthritis. *N Engl J Med.* 2016;374(26):2563-2574.

39. Corbett M, Soares M, Jhuti G, et al. Tumour necrosis factor-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. *Health Technol Assess.* 2016;20(9):1-334, v-vi.
40. Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol.* 2016;68(2):282-298.
41. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis.* 2011;70(6):896-904.
42. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2008;58(5):826-850.
43. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol.* 2014;70(3):512-516.
44. Gottlieb A, Korman NJ, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol.* 2008;58(5):851-864.
45. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *The Journal of investigative dermatology.* 2013;133(2):377-385.
46. Huerta C, Rivero E, Rodriguez LA. Incidence and risk factors for psoriasis in the general population. *Archives of dermatology.* 2007;143(12):1559-1565.
47. Samarasekera E, Sawyer L, Parnham J, Smith CH. Assessment and management of psoriasis: summary of NICE guidance. *Bmj.* 2012;345:e6712.
48. Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. *J Am Acad Dermatol.* 2012;66(3):369-375.
49. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. *Br J Dermatol.* 1999;141(2):185-191.
50. Institute for Clinical and Economic Review. Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value. 2016; Available at https://icer-review.org/wp-content/uploads/2016/11/NE_CEPAC_Psoriasis_Evidence_Report_FINAL_012317.pdf. Accessed December 4, 2017.
51. Langley RGB, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatolog Treat.* 2015;26(1):23-31.
52. Mease PJ. Psoriatic arthritis: update on pathophysiology, assessment and management. *Ann Rheum Dis.* 2011;70 Suppl 1:i77-84.
53. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. *N Engl J Med.* 2017;376(10):957-970.
54. Ramiro S, Smolen JS, Landewe R, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis.* 2016;75(3):490-498.
55. Gossec L, Smolen JS, Gaujoux-Viala C, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis.* 2012;71(1):4-12.

56. Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheumatol.* 2016;68(5):1060-1071.
57. Cheifetz AS. Management of active Crohn disease. Jama. 2013;309(20):2150-2158.
58. Hutfless S, Almashat S, Berger Z, et al. AHRQ Comparative Effectiveness Reviews. Pharmacologic Therapies for the Management of Crohn's Disease: Comparative Effectiveness. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014.
59. Lichtenstein GR, Hanauer SB, Sandborn WJ, Practice Parameters Committee of American College of G. Management of Crohn's disease in adults. *Am J Gastroenterol.* 2009;104(2):465-483; quiz 464, 484.
60. Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *The Lancet.* 2015;386(10006):1825-1834.
61. Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology.* 2013;145(6):1459-1463.
62. National Clinical Guideline C. National Institute for Health and Clinical Excellence: Guidance. Crohn's Disease: Management in Adults, Children and Young People. London: Royal College of Physicians (UK) Copyright (c) October 2012, National Clinical Guideline Centre; 2012.
63. Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of G. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.* 2010;105(3):501-523; quiz 524.
64. Talley NJ, Abreu MT, Achkar JP, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol.* 2011;106 Suppl 1:S2-25; quiz S26.
65. Danese S, Fiocchi C. Ulcerative colitis. The New England journal of medicine. 2011;365(18):1713-1725.
66. Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. *J Crohns Colitis.* 2010;4(4):431-437.
67. Seah D, De Cruz P. Review article: the practical management of acute severe ulcerative colitis. *Aliment Pharmacol Ther.* 2016;43(4):482-513.
68. Archer R, Tappenden P, Ren S, et al. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): clinical effectiveness systematic review and economic model. *Health Technol Assess.* 2016;20(39):1-326.
69. National Institute for Health and Care Excellence (NICE). Ulcerative colitis: management. June 2013. https://www.nice.org.uk/guidance/cg166/resources/ulcerative-colitis-management-pdf-35109695126725. Accessed October 30, 2017.
70. National Institute for Health and Care Excellence (NICE). Vedolizumab for treating moderately to severely active ulcerative colitis. June 2015. https://www.nice.org.uk/guidance/ta342. Accessed May 17, 2017.
71. Jairath V, Zou GY, Parker CE, et al. Placebo response and remission rates in randomised trials of induction and maintenance therapy for ulcerative colitis. *Cochrane Database Syst Rev.* 2017;9:CD011572.
72. Lexicomp® Online, Lexi-Drugs, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2017. Accessed November 2, 2017.
73. DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 – Available from http://www.ebscohost.com/dynamed/. Registration and login required. Accessed June 7, 2017.

74. Gartlehner G, Glechner A, Kien C, et al. Targeted Immune Modulators Drug Class Review: Final Update 5 Report, June 2016. Drug Effectiveness Review Project at the Pacific Northwest Evidence Practice Center, Portland, Oregon, in partnership with Cecil G. Sheps Center for Health Services Research at RTI-UNC Evidence-based Practice Center, Chapel Hill, NC.
75. Cimzia (certolizumab pegol) [product information]. Smyrna, GA: UCB, Inc., Jan 2017.
76. National Institute for Health and Care Excellence. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. Updated July 2017. https://www.nice.org.uk/guidance/ta199. Accessed December 1, 2017.
77. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med.* 2017;377(4):317-328.
78. Mease PJ, Gottlieb AB, van der Heijde D, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. *Ann Rheum Dis.* 2017;76(9):1550-1558.
79. Mease P, Genovese MC, Gladstein G, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis Rheum.* 2011;63(4):939-948.
80. Kavanaugh A, Husni ME, Harrison DD, et al. Safety and Efficacy of Intravenous Golimumab in Patients With Active Psoriatic Arthritis: Results Through Week Twenty-Four of the GO-VIBRANT Study. *Arthritis Rheumatol.* 2017;69(11):2151-2161.
81. Deodhar A, Reveille JD, Harrison DD, et al. Safety and Efficacy of Golimumab Administered Intravenously in Adults with Ankylosing Spondylitis: Results through Week 28 of the GO-ALIVE Study. *J Rheumatol.* 2017.
82. Landells I, Marano C, Hsu MC, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. *J Am Acad Dermatol.* 2015;73(4):594-603.
83. Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis.* 2017;76(1):79-87.
84. Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *The Lancet.* 2017;389(10086):2317-2327.
85. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. *N Engl J Med.* 2017;377(16):1537-1550.
86. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. *N Engl J Med.* 2017;377(16):1525-1536.
87. Otezla (apremilast) [product information]. Summit, NJ: Celegene Corporation, Jun 2017.
88. Taltz (ixekizumab) [product information]. Indianapolis, IN: Eli Lilly and Company, Jul 2017.
89. Tysabri (natalizumab) [product information]. Cambridge, MA: Biogen Inc., Aug 2017.
90. Xeljanz and Xeljanz XR (tofacitinib) [product information]. New York, NY: Pfizer Inc., Aug 2017.
91. Remicade (infliximab) [product information]. Horsham, PA: Janssen Biotech, Inc., Oct 2017.
92. Kevzara (sarilumab) [product information]. Bridgewater, NJ and Tarrytown, NY: sanofi-aventis and Regeneron Pharmaceuticals, May 2017.
93. Sarilumab Medical Review. US Food and Drug Administration Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761037Orig1s000MedR.pdf. Accessed September 5. 2017.
94. Actemra (tocilizumab) [product information]. South San Francisco, CA: Genentech, Inc, August 2017.

95. Langley RG, Tsai TF, Flavin S, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial. *Br J Dermatol.* 2017.
96. Center for Drug Evaluation and Research. Review and Evaluation of Tremfya (guselkumab) Injection. February 1, 2016. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761061Orig1s000Admincorres.pdf. Accessed December 19, 2017.

Appendix 1: Current Preferred Drug List

Generic	Brand	Formulation	Route	PDL
ETANERCEPT	ENBREL	VIAL	SUB-Q	Y
ETANERCEPT	ENBREL	SYRINGE	SUB-Q	Y
ETANERCEPT	ENBREL SURECLICK	PEN INJCTR	SUB-Q	Y
ETANERCEPT	ENBREL	SYRINGE	SUB-Q	Y
ADALIMUMAB	HUMIRA	SYRINGEKIT	SUB-Q	Y
ADALIMUMAB	HUMIRA PEDIATRIC CROHN'S	SYRINGEKIT	SUB-Q	Y
ADALIMUMAB	HUMIRA PEN	PEN IJ KIT	SUB-Q	Y
ADALIMUMAB	HUMIRA PEN CROHN-UC-HS STARTER	PEN IJ KIT	SUB-Q	Y
ADALIMUMAB	HUMIRA PEN PSORIASIS-UVEITIS	PEN IJ KIT	SUB-Q	Y
ADALIMUMAB	HUMIRA	SYRINGEKIT	SUB-Q	Y
INFLIXIMAB	REMICADE	VIAL	INTRAVEN	N
CERTOLIZUMAB PEGOL	CIMZIA	KIT	SUB-Q	N
CERTOLIZUMAB PEGOL	CIMZIA	SYRINGEKIT	SUB-Q	N
INFLIXIMAB-DYYB	INFLECTRA	VIAL	INTRAVEN	N
INFLIXIMAB-ABDA	RENFLEXIS	VIAL	INTRAVEN	N
VEDOLIZUMAB	ENTYVIO	VIAL	INTRAVEN	N
SECUKINUMAB	COSENTYX (2 SYRINGES)	SYRINGE	SUB-Q	N
SECUKINUMAB	COSENTYX SYRINGE	SYRINGE	SUB-Q	N
SECUKINUMAB	COSENTYX PEN	PEN INJCTR	SUB-Q	N
SECUKINUMAB	COSENTYX PEN (2 PENS)	PEN INJCTR	SUB-Q	N
IXEKIZUMAB	TALTZ AUTOINJECTOR	AUTO INJCT	SUB-Q	N
IXEKIZUMAB	TALTZ AUTOINJECTOR (2 PACK)	AUTO INJCT	SUB-Q	N
IXEKIZUMAB	TALTZ AUTOINJECTOR (3 PACK)	AUTO INJCT	SUB-Q	N
IXEKIZUMAB	TALTZ SYRINGE	SYRINGE	SUB-Q	N
BRODALUMAB	SILIQ	SYRINGE	SUB-Q	N
GUSELKUMAB	TREMFYA	SYRINGE	SUB-Q	N
GOLIMUMAB	SIMPONI	PEN INJCTR	SUB-Q	N
GOLIMUMAB	SIMPONI	SYRINGE	SUB-Q	N
GOLIMUMAB	SIMPONI ARIA	VIAL	INTRAVEN	N
ANAKINRA	KINERET	SYRINGE	SUB-Q	N
ABATACEPT/MALTOSE	ORENCIA	VIAL	INTRAVEN	N
ABATACEPT	ORENCIA	SYRINGE	SUB-Q	N
ABATACEPT	ORENCIA CLICKJECT	AUTO INJCT	SUB-Q	N

CANAKINUMAB/PF	ILARIS	VIAL	SUB-Q	N
APREMILAST	OTEZLA	TABLET	ORAL	N
APREMILAST	OTEZLA	TAB DS PK	ORAL	N
USTEKINUMAB	STELARA	SYRINGE	SUB-Q	N
USTEKINUMAB	STELARA	VIAL	INTRAVEN	N
TOCILIZUMAB	ACTEMRA	VIAL	INTRAVEN	N
TOCILIZUMAB	ACTEMRA	SYRINGE	SUB-Q	N
SARILUMAB	KEVZARA	SYRINGE	SUB-Q	N
RITUXIMAB	RITUXAN	VIAL	INTRAVEN	N
TOFACITINIB CITRATE	XELJANZ	TABLET	ORAL	N
TOFACITINIB CITRATE	XELJANZ XR	TAB ER 24H	ORAL	N
NATALIZUMAB	TYSABRI	VIAL	INTRAVEN	N

Appendix 2: Medline Search Strategy on 10/30/2017

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp abatacept/ 2730
2 exp Adalimumab/ 4382
3 anakinra.mp. 1481
4 apremilast.mp. 332
5 belimumab.mp. 539
6 brodalumab.mp. 160
7 canakinumab.mp. 436
8 exp Certolizumab Pegol/ 494
9 exp Etanercept/ 5510
10 golimumab.mp 904
11 guselkumab.mp. 50
12 exp Infliximab/ 9326
13 ixekizumab.mp. 214
14 exp Natalizumab/ 1356
15 exp Rituximab/ 12191
16 sarilumab.mp. 42
17 secukinumab.mp. 447
18 tocilizumab.mp. 2284
19 tofacitinib.mp. 768
20 exp Ustekinumab/ 643
21 vedolizumab.mp. 412
22 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 37230
23 exp Arthritis, Rheumatoid/ 111774
24 exp Spondylitis, Ankylosing/ 14540
25 exp Crohn Disease/ 37296
26 exp Arthritis, Juvenile/ 10372
27 exp Psoriasis/ 37269
28 exp Arthritis, Psoriatic/ 5496
29 exp Colitis, Ulcerative/ 32987
30 23 or 24 or 25 or 26 or 27 or 28 or 29 224465
32 22 and 31 14620
33 limit 32 to (English language and humans and yr="2017-Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 252

Appendix 3: Prescribing Information Highlights for Sarilumab and Guselkumab

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

KEVZARA® (sarilumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

WARNING: RISK OF SERIOUS INFECTIONS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death including bacterial, viral, invasive fungal, and other opportunistic infections have occurred in patients receiving KEVZARA. (5.1)**
- **If a serious infection develops, interrupt KEVZARA until the infection is controlled. (5.1)**
- **Cases of tuberculosis (TB) have been reported. Prior to starting KEVZARA, test for latent TB; if positive, start treatment for TB. (5.1)**
- **Closely monitor patients for signs and symptoms of infection during treatment with KEVZARA. (5.1)**

INDICATIONS AND USAGE

KEVZARA® is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs). (1)

DOSAGE AND ADMINISTRATION

- KEVZARA may be used as monotherapy or in combination with methotrexate (MTX) or other conventional DMARDs. (2.1)
- The recommended dosage of KEVZARA is 200 mg once every two weeks, administered as a subcutaneous injection. (2.1)

General Considerations for Administration

- KEVZARA initiation is not recommended in patients with ANC less than 2000/mm^3, platelets less than 150,000/mm^3 or liver transaminases above 1.5 times ULN. (2.2)

Dosage Modifications

- Modify dosage to manage neutropenia, thrombocytopenia, and/or elevated liver transaminases. (2.1, 2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/1.14 mL or 200 mg/1.14 mL solution in a single-dose pre-filled syringe (3)

CONTRAINDICATIONS

KEVZARA is contraindicated in patients with known hypersensitivity to sarilumab or any of the inactive ingredients. (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid KEVZARA use during an active infection. (5.1)
- Neutropenia, Thrombocytopenia, Elevated Liver Enzymes, Lipid Abnormalities: Monitor laboratory parameters. (5.2)
- Gastrointestinal (GI) Perforation: Risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids. Promptly evaluate acute abdominal signs or symptoms. (5.3)
- Hypersensitivity reactions. (5.5)
- Live vaccines: Avoid use with KEVZARA due to the risk of infection. Follow vaccination guidelines. (5.7, 7.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence at least 3%) are neutropenia, increased ALT, injection site erythema, upper respiratory infections and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2017

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TREMFYA® (guselkumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------

TREMFYA is an interleukin-23 blocker indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. (1)

----------DOSAGE AND ADMINISTRATION----------

100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/mL in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------

None (4)

TREMFYA® (guselkumab)

----------WARNINGS AND PRECAUTIONS----------

- Infections: TREMFYA may increase the risk of infection. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue TREMFYA until the infection resolves. (5.1)
- Tuberculosis (TB): Evaluate for TB prior to initiating treatment with TREMFYA. (5.2)

----------ADVERSE REACTIONS----------

Most common (≥1%) adverse reactions associated with TREMFYA include upper respiratory infections, headache, injection site reactions, arthralgia, diarrhea, gastroenteritis, tinea infections, and herpes simplex infections. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2017

Appendix 4: Prior Authorization Criteria

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

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 yo	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo(Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥18 yo (Humira)
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			
Broadalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo

Certolizumab (CIMZIA)	≥18 yo	≥18 yo			≥18 yo	≥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 (Remicade) ≥18 yo (biosimilars)	
Ixekizumab (TALTZ)				≥18 yo	≥18 yo			
Rituximab (RITUXAN)						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Sarilumab (KEVZARA)						≥18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo
Tofacitinib (XELJANZ)					≥18 yo	≥18 yo		
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo			
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: 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; MKD = Mevalonate Kinase Deficiency; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; 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.

Approval Criteria		
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? Message: • 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 screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

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 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. Has the patient failed to respond 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 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.
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 #16

Approval Criteria		
13. Has the patient failed to respond 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?	**Yes:** Go to #14 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the request for tofacitinib?	**Yes:** Go to #15	**No:** Approve for up to 6 months.
15. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus or cyclosporine? Note: Tofacitinib may be used concurrently with methotrexate or other oral DMARD drugs.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 6 months.
16. 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 #17	**No:** Go to #18

Approval Criteria		
17. Has the patient failed to respond 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 • For Crohn's Disease patients only: 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.
18. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *induction* of remission?	**Yes:** Approve for length of treatment.	**No:** Go to #19
19. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *maintenance* of remission?	**Yes:** Go to #20	**No:** Pass to RPh. Deny; medical appropriateness.
20. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for maintenance of remission, in conjunction with a low-dose corticosteroid, for ≥6 months: • Azathioprine, leflunomide, or methotrexate • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *1/18 (DM; JP); 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/21/13*