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

Date of Review: January 2019
Generic Name: tildrakizumab-asmn
Generic Name: baricitinib

End Date of Literature Search: 10/18/2018
Brand Name (Manufacturer): Ilumya™ (Merck & Co., Inc.)
Brand Name (Manufacturer): Olumiant® (Eli Lilly and Company)
Dossier Received: Ilumya™: Yes; Olumiant®: Yes

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

Purpose for Class Update: New comparative evidence for existing biologics for autoimmune conditions (also called targeted immune modulators [TIMs]) will be reviewed**.** In addition, safety and efficacy for two new biologic response modifiers recently approved by the United States (U.S.) Food and Drug Administration (FDA) will evaluated. Tildrakizumab-asmn is approved for subcutaneous administration in the treatment of adults with moderate-to-severe plaque psoriasis (PsO) and oral baricitinib is approved for treatment of adult patients with moderate-to-severe rheumatoid arthritis (RA).

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

Conclusions:
CLASS UPDATE
- A 2018 Drug Effectiveness Review Project (DERP) report evaluated evidence published from January 1980 through November 2017.[1] New evidence was identified for the comparative efficacy of biologic agents in RA, PsO, PsA, and CD in adults.[1] No new evidence was identified for treatment of AS or UC in adults. No new evidence was identified to assess the efficacy of TIMs in alleviating symptoms for JIA, PsA, PsO, CD or UC in children.[1] Only the conclusions based on moderate quality evidence are summarized in this drug class update.

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- A large randomized controlled trial (RCT) reported similar efficacy between adalimumab and certolizumab pegol in treating RA patients (n=915) based on results from a short term trial. The American College of Rheumatology (ACR) 20 response rates were 71% versus 69% at 12 weeks (p=0.467; strength of evidence: moderate).[1]
- One fair-quality, non-inferiority RCT assessed the comparative benefits of adalimumab and tofacitinib in 1146 patients with RA who had an inadequate response to methotrexate treatment.[2] At 6 months, patients treated with adalimumab and tofacitinib in combination with methotrexate achieved similar ACR 50 response rates (44% vs. 46%, p=Not Reported [NR]); ACR 50 response for patients with tofacitinib monotherapy was numerically lower (38%).[2] The combination treatment of tofacitinib and MTX reached formal non-inferiority compared with adalimumab and MTX combination treatment (non-inferiority boundary -13 percentage points).[2] Non-inferiority was not reached by tofacitinib monotherapy.[2]
- Harms associated with TIMs including overall adverse events, discontinuation due to adverse events, and serious adverse events were evaluated in 35 randomized controlled trials (RCTs) and 56 head-to-head observational trials.[1] No significant differences in risk or harm between drugs were identified (strength of evidence: low).[1]
- 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.[1]

- National Institute for Health and Care Excellence (NICE) published five new high quality guidance documents for baricitinib in management of RA[3], brodalumab and guselkumab in treating moderate-to-severe PsO,[4,5] and ixekizumab and tofacitinib for treating active PsA after inadequate response to disease modifying anti-rheumatic drugs (DMARDs).[6]
- The European League Against Rheumatism (EULAR) recommendations for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) were updated to include rituximab as a first-line agent in 2015.[7]

TILDRAKIZUMAB-ASMN

- The approval of tildrakizumab-asmn for moderate-to-severe PsO was based on evidence from 2 similarly designed phase 3 trials, reSURFACE1 and reSURFACE2.[8]
- There is moderate quality evidence that treatment with tildrakizumab results in statistically significant symptom improvement (as evaluated by PASI75 and PGA response) compared to placebo at 12 weeks. Compared to placebo, tildrakizumab 100 mg (the FDA approved dose) demonstrated a statistically significant improvement in PASI75 at week 12 in ReSURFACE1 (6% vs. 64%; Absolute Risk Reduction (ARR) 58%; Number Needed to Treat (NNT) 2; p<0.0001) and ReSURFACE2 (6% vs. 61%,ARR 55%, NNT 2, p<0.0001).[8] Similar improvements were noted when placebo was compared to tildrakizumab 100 mg for proportion of patients achieving PGA response in ReSURFACE1 (7% vs. 58%, ARR 51%, NNT 2, p<0.0001) and ReSURFACE2 (4% vs. 55%, ARR 51%, NNT 2, p<0.001).[8]
- There is moderate quality evidence from the ReSURFACE 2 trial that compared to etanercept, tildrakizumab 100 mg improves PASI75 response over 12 weeks (48% vs. 61%, ARR 18%, NNT 6, p<0.001).[8] However, no statistically significant difference in PGA response was observed when etanercept was compared to tildrakizumab in ReSURFACE2 (48% vs. 55%, p<0.663).[8]
- In reSURFACE1 and reSURFACE2, the proportion of subjects reporting at least one adverse effect (AE) in weeks 0 through 12 was similar in all treatment groups (tildrakizumab 200 mg: 42%/49%; tildrakizumab 100 mg: 47%/44%; placebo: 48%/55%; etanercept: 54%).[9] The most common AEs in both reSURFACE trials were nasopharyngitis and upper respiratory tract infections. In reSURFACE 2, injection site erythema was more common in etanercept than tildrakizumab (tildrakizumab 200 mg: 1%; tildrakizumab 100 mg: 1%; placebo: 1%; etanercept: 9%).[9]

- There is insufficient evidence to determine differences in long-term efficacy, long-term safety, remission rates, health-related quality of life, or functional improvement with tildrakizumab compared to other treatments for moderate to severe PsO.

BARICITINIB

- The efficacy and safety of baricitinib for RA was assessed in four randomized, multi-center, phase 3 studies (RA-BEGIN, RA-BEAM, RA-BUILD, and RA-BEACON).[10-13]
- Baricitinib 4 mg was compared to placebo in adults with RA who had an inadequate response to MTX (RA-BEAM), [11] an inadequate response to conventional synthetic DMARDs (RA-BUILD), [12] and in patients refractory to biologic agents (RA-BEACON).[13] In all 3 trials, the primary endpoint was the proportion of patients achieving ACR20 response at week 12. Moderate quality evidence demonstrates the effectiveness (based on ACR 20 response) of baricitinib compared to placebo in RA-BEAM (70% vs. 40%, ARR 30%, NNT 4, p <0.001), [11] RA-BUILD (62% vs. 39%, ARR 23%, NNT 5, p<0.001), [12] and RA-BEACON (55% vs. 27% ARR 28%, NNT 4, p <0.001).[13]
- In RA-BEAM, comparison of baricitinib to adalimumab was a secondary, noninferiority endpoint (estimated power for test of noninferiority, 93%; prespecified noninferiority margin of 12%).[11] Baricitinib was found to be noninferior to adalimumab at week 12 for the ACR20 response (70% for baricitinib and 61% for adalimumab; 95% CI, 2% to 15%; p=0.014).[11] According to the statistical analysis plan, baricitinib was therefore considered to be significantly superior to adalimumab (P = 0.01).[11]
- The most common adverse effects noted in clinical trials with baricitinib 2 and 4 mg included upper respiratory tract infections (14-16%), nausea (3%), and herpes infections (0.8-1.8%).[14]
- There is insufficient evidence to determine differences in long-term efficacy, long-term safety, remission rates, health-related quality of life, or functional improvement with baricitinib compared to other treatments for moderate to severe RA.

Recommendations:

- Modify PA criteria to reflect updated indications and age ranges for specific biologic response modifiers as follows:
    - Certolizumab for treatment of adults with moderate-to-severe PsO who are candidates for systematic therapy
    - Tofacitinib for management of adults with moderate-to-severe UC
    - Adalimumab for treatment of non-infectious uveitis for pediatric patients aged 2 years and older
    - Rituximab for treatment of adults with moderate-to-severe pemphigus vulgaris
    - Remove step therapy for rituximab when prescribed for Granulomatosis with Polyangiitis or Microscopic Polyangiitis to maintain remission
- Maintain tildrakizumab-asmn as a non-preferred drug to the Preferred Drug List (PDL) and modify PA criteria to include tildrakizumab for use in moderate-to-severe plaque psoriasis for adults.
- Maintain baricitinib as a non-preferred drug to the PDL and modify PA criteria to include baricitinib for use in moderate-to-severe rheumatoid arthritis for adults.
- After evaluation of comparative costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy

The last comparative review of biologic drugs for autoimmune conditions was presented to the Pharmacy and Therapeutics (P and T) Committee at the January 2018 meeting. Two biologic response modifiers, sarilumab and guselkumab, were added to the prior authorization criteria for biologic agents. The 2 preferred

agents on the Oregon preferred drug list (PDL), adalimumab and etanercept, have broad indications for use including AS, JIA, PsO, PsA, and RA. Adalimumab is also approved for management of inflammatory bowel diseases including CD and UC. All the other drugs in the biologic class are non-preferred based on evidence presented at previous Pharmacy and Therapeutics meetings and require prior authorization (PA) prior to patient use or administration as outlined in **Appendix 1** and **Appendix 4**.

OHP FFS Utilization:
In the second quarter of 2018 there were approximately 159 pharmacy claims for biologic agents in the fee-for-service (FFS) population. Seventy-six percent of the claims were for the preferred agents of etanercept or adalimumab. For the non-preferred agents, there were 1-2 claims for infliximab, ustekinumab, abatacept, golimumab, natalizumab and 3-8 claims for certolizumab, apremilast, tofacitinib, tocilizumab and secukinumab. There were no pharmacy claims for brodalumab, canakinumab, ixekizumab, rituximab, or vedolizumab.

Background:
Conventional synthetic DMARDs (csDMARDs) include methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and leflunomide (LEF). Biologic DMARDs (bDMARDs) include tumor necrosis factor inhibitors (TNFis) [adalimumab, certolizumab, etanercept, golimumab, infliximab], the T-lymphocyte inhibitor (abatacept), the anti-B cell agent (rituximab), interleukin (IL)-6 receptor blocking agents (tocilizumab and sarilumab), IL-1 receptor antagonists (canakinumab and anakinra), the IL-12 receptor antagonist (ustekinumab) and IL-17 receptor antagonists (brodalumab, ixekizumab, and secukinumab).[15] Janus kinase (JAK) inhibitors (tofacitinib and baricitinib) are classified as targeted synthetic DMARDs (tsDMARDs).

<u>Rheumatoid Arthritis</u>
Rheumatoid arthritis is characterized by inflammation of synovial tissues and progressive erosion of bone leading to joint destruction and disability. The 2015 ACR [16] and 2016 European League Against Rheumatism (EULAR) [17] recommendations suggest that treatment begin with csDMARDs as soon as diagnosis of RA is established. Biologic DMARDs are recommended for patients with a suboptimal response or intolerance to csDMARDs such as MTX. The following drugs are currently approved by the FDA for the treatment of RA: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab, and tofacitinib. Over the past decade, management of RA has shifted from controlling symptoms to preventing and controlling damage.[18] Additionally, with the availability of bDMARDs and tsDMARDs, a "treat-to-target" approach is now recommended, where the goals of treatment target remission or low disease activity and maintenance of remission.[16] These goals have been shown to lead to better outcomes such as prevention of progression of joint damage and improved quality of life.[18]

Primary endpoints used in RA clinical trials include the ACR response, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the Disease Activity Score 28 (DAS-28). The ACR response rates are binary composite outcomes consisting of the following outcomes on disease activity: tender and swollen joint counts, patient's assessment of pain, patient and physician's global assessments of disease activity and an acute-phase reactant value (either the erythrocyte sedimentation rate or a C-reactive protein level).[19] The ACR response score is a composite endpoint with 7 domains used to calculate the proportion of patients achieving a target percentage of improvement from baseline and is a considered a measure of efficacy and overall disease activity.[19] Patients are said to meet ACR 20 criteria when they have at least 20% reductions in tender and swollen joint counts in at least 3 of the 5 remaining domains.[19] ACR 50 and ACR 70 criteria are similar, but with improvement of at least 50% and 70% in at least 3 domains.[19] ACR 50 and 70 are considered more clinically significant than ACR 20.[19] The HAQ-DI is a widely used self-reported measure of functional capacity. Scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[20] The minimal clinically important difference is 0.22 units.[21] The DAS-28 is another index of disease activity (similar to the ACR response). The DAS is a continuous composite outcome that consists of: 1) the number of painful joints (Ritchie Articular

Index, 0-78 joints), 44-joint count for swollen joints, erythrocyte sedimentation rate (ESR) and patient global assessment of disease activity or general health using a visual analogue scale.[22] A DAS-28 score greater than 5.1 corresponds to high disease activity and less than 3.2 of low disease activity. A DAS score of 2.6 is considered to correspond to remission.[23]

Plaque Psoriasis

Plaque psoriasis accounts for about 80% to 90% of all patients with psoriasis.[24] Psoriasis affects about 3% of the population and generally occurs before age 35.[25] Typically, PsO is classified as mild, moderate or severe. Mild disease involves less than 5% of the body surface area and has little to no impact on quality of life or function. Mild PsO is not a funded condition per the Health Evidence Review Commission (HERC) Guideline Note 57.[26] Per NICE guidance, topical medications including corticosteriods, vitamin D analogs (e.g., calcipotriene) , retinoids (e.g., tazarotene) or calcineurin inhibitors (e.g., tacrolimus or pimecrolimus) are first line agents for PsO.[27] Phototherapy is an option for moderate-to-severe PsO 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 are added for moderate-to-severe PsO not controlled by other therapies. Injectable biologic agents used to treat PsO include adalimumab, brodalumab, certolizumab, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, tildrakizumab, ustekinumab, and secukinumab. An oral phosphodiesterase 4 (PD4) inhibitor, apremilast, is also approved for treatment of moderate-to-severe PSO.

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.[28] The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. Because the PASI only evaluates skin involvement on the trunk, head, arms and legs, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[28,29] 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.[28] 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.[29] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, improvements of 100%, indicating complete disease clearance, are considered more clinically significant.[30] The sPGA is another physician-reported symptom severity scale which evaluates symptom severity at a single point in time with higher scores indicating more severe disease (range 0 to 5). Responders to therapy are typically defined as patients with a sPGA score of 0 or 1, corresponding to clear or almost clear skin or patients with an improvement of at least 2 points. In clinical trials of patients with moderate to severe disease, the proportion of patients with a sPGA score of 0 or 1 has a strong correlation with a 75% improvement in PASI.[30] Finally, the PSI evaluates patient-reported rather than physician-assessed symptoms. Eight individual symptoms in the prior 24 hours are assessed including itch, redness, scaling, burning, stinging, cracking, flaking and pain.[30] Individual symptoms are rated from 0 to 4 with total scores ranging from 0 to 32 points.[30] Patients with total scores of 8 or less with no single item rated greater than 1 are generally considered responders to therapy.[31]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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:

Drug Effectiveness Review Project –Targeted Immune Modulators

The Drug Effectiveness Review Project (DERP) authors published a review evaluating the safety and efficacy of targeted immune modulators (TIMs) in May 2018.[1] The review evaluated recent evidence for the following medications: abatacept, adalimumab, adalimumab-atto, alefacept, anakinra, apremilast, brodalumab, canakinumab, certolizumab pegol, etanercept, etanercept-szzs, golimumab, infliximab, infliximab-abda, infliximab-dyyb, ixekizumab, natalizumab, risankizumab, rituximab, sarilumab, secukinumab, tocilizumab, tofacitinib, ustekinumab, and vedolizumab. Risankizumab was not yet approved by the FDA at the time of the review, but is expected to be approved in the near future.[1] Sirukumab was initially included as a medication of interest, but the manufacturer has since retracted the drug from the FDA approval process.[1] The literature search was conducted from January 1980 through November 2017.

The first key question of the DERP summary evaluated efficacy and long term effectiveness of TIMs in alleviating symptoms and stabilizing disease in RA, JIA, AK, PsA, CD, UC, and PsO. The second key question compared adverse events associated with TIMs in adults and children as separate populations. The third question assessed differences in the effectiveness or harms of TIMs in the following subgroups: age, racial groups, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease.[1] As equipotency among the reviewed TIMs is not well established, assumptions were made that comparisons made within the recommended dosing range were appropriate.[1] New evidence was identified for RA, PsA, and CD in adults.[1] No new evidence was identified for treatment of AS, PsO, or UC in adults. No new evidence was identified to assess the efficacy of TIMs in alleviating symptoms for JIA, PsA, PsO, CD or UC in children.[1] Only the conclusions based on moderate quality evidence are summarized in this report.

I. Efficacy

A. Rheumatoid Arthritis

All the recently published trials were funded by the pharmaceutical industry. Efficacy assessments were stratified according to utilization of TIMs as first step treatments and utilization of TIMs as second step agents. The comparative effectiveness of TIMs as first step treatments was evaluated in 2 recent, fair quality RCTs identified by the DERP authors.[1]

Adalimumab compared to Certolizumab

A large, fair-quality, RCT randomized 915 patients with active RA disease despite MTX treatment and who had prognostic factors for severe disease progression to adalimumab or certolizumab pegol.[32] Adalimumab was administered as 40 mg every 2 weeks and certolizumab pegol was administered as 400 mg at weeks 0, 2, and 4 followed by 200mg once every 2 weeks.[32] Both regimens were administered concurrently with methotrexate. Investigators reported similar efficacy between adalimumab and certolizumab pegol based on ACR 20 response rates after 12 weeks of treatment which were 71% and 69%, respectively; p=0.467 (strength of evidence: moderate).[32] The study was sponsored by the manufacturer of certolizumab pegol.

Adalimumab compared to Tofacitinib

One fair-quality, non-inferiority RCT assessed the comparative benefits of adalimumab and tofacitinib in 1146 patients with rheumatoid arthritis who had an inadequate response to methotrexate treatment.[2] The ORAL Standard trial randomized patients to adalimumab combination therapy (40 mg every 2 weeks and

MTX), tofacitinib combination therapy (5 mg twice daily and MTX), or tofacitinib monotherapy (5 mg twice daily).[2] At 6 months, patients treated with adalimumab and tofacitinib in combination with MTX achieved similar ACR 50 response rates (44% vs. 46%; p value NR).[2] The ACR response rate for patients treated with tofacitinib monotherapy was 38% (p value NR).[2] The combination treatment of tofacitinib and MTX reached formal non-inferiority compared with adalimumab and MTX combination treatment (non-inferiority boundary -13 percentage points).[2] Non-inferiority was not reached by tofacitinib monotherapy.[2] Quality of evidence was rated as moderate. This trial was sponsored by the manufacturer of tofacitinib.

The comparative effectiveness of TIMs as second-step treatments was evaluated in 1 recent, fair quality RCT identified by the DERP authors.[1]

Abatacept compared to Secukinumab

A multinational RCT funded by the manufacturer of secukinumab evaluated patients who had moderate-to-high disease activity despite previous treatment with TNF-inhibitors.[33] Five hundred fifty one patients were randomized to receive abatacept (dosage based on body weight: patients with <60 kg received 500 mg, patients between 61 and 100 kg received 750 mg, and patients over 100 kg 1000 mg), or intravenous secukinumab (10 mg/kg at baseline, and weeks 2 and 4) followed by subcutaneous secukinumab at a dose of 150 mg or 75 mg every 4 weeks, or placebo.[33] Secukinumab is currently not approved for the treatment of rheumatoid arthritis. Because patients who were non-responders to abatacept at week 16 were re-randomized to secukinumab at week 24, DERP authors reported results for week 24 only.[33] American College of Rheumatology 50 response rates were numerically higher for patients on abatacept compared with patients treated with secukinumab 150 mg or secukinumab 75 mg (28% vs. 17% vs. 12%, p value not reported).[33] Likewise, changes in the Health Assessment Questionnaire were higher for abatacept than secukinumab-treated patients (-0.6 vs. -0.4 vs. -0.3, p value NR).[33] The study did not report any statistical comparisons between abatacept and secukinumab treated patients. Comparisons of the crude response rates (self-calculated by DERP) rendered statistically significant differences in responses between abatacept and secukinumab 150 mg (P=0.03) and secukinumab 75 mg (P<0.001).[33]

B. Psoriatic Arthritis

The following drugs are currently approved by the FDA for the treatment of psoriatic arthritis: abatacept, apremilast, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab, tofacitinib and ustekinumab. Three trials assessed the comparative effectiveness of targeted immune modulators in adult patients with psoriatic arthritis. However, the evidence was evaluated as insufficient for the comparison between adalimumab, etanercept, and infliximab and low quality between adalimumab and tofacitinib and between adalimumab and ixekizumab.[1]

C. Crohn's Disease

The following drugs are currently approved by the FDA for the treatment of Crohn's disease: adalimumab, certolizumab pegol, infliximab, natalizumab, ustekinumab and vedolizumab. Two trials assessed the comparative effectiveness of targeted immune modulators for the treatment of Crohn's disease. There was insufficient evidence to compare the efficacy of efficacy of switching to adalimumab or continuing with infliximab in patients with a satisfactory response to infliximab therapy.[1]

II. Safety

Ninety-one studies provided direct evidence on harms associated with TIMs in adult patients: 35 RCTs and 56 head-to-head observational studies.[1] The short durations and small sample sizes of randomized trials limited the validity of adverse events assessment with respect to rare but serious adverse events.[1] The majority of randomized trials included for this key question were funded by the pharmaceutical industry. Many of the observational studies were independently funded. There was insufficient evidence to evaluate the comparative safety risks of TIMs in children. The majority of trials were conducted in patients with rheumatoid arthritis and plaque psoriasis; 3 in patients with psoriatic arthritis; only 1 trial was in patients with Crohn's disease.[1] The duration of trials varied from 12 weeks to 13 months, and the rate of adverse events in the included trials varied from 15% to 100%, but was generally greater than 50%.[1] The most common

adverse events that occurred in the included trials were: headache, urinary tract infection, respiratory infections, diarrhea, and muscle pain.[1] Twenty five RCTs reported on overall adverse events and of these, 24 studies reported no significant differences in risks among drugs (strength of evidence: low). [1] Twenty three RCTs provided data on discontinuation due to adverse events and of these, 20 RCTs found no statistically significant difference among various targeted immune modulators (strength of evidence: low) .[1] For serious adverse events, 25 RCTs provide data, of which 24 RCTs revealed no statistically significant differences among compared drugs(strength of evidence: low).[1]

III. Subgroup Evaluations

The majority of the trials did not contain any information about the effectiveness and harms of targeted immune modulators in one subgroup of patients compared with another or compared with the general population.[1]

New Guidelines:

European League Against Rheumatism

The European League Against Rheumatism (EULAR) recommendations for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) were updated in 2015.[7] The 2015 update was developed by an international task force representing EULAR, the European Renal Association and the European Vasculitis Society (EUVAS). The types of vasculitis specifically addressed in the update include: granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome).
Strong recommendations based on high quality evidence for treatment of GPA or MPA include:

- For remission-induction of new-onset organ-threatening or life-threatening AAV treatment with a combination of glucocorticoids and either cyclophosphamide or rituximab is recommended.[7]
- For remission-maintenance of AAV treatment with a combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil is recommended.[7]

National Institute for Health and Care Excellence

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

Baricitinib for Moderate-to-Severe Rheumatoid Arthritis[3]

1. Baricitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional DMARDs, only if disease is severe (DAS28 of more than 5.1).[3]
2. Baricitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD, only if disease is severe (DAS28 of more than 5.1) and they cannot have rituximab.[3]
3. Baricitinib can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in sections 1 and 2 are met.[3]
4. Continue treatment only if there is a moderate response measured using EULAR criteria at 6 months after starting therapy. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained.[3]

Brodalumab for Treating Moderate-to-Severe Plaque Psoriasis[4]

1. Brodalumab is recommended as an option for treating plaque psoriasis in adults, only if:
   - the disease is severe, as defined by a total PASI of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 and
   - the disease has not responded to other systemic therapies, including cyclosporine, methotrexate and PUVA (psoralen and long-wave ultraviolet A radiation), or these options are contraindicated or not tolerated.[4]
2. Stop brodalumab at 12 weeks if the psoriasis has not responded adequately, defined as:
   - a 75% reduction in the PASI score (PASI 75) from when treatment started or a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.[4]

Guselkumab for Treating Moderate to Severe Plaque Psoriasis[5]

1. Guselkumab is recommended as an option for treating plaque psoriasis in adults, only if:
   - the disease is severe, as defined by a total PASI of 10 or more and a DLQI of more than 10 and
   - the disease has not responded to other systemic therapies, including cyclosporine, methotrexate and PUVA (psoralen and long-wave ultraviolet A radiation), or these options are contraindicated or not tolerated.[5]
2. Stop guselkumab treatment at 16 weeks if the psoriasis has not responded adequately. An adequate response is defined as:
   - a 75% reduction in the PASI score (PASI 75) from when treatment started or
   - a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.[5]

Ixekizumab for Treating Active Psoriatic Arthritis after Inadequate Response to DMARDs[6]

1. Ixekizumab alone, or with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults, only if:
   - it is used as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2)[34] or
   - the person has had a tumour necrosis factor (TNF)-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after the first 12 weeks or
   - TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis).[6]
2. Assess the response to ixekizumab after 16 weeks of treatment. Only continue treatment if there is clear evidence of response, defined as an improvement in at least 2 of the 4 Psoriatic Arthritis Response Criteria (PsARC), 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist, to determine whether continuing treatment is appropriate based on skin response (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, recommendation 1.3).[6]

Tofacitinib for Treating Active Psoriatic Arthritis after Inadequate Response to DMARDs[35]

1. Tofacitinib, with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults, only if:
   - it is used as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis

(recommendations 1.1 and 1.2)[34] or

- the person has had a tumour necrosis factor (TNF)-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks or
- TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis).[35]

2. Assess the response to tofacitinib after 12 weeks of treatment. Only continue treatment if there is clear evidence of response, defined as an improvement in at least 2 of the 4 PsARC, 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist, to determine whether continuing treatment is appropriate based on skin response (as described in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, recommendation 1.3).[35]

New Formulations or Indications:

1. Certolizumab pegol (Cimzia®) received an expanded indication from the FDA for adults with moderate-to-severe PsO who are candidates for systemic therapy or phototherapy.[36] The FDA approval is based on data from 3 RCTs consisting of CIMPASI-1, CIMPASI-2 and CIMPACT. [37] In CIMPASI-1 (n=234) and CIMPASI-2 (n=227) the coprimary efficacy endpoints assessed at week 16 were the proportion of patients with moderate to severe PsO achieving PASI 75 and PGA 0/1 when certolizumab pegol (CZP) was compared to placebo.[37] At week 16, significantly higher PASI 75 responder rates were observed for CZP 400 mg (CIMPASI-1, 75.8%; CIMPASI-2, 82.6%) and CZP 200 mg (CIMPASI-1, 66.5%; CIMPASI-2, 81.4%) than placebo (CIMPASI-1, 6.5%; CIMPASI-2, 11.6%; p<0.0001 for all).[37] At week 16, significantly higher PGA 0/1 responder rates were observed for CZP 400 mg (CIMPASI-1, 57.9%; CIMPASI-2, 71.6%) and CZP 200 mg (CIMPASI-1, 47.0%; CIMPASI-2, 66.8%) than placebo (CIMPASI-1, 4.2%; CIMPASI-2, 2.0%; P<0.0001 for all).[37]

In the third phase 3 trial, CIMPACT (n=559), patients with moderate-to-severe PsO were randomized 3:3:1:3 to certolizumab 400 mg, certolizumab 200 mg, or placebo every 2 weeks for 16 weeks or etanercept 50 mg twice weekly for 12 weeks.[38] The primary endpoint was PASI 75 responder rate at week 12.[38] All endpoints were significantly greater for certolizumab versus placebo with the greatest response seen with the 400 mg dose (PASI 75 67% for CZP 400 mg vs. 5% for placebo; p<0.0001).[36] The proportion of patients who experienced a PASI 75 response with CZP 400 mg was superior to etanercept at 12 weeks (67% CZP 400 mg vs. 53% for etanercept; p<0.152).[38] Adverse events were consistent with the anti-tumor necrosis factor class of drugs drug all 3 trials.[38]

According to the updated label, the recommended dose of CZP for adults with moderate-to-severe plaque psoriasis is 400 mg (given as two subcutaneous injections of 200 mg each) every other week. For some patients (with body weight ≤ 90 kg), CZP 400 mg (given as two subcutaneous injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every other week can be considered.[36]

2. Tofacitinib (Xeljanz®) received expanded approval in adults with moderately to severely active UC in May 2018.[39] Tofacitinib was previously approved in 2012 for RA and in 2017 for PsA. The efficacy of tofacitinib for the treatment of moderately to severely active UC was demonstrated in three controlled clinical trials.[40] Two 8-week placebo-controlled trials demonstrated that 10 mg of tofacitinib given twice daily induces remission in 17-18% of patients compared with 8% of the patients treated with placebo.[40] In a placebo-controlled trial among patients who achieved a clinical response by week 8, tofacitinib 5 mg or 10 mg given twice daily was effective in inducing remission by week 52 in 34% and 41% of patients, respectively compared to 11% of placebo-treated patients.[40] The safety of chronic use of tofacitinib for ulcerative colitis was studied in the 52-week placebo-controlled trial. Additional supportive safety information was collected from patients who received treatment in an open-label long-term study.

3. Adalimumab (Humira®) received expanded indications for 2 different autoimmune conditions. The treatment of non-infectious uveitis is now approved for pediatric patients 2 years of age and older as of August 2018.[41] This expanded indication is supported by evidence from a randomized, controlled clinical study in 90 pediatric patients. In October 2018, adalimumab labeling was revised to include treatment of moderate to severe hidradenitis suppurativa (HS) in patients 12 years of age and greater.[41] Hidradenitis suppurativa is not currently funded by the Oregon Health Plan (OHP).[42]

4. Hyrimoz® (adalimumab-adaz), a new biosimilar adalimumab product produced by Sandoz, received FDA approval in November 2018.[43] Although FDA approved, this adalimumab biosimilar will not be marketed in the U.S. until 2023, according to a licensing agreement sealed with AbbVie. The U.S. approval of adalimumab-adaz covers the same indications as the reference product, namely RA, JIA, PsA, AS, CD, UC, and PsO. As with adalimumab, the biosimilar carries a boxed warning for serious infection and malignancy risk. The FDA approval was based on a comprehensive data package comprising analytical, preclinical, and clinical research demonstrating that Hyrimoz matches the reference biologic in terms of safety, efficacy, and quality. A randomized, double-blind, three-arm, parallel biosimilarity study confirmed the pharmacokinetics, immunogenicity, and safety of Hyrimoz. The study met the primary endpoint, demonstrating bioequivalence for all primary pharmacokinetic parameters.

4. Rituximab (Rituxan) received expanded approval for the treatment of adults with moderate to severe pemphigus vulgaris (PV).[44] Pemphigus vulgaris is a life-threatening auto-immune disease characterized by progressive painful blistering of the skin and mucous membranes.[45] The study that led to the FDA approval was a multi-center, open-label study which randomized 90 patients with moderate or severe PV to treatment with either rituximab plus short-term prednisone (n=46) or prednisone alone (n=44).[45] At 24 months, 89% of patients treated with the combination were in complete remission and no longer on therapy compared with 34% of those assigned to prednisone alone (55% absolute difference, 95% CI 38.4%-71.7%; P<0.0001).[45] Patients assigned to rituximab plus short-term prednisone had fewer severe adverse events than those assigned to prednisone alone, likely due to lower cumulative doses of prednisone used in the rituximab group during the study.[45] The recommended rituximab dosing for adults with pemphigus vulgaris is 1000 mg via intravenous (IV) infusion every 2 weeks for 2 doses in combination with a tapering dose of glucocorticoids.[44] Maintenance treatment can be continued with rituximab 500 mg via IV infusion at month 12 and every 6 months thereafter or based on clinical evaluation.[44] Methylprednisolone 100 mg intravenous or equivalent glucocorticoid is recommended 30 minutes prior to each infusion.[44]

New FDA Safety Alerts: No new safety alerts were identified.

Randomized Controlled Trials:
A total of 418 citations were manually reviewed from the initial literature search. After further review, 418 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

DRUG EVALUATION: Tildrakizumab-asmn (Ilumya™)

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

Clinical Efficacy:
Tildrakizumab-asmn is an interleukin (IL)-23 inhibitor approved for treatment of moderate-to-severe PsO in adults who are candidates for systemic therapy or phototherapy.[9] The suffix "-asmn" is used to differentiate this originator biologic from future biosimilar versions of tildrakizumab.[46] The recommended dose of tildrakizumab-asmn is 100 mg subcutaneously at weeks 0, 4 and then every 12 weeks.[9] The approval of tildrakizumab-asmn was based on evidence from 2 similarly designed phase 3 trials, reSURFACE1 and reSURFACE2.[8] Each trial consisted of 3 separate parts; reSURFACE1 was conducted over 64 weeks and reSURFACE2 evaluated tildrakizumab over 52 weeks. The primary objective of the reSURFACE studies was to evaluate the efficacy and safety of tildrakizumab compared to placebo after 12 weeks.

Part 1 of the reSURFACE1 trial was a 12 week, double-blind, placebo-controlled study in which 772 patients were randomized to two doses of tildrakizumab (100 mg and 200 mg) or to placebo. Part 1 of the reSURFACE2 trial (n=1090) evaluated the same two doses of tildrakizumab versus placebo and added an active comparator arm with etanercept over a 12 week period. Part 2 of the reSURFACE1 trial was a 16 week, double-blind treatment period in which tildrakizumab patients received another dose at week 16; re-randomized placebo patients received either tildrakizumab 200 or 100 mg at weeks 12 and 16 to evaluate maintenance of response. In part 2 of the reSURFACE2 trial, participants were re-randomized from placebo to tildrakizumab administered at weeks 12 and 16 and etanercept was given once weekly. In part 3 of both studies, participants received doses of tildrakizumab or placebo until week 64 (reSURFACE 1) or week 52 (reSURFACE 2).

The co-primary endpoints were the proportion of patients achieving PASI75 and PGA response (score of 0 or 1 with at least a two grade reduction from baseline) at week 12. In reSURFACE1, 64% (n=197) of patients treated with tildrakizumab 100 mg (the FDA approved dose) achieved PASI75 at week 12 compared to 6% (n=9) of patients in the placebo arm (p<0.0001; 95% CI 51.0 to 64.1; ARR 58%; NNT 2).[8] One hundred seventy nine patients (58%) in the 100 mg group achieved PGA responses, compared with 11 patients (7%) in the placebo group (p<0.0001; 95% CI 43.6 to 57.4; ARR 51%; NNT 2).[8] In reSURFACE2 61% (n=188) of patients in the tildrakizumab 100 mg arm achieved PASI 75 at week 12, compared to 6% (n=9) in the placebo arm (p<0.0001; 95% CI: 48.3 to 61.8; ARR 55%; NNT 2).[8] Similar results were observed in the ReSURFACE2 trial when tildrakizumab was compared to placebo to evaluate the PGA response: 168 patients (55%) in the 100 mg group achieved a PGA response, compared with 7 patients (4%) in the placebo group (p<0.0001; 95% CI 43.2 to 56.5; ARR 51%; NNT 2).[8]

In ReSURFACE2 and significant differences between tildrakizumab and etanercept were observed with improvements in the PASI75 response but not the PGA response. At week 12, 188 patients (61%) in the tildrakizumab 100 mg group achieved PASI 75, compared 151 patients (48%) in the etanercept group (p<0.001; 95% CI 5.3 to 20.7; ARR 13; NNT 8).[8] At week 12, 168 patients (55%) achieved PGA response compared to 149 patients (48%) in the etanercept group (p=0.0663; 95% CI -0.5 to 15.0).[8] Although a higher proportion of patients in the tildrakizumab 100 mg group than in the etanercept group achieved PASI 75 at week 12, the proportion of patients achieving PGA responses did not differ significantly between these groups at week 12.[8] Additional trial details are presented in **Table 3**.

Trial Limitations:
The 12 week endpoint of PASI75 response may have been too early to adequately assess efficacy of tildrakizumab compared to placebo or etanercept. Etanercept, a TNFi, was used as the primary active comparator. It may have been more appropriate to compare tildrakizumab with another interleukin inhibitor such as the IL-12/IL-23 inhibitor, ustekinumab. Although the most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score, improvements of 100%, indicating complete disease clearance, are considered more clinically significant.[30]

Clinical Safety:
In reSURFACE1 and reSURFACE2, the proportion of subjects reporting at least one adverse effect (AE) in weeks 0 through 12 was similar in all treatment groups (tildrakizumab 200 mg: 42%/49%; tildrakizumab 100 mg: 47%/44%; placebo: 48%/55%; etanercept: 54%). The most common AEs in both reSURFACE trials were nasopharyngitis and upper respiratory tract infections. In reSURFACE 2, injection site erythema was more common in etanercept than tildrakizumab (tildrakizumab 200 mg: 1%; tildrakizumab 100 mg: 1%; placebo: 1%; etanercept: 9%).[8] The rate of severe infections, malignancies, skin cancers, major cardiovascular events, and drug-related hypersensitivity reactions was low in both studies, and there was no significant difference between the active treatment groups.[8] Discontinuation due to AEs was not frequently reported. In both reSURFACE trials, the overall rate of serious adverse effects (SAEs) in the first 12 weeks was low and comparable among the treatment groups (tildrakizumab 200 mg: 3%/2%; tildrakizumab 100 mg: 2%/1%; placebo: 1%/3%; etanercept: 2%).[8] The most common adverse reactions identified in during the first 12 to 16 weeks of therapy with tildrakizumab are outlined in **Table 1**.[9]

Table 1. Adverse Reactions Occurring in ≥1% of Subjects in the Tildrakizumab Group and More Frequently than in the Placebo Group[9]

Adverse Reaction	**Tildrakizumab 100 mg (n=705) N (%)**	**Placebo (N=355) N (%)**
Upper respiratory infection	98 (14)	41 (12)
Injection Site Reactions	24 (3)	7 (2)
Diarrhea	13 (2)	5 (1)

In summary, efficacy of tildrakizumab-asmn for moderate-to-severe PsO is based on evidence from 2 similarly designed phase 3 trials, reSURFACE1 and reSURFACE2.[8] There is moderate quality evidence that treatment with tildrakizumab results in statistically significant symptom improvement (as evaluated by PASI75 and PGA response) compared to placebo at 12 weeks.[8] There is moderate quality evidence that compared to etanercept, tildrakizumab improves PASI75 response over 12 weeks from the ReSURFACE2 trial.[8] However, no statistically significant difference in PGA response was observed when etanercept was compared to tildrakizumab in ReSURFACE2.[8] There is insufficient evidence to determine differences in long-term efficacy, long-term safety, remission rates, health-related quality of life, or functional improvement with tildrakizumab compared to other treatments for moderate to severe PsO.

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

Comparative Endpoints:
Clinically Meaningful Endpoints:
1) Symptomatic improvement (PASI100)
2) Functional status
3) Quality of life

Primary Study Endpoint:
1) Proportion of patient's achieving PASI 75 and PGA 0/1

4) Serious adverse events
5) Study withdrawal due to an adverse event

Table 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	IL-23 inhibitor
Oral Bioavailability	N/A – administered via subcutaneous injection
Distribution and Protein Binding	Volume of distribution = 10.8 liters
Elimination	Systemic clearance = 0.32 L/day
Half-Life	23 days
Metabolism	Metabolic pathway has not been characterized

Abbreviations: IL=Interleukin, L = liter, N/A = not applicable

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Reich, et al.[8] reSURFACE 1 PG, DB, MC, RCT Duration: 64 weeks Part I: 12 week DB, PC treat period N=772 Part 2: 16 week DB to evaluate response to active treatment N=743	1. Tildrakizumab 100 mg SC at weeks 0 and 4 2. Tildrakizumab 200 mg SC at weeks 0 and 4 3. Placebo SC at weeks 0 and 4	Demographics: 1. Male 68% 2. Age: 47 yo 3. Race: White: 68% Asian: 26% 4. Mean BSA: 29% 5. Mean PASI score: 20 6. Previous treatment with bDMARDs: 23% Key Inclusion Criteria: 1.Adults aged ≥18 yo 2.Moderate-to-severe PsO (BSA >10%, PGA score >3, PASI score >12 at baseline) 3. Candidate for phototherapy or systemic therapy Key Exclusion Criteria: 1. Active or latent TB 2. Presence of any infection requiring	ITT: 1. 309 2. 308 3. 155 PP: 1. 300 2. 298 3. 146 Attrition: 1. 9 (3%) 2.10 (3%) 3. 9 (6%)	Co-Primary Endpoints: Proportion of patients achieving PASI 75 and PGA response (0 or 1 and ≥2 grade score reduction form baseline) at week 12 Proportion of patients achieving PASI 75 at week 12 1. 197 (64%) 2. 192 (62%) 3. 9 (6%) p<0.0001 for 1 vs. 3 95% CI: 51.0 to 64.1 p<0.0001 for 2 vs. 3 95% CI 49.6 to 62.8 Proportion of patients achieving PGA response at week 12 1. 179 (58%) 2. 182 (59%) 3. 11 (7%) p<0.001 for 1 vs. 3 95% CI 43.6 to 57.4 p<0.0001 for 2 vs. 3	58%/2 56%/2 51%/2	SAEs up to week 12 1. 5 (2%) 2. 8 (3%) 3. 1 (1%) Discontinued due to AE up to week 12 1. 0 2. 5 (2%) 3. 1 (1%) Severe Infections up to week 12 1. 1 (<1%) 2. 1 (<1%) 3. 0 Malignancies up to week 12 1. 0 2. 0 3. 0	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized 2:2:1 via IVWRS stratified by bodyweight (≤90 kg or >90kg), region, and previous treatment with bDMARDs. Baseline characteristics similar among treatment groups. Performance Bias: Low. Medications were identical in appearance and packaging. Detection Bias: Low. Investigators, participants, and study personnel blinded to group allocation until end of study. Attrition Bias: Low. Attrition rates similar for all 3 groups and <10%.Missing data imputed using non-responder data. Reporting Bias: High. Protocol available. Co-primary endpoints reported as separate results (not combined).Funded by Merck. Merck also involved in study design, data analysis and data interpretation. Other Bias: High. A large percent of the authors have served as consultants or paid speakers for many clinical trials sponsored by other manufacturers. **Applicability**:

Part 3: 36 week period to evaluate long term efficacy and safety N=676		systemic antibiotics within 2 weeks prior to enrollment or severe infection requiring IV antibiotics 8 weeks prior to screening 3. Prior malignancy 4. Live vaccine w/in 4 weeks of study		95% CI 44.8 to 58.5 Secondary Endpoints: Proportion of patients achieving PASI 90 at week 12 1. 107 (35%) 2. 109 (35%) 3. 4 (3%) p<0.0001 for 1 vs. 3 95% CI 25.9 to 38.0 p<0.0001 for 2 vs. 3 95% CI 26.8 to 38.8	52%/2 32%/4 32%/4	 Deaths up to week 12 1. 0 2. 0 3. 0 p-values and 95% CI NR for all		Patient: Reasonable patient group identified through inclusion/exclusion criteria. 77% had not tried a bDMARD prior to study enrollment. Intervention: Dosing of tildrakizumab determined in Phase 2 trials. Comparator: Placebo appropriate to determine efficacy, though a comparative efficacy study would have provided more information regarding place in therapy. Outcomes: PASI 75 and PGA are validated assessments used in other PsO trials. Setting: 112 sites in 5 countries: Australia, Canada, Japan, the UK and the US.
2. Reich, et al.[8] reSURFACE 2 PG, DB, MC, RCT N=1090 Duration: 52 weeks Part I: 12 week DB, PC, active comparator treat period N=1090 Part 2: 16 week DB to evaluate response to active treatment N=1025 Part 3: 24 week period to evaluate long term	1. Tildrakizumab 100 mg SC at weeks 0 and 4 2. Tildrakizumab 200 mg SC at weeks 0 and 4 3. Placebo SC at weeks 0 and 4 4. Etanercept 50 mg SC twice weekly	Demographics: 1. Male 72% 2. Age: 47.5 yo 3. Race: White: 91% Asian: 3% 4. BSA: 17% 5. PASI score:20 6. Previous treatment with bDMARDs: 12% Key Inclusion Criteria: see reSURFACE 1 criteria Key Exclusion Criteria: 1. Active or latent TB 2. Presence of any infection requiring systemic antibiotics within 2 weeks prior to enrollment severe infection requiring IV antibiotics 8 weeks prior to screening 3. Prior malignancy 4. Recieved live vaccination within 4 weeks prior to enrollment 5. Prior use of etanercept	ITT: 1. 307 2. 314 3. 156 4. 313 PP: 1. 295 2. 300 3. 134 4. 289 Attrition: 1.12 (4%) 2.14 (4%) 3.24 (8%)	Co-Primary Endpoints: Proportion of patients achieving PASI 75 and PGA response (0 or 1 and ≥2 grade score reduction form baseline) at week 12 Proportion of patients achieving PASI 75 at week 12 1. 188 (61%) 2. 206 (66%) 3. 9 (6%) 4. 151 (48%) p<0.0001 for 1 vs. 3 95% CI: 48.3 to 61.8 p<0.0001 for 2 vs. 3 95% CI: 52.9 to 65.9 p<0.001 for 1 vs. 4 95% CI: 5.3 to 20.7 p<0.0001 for 2 vs. 4 95% CI: 9.7 to 24.9 Proportion of patients achieving PGA response at week 12 1. 168 (55%) 2. 186 (59%) 3. 7 (4%) 4. 149 (48%) p<0.0001 for 1 vs. 3 95% CI: 43.2 to 56.5 p<0.0001 for 2 vs. 3	 55%/2 60%/2 13%/8 18%/6 51%/2	SAEs up to week 12 1. 4 (1%) 2. 6 (2%) 3. 4 (3%) 4. 7 (2%) Discontinued due to AE up to week 12 1. 3 (1%) 2. 3 (1%) 3. 2 (1%) 4. 6(2%) Severe infections up to week 12 1. 0 2. 1 (<1%) 3. 1 (1%) 4. 0 Malignancies up to week 12 1. 1 (<1%) 2. 2 (<1%) 3. 0 4. 1 (<1%) Deaths up to week 12 1.1 (<1%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized 2:2:1:2 via IVWRS stratified by bodyweight (≤90 kg or >90kg), region, previous treatment with bDMARDs, response to MTX. Performance Bias: Low. Medications were identical in appearance and packaging. Detection Bias: Low. Investigators, participants, and study personnel blinded to group allocation until end of study. Attrition Bias: Low. Attrition similar between all 3 groups and <10% of enrolled subjects. Reporting Bias: High. Co-primary endpoints reported as separate results (not combined).Funded by Merck. Merck also involved in study design, data analysis and data interpretation. Other Bias: High. A large percent of the authors have served as consultants or paid speakers for many clinical trials sponsored by other manufacturers. **Applicability**: Patient: Reasonable patient group identified through inclusion/exclusion criteria Intervention: Dosing of tildrakizumab determined in Phase 2 trials Comparator: Etanercept dosing appropriate. More useful comparator would have been another IL-inhibitor such as ustekinumab. Outcomes: PASI 75 and PGA are validated assessments used in other PsO trials.

efficacy and safety N=794				95% CI: 47.9 to 60.8 p<0.0663 for 1 vs. 4 95% CI: -0.5 to 15.0 p<0.0031 for 2 vs. 4 95% CI: 4.0 to 19.3 <u>Secondary Endpoints</u>: Proportion of patients achieving PASI 90 at week 12 1. 119 (39%) 2. 115 (37%) 3. 2 (1%) 4. 67 (21%) p<0.0001 for 1 vs. 3 95% CI: 31.1 to 43.4 p<0.001 for 2 vs. 3 95% CI: 29.2 to 41.1 p<0.001 for 1 vs. 4 95% CI: 10.3 to 24.4 p<0.0001 for 2 vs. 4 95% CI: 8.3 to 22.1	55%/2 NS 11%/9 38%/3 36%/3 18%/6 16%/7	2.0 3.0 4.0 p value and 95% CI NR for all		<u>Setting</u>: 123 sites in 13 countries: Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Israel, Netherlands, Poland, and the US
<u>Abbreviations</u>: AEs = adverse effects: ARR = absolute risk reduction; bDMARD = biologic disease modifying antirheumatic drug; BSA = body surface area; DB = double blind, CI = confidence interval; IL = interleukin; ITT = intention to treat; IVRWS = interactive voice and web response system; MC = multi-center; MTX = methotrexate; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; PASI = Psoriasis Area and Severity Index; PC = placebo controlled; PG = parallel group; PGA = Physician's Global Assessment; PP = per protocol; PsO = plaque psoriasis; RCT = randomized controlled trial; SAEs = serious adverse effects: SC = subcutaneous; TB - tuberculosis								

NEW DRUG EVALUATION: Baricitinib (Olumiant®)

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

Clinical Efficacy:

Baricitinib is an oral JAK inhibitor approved for treatment of adult patients with moderate-to-severe RA who have had an inadequate response to one or more TNFi therapies.[14] The recommended dose of baricitinib is 2 mg orally once a day as monotherapy or in combination with MTX.[14] Baricitinib has not been studied in combination with JAK inhibitors, bDMARDs, or potent immunosuppressants such as azathioprine or cyclosporine.[14] The efficacy and safety of baricitinib was assessed in four randomized, multi-center, phase 3 studies (RA-BEGIN, RA-BEAM, RA-BUILD, and RA-BEACON).[10-13] See **Table 6** for additional details about each trial design and results from each trial.

Study 1 (RA-BEGIN) was a double-blind, active-controlled, 52-week non-inferiority study of baricitinib administered as monotherapy or in combination with MTX to patients (N=588) with early RA who had no or limited prior treatment with DMARDs.[10] Concomitant treatment with stable doses of csDMARDs, NSAIDs, and glucocorticoids (≤10 mg of prednisone or equivalent) was permitted during the trial.[10] The primary end point assessment was a noninferiority comparison of baricitinib monotherapy to MTX monotherapy based on the proportion of patients achieving an ACR20 response at week 24.[10] The prespecified noninferiority margin was 12%.[10] The study met its primary noninferiority objective as the ACR20 response rate at week 24 for baricitinib versus MTX was 77% and 62%, respectively (p≤0.001 for noninferiority) and was also found to be superior statistically (p≤0.05; 95% CI Not Reported (NR) for superiority); ARR 15%; NNT 7).[10]

Study 2 (RA-BEAM) was a double-blind, placebo- and active-controlled, 52-week trial in patients with moderate-to-severe RA who had an inadequate response (IR) to MTX.[11] Patients (n=1307) with active RA who were receiving background therapy with MTX were randomly assigned to one of three regimens in a 3:3:2 ratio: placebo (switched to baricitinib after 24 weeks), 4 mg of baricitinib once daily, or 40 mg of adalimumab every other week.[11] Concomitant stable doses of csDMARDs, nonsteroidal anti-inflammatory drugs, analgesics, or glucocorticoids (≤10 mg of prednisone or the equivalent per day) were permitted.[11] The primary endpoint was ACR20 response at week 12 for baricitinib compared to placebo.[11] At 12 weeks more patients had an ACR20 response with baricitinib than with placebo (70% vs. 40%, P<0.001; 95% CI NR; ARR 30%; NNT 4).[11] Comparison of baricitinib to adalimumab was a secondary, noninferiority endpoint (estimated power for test of noninferiority, 93%; prespecified noninferiority margin of 12%).[11] Baricitinib was found to be noninferior to adalimumab at week 12 for the ACR20 response (70% for baricitinib and 61% for adalimumab; 95% CI, 2% to 15%; p=0.014).[11] According to the statistical analysis plan, baricitinib was therefore considered to be significantly superior to adalimumab (P = 0.01).[11]

Study 3 (RA-BUILD) was designed to determine the safety and efficacy of baricitinib in patients with moderate-to-severe RA who had an IR to or were intolerant to previous treatment with csDMARDs.[12] In this double-blind, 24-week study, bDMARD-naïve patients (n=684) were randomly assigned 1:1:1 to placebo or baricitinib (2 or 4 mg) once daily, stratified by region and the presence of joint erosions.[12] Concomitant treatment with stable doses of csDMARDs, NSAIDs, and glucocorticoids (≤10 mg of prednisone or equivalent) was permitted.[12] The primary endpoint was the proportion of patients achieving ACR20 response at week 12 for the comparison of baricitinib 4 mg versus placebo.[12] More patients achieved ACR20 response at week 12 with baricitinib 4 mg than with placebo (62% vs. 39%, p≤0.001; 95% CI NR; ARR 23; NNT 5).[12]

Study 4 (RA-BEACON) was designed to evaluate the safety and efficacy of baricitinib in the treatment of patients with moderate-to-severe RA who have had an IR to a TNFi, despite ongoing treatment with csDMARDs.[13] In this double-blind, placebo-controlled study, patients (n=527) were randomised 1:1:1 to once-daily placebo or baricitinib 2 or 4 mg for 24 weeks. Concomitant treatment with stable doses of csDMARDs, NSAIDs, and glucocorticoids (≤10 mg of prednisone or equivalent) was allowed. The primary end point was the proportion of patients who had an ACR20 response at week 12.[13] Significantly more patients receiving baricitinib at the 4-mg dose than those receiving placebo had an ACR20 response at week 12 (55% vs. 27%, P<0.001; 95% CI NR; ARR 28%; NNT 4).[13] Secondary measures included ACR50 and ACR70 response rates at week 24. Proportion of patients with ACR 50 response at week 24 for baricitinib 4 mg compared to placebo was significant, (29% vs. 13%; p≤0.001, 95 CI NR), although the response rate dropped substantially from the ACR 20 assessment.[13] Similar results were observed with ACR 70 response rates at week 24 (baricitinib 4mg 17% vs. placebo 3%; p ≤0.001; 95% CI NR).[13]

Study Limitations:

The primary endpoint in all 4 trials was ACR20, although ACR50 and ACR70 are considered more clinically significant than ACR 20.[19] In addition, in all 4 trials the ACR20 assessment was a short term evaluation conducted between 12 and 24 weeks for reasons that were not clarified by the investigators. In the RA BEGIN trial the entry criterion requiring an elevated hsCRP (≥3.6) at baseline resulted in a screen failure rate of 50%. A high screen failure rate can reduce the external validity of a study; however, the population enrolled did have early active RA, as was the intent of the protocol. The dosage of MTX was limited to 20 mg once weekly and was not adjusted in patients having an inadequate response to treatment. Other initial treatment regimens, such as MTX in combination with other csDMARDs, were not evaluated. In RA-BEAM the study has limited ability to assess the efficacy of baricitinib with other background csDMARDs due to the enrollment of MTX-refractory patients, of whom only 15% to 18% in each treatment arm were on other csDMARDs. The limitations of the RA-BEAM analysis include the use of carrying forward the last observations before rescue or discontinuation. This method assumes that the patient-reported observations do not change over time. RA-BUILD and RA-BEACON were conducted over 24 weeks, which is a relatively short-term duration to provide definite conclusions regarding the long term safety and efficacy of baricitinib. RA-BUILD included two active baricitinib dose regimens but was not designed to compare these doses for statistically significant difference.

Clinical Safety:

The most common adverse effects noted in clinical trials with baricitinib included upper respiratory tract infections, nausea, and herpes infections. Adverse reactions occurring in greater than or equal to 1% of baricitinib patients are outlined in **Table 4**.

Table 4. Adverse reactions occurring in baricitinib patients compared to placebo up to week 16[14]

Events	Placebo (n=1070)	Baricitinib 2 mg (n=479)	Baricitinib 4 mg (n=997)
Upper Respiratory Infections	11.7%	16.3%	14.7%
Nausea	1.6%	2.7%	2.8%
Herpes Simplex	0.7%	0.8%	1.8%
Herpes Zoster	0.4%	1.0%	1.4%

Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), has been observed at an increased incidence in patients treated with baricitinib compared with placebo during clinical trials.[14] In addition, arterial thrombosis events in the extremities have been reported in clinical studies with baricitinib.[14] During the 0- to 52-week treatment period, venous thrombosis were reported in 2 patients treated with baricitinib 2 mg (0.6 per 100 patient-years) and 7 patients treated with baricitinib 4 mg (0.8 per 100 patient-years).[14] The FDA has determined that analysis of spontaneous post-marketing AEs will not be sufficient to assess the signal of a serious risk of thrombosis and has required the manufacturer to conduct an ongoing randomized controlled clinical trial to

evaluate the long-term safety of baricitinib in patients with RA. The risk of serious infections, malignancies, and thrombosis are all described as serious adverse reactions with baricitinib in the product labeling and are highlighted via the black box warning.[14]

In summary, the efficacy and safety of baricitinib for RA was assessed in four randomized, multi-center, phase 3 studies (RA-BEGIN, RA-BEAM, RA-BUILD, and RA-BEACON).[10-13] Baricitinib 4 mg was compared to placebo in adults with RA who had an inadequate response to MTX (RA-BEAM), [11] an inadequate response to conventional synthetic DMARDs (RA-BUILD), [12] and in patients refractory to biologic agents (RA-BEACON).[13] In all 3 trials, the primary endpoint was the proportion of patients achieving ACR20 response at week 12. Moderate quality evidence demonstrates the effectiveness (based on ACR 20 response) of baricitinib compared to placebo in RA-BEAM (70% vs. 40%, ARR 30%, NNT 4, p <0.001), [11] RA-BUILD (62% vs. 39%, ARR 23%, ARR 5, p<0.001), [12] and RA-BEACON (55% vs. 27% ARR 28%, NNT 4, p <0.001).[13] In RA-BEAM, comparison of baricitinib to adalimumab was a secondary, noninferiority endpoint (estimated power for test of noninferiority, 93%; prespecified noninferiority margin of 12%).[11] Baricitinib was found to be noninferior to adalimumab at week 12 for the ACR20 response (70% for baricitinib and 61% for adalimumab; 95% CI, 2% to 15%; p=0.014).[11] According to the statistical analysis plan, baricitinib was therefore considered to be significantly superior to adalimumab (P = 0.01).[11] There is insufficient evidence to determine differences in long-term efficacy, long-term safety, remission rates, health-related quality of life, or functional improvement with baricitinib compared to other treatments for moderate to severe RA.

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

Comparative Endpoints:

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

Primary Study Endpoint:
2) ACR 20 response at week 24

Table 5. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	JAK 1 and 2 inhibitor
Oral Bioavailability	80%
Distribution and Protein Binding	Volume of distribution 76 L (after intravenous administration), 50% bound to plasma proteins and 45% bound to serum proteins
Elimination	Clearance = 8.9 L/hour; primarily though renal elimination (75%) and in feces (20%)
Half-Life	12 hours
Metabolism	~6% metabolized, with CYP3A4 identified as the main metabolizing enzyme

Abbreviations: JAK – Janus Kinase; L – liter

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Fleischmann et al.[10] RA-BEGIN Phase 3 RCT, DB, MC, active comparator (MTX) Adult patients with active RA who had limited or no prior treatment with DMARDs. N=588 Duration: 52 weeks	1. MTX 10 mg titrated up to 20mg once weekly over 8 wks* 2. BARI 4mg po once daily 3. BARI 4mg po once weekly AND MTX 10 mg titrated up to 20mg once weekly over 8 wks N=584 52 weeks 190 centers in 18 countries *Starting at week 24, non-responders in Arm #1 were rescued with BARI 4mg po once daily + MTX once weekly	Demographics: 1. Mean Age: 50 yo 2. Women ≥70% 3. Mean RA duration: 1.5 yrs 4. DMARD naïve: 91% Key Inclusion Criteria: 1. Adults aged ≥18 yo with active, early onset RA 2. No or ≤3 doses of MTX 3. Active disease (≥6/68 tender joints and ≥6/66 swollen joints); hsCRP ≥3.6 mg/L 4. RF or ACPA positive Key Exclusion Criteria: 1. Prior use of csDMARDs other than MTX 2. Prior use of a bDMARD 3. Use of >10 mg/day of prednisone or equivalent 4. Recent clinically significant infection 5. ALT > 1.5 ULN, Hgb > 10 gm/dl, or neutropenia < 1200 cells/µl 6. Lymophpenia < 750 cells/µl or GFR < 40 ml/min/1.73m^2	ITT: 1. 210 2. 159 3. 215 PP: 1. 161 2. 136 3. 173 Attrition: 1. 49 (23%) 2. 23 (14%) 3. 42 (20%)	Primary Endpoint: Non-inferiority comparison of BARI monotherapy to MTX monotherapy based on ACR 20 response at week 24 1. 130 (62%) 2. 159 (77%) P<0.001 95% CI 5.5 to 24.1 Secondary Endpoints: Superiority of BARI to MTX on ACR 20 at week 24 1. 130 (62%) 2. 159 (77%) 3. 168 (78%) p≤0.05 for 1 vs. 2 p≤0.05 for 1 vs. 3 95% CI NR Superiority of BARI to MTX in HAQ-DI at week 24 1. 146 (70%) 2. 129 (81%) 3. 169 (79%) p<0.05 for 1 vs. 2 p<0.05 for 1 vs. 3 95% CI NR Superiority of BARI to MTX in SDAI remission score ≤3.3 at week 24 1. 22 (10%) 2. 35 (22%) 3. 49 (23%) p<0.05 for 1 vs. 2 p<0.05 for 1 vs. 3 95% CI NR Proportion of patients achieving ACR 50 at week 24 1. 91 (43%)	15%/7 16%/7 11%/9 9%/12 12%/9 13%/8	TEAEs at week 52 1. 151 (72%) 2. 113 (71%) 3. 167 (78%) SAEs at week 52 1. 5 (2%) 2. 6 (4%) 3. 18 (8%) Discontinuation due to AEs at week 52 1. 11 (5%) 2. 9 (6%) 3. 23 (11%) Infections 1. 80 (38%) 2. 69 (43%) 3. 108 (50%) Serious Infections 1. 8 (4%) 2. 6 (4%) 3. 5 (2%) p-values and 95%CI NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Patients were randomized 4:3:4 and stratified by geographic region and presence of joint erosions on centrally read baseline radiographs. Baseline characteristics similar between groups. Method of randomization unclear. Performance Bias: Low. Active and placebo MTX supplied as identical opaque capsules. Detection Bias: Low. Patients, investigators, and all study personnel blinded to study data and treatment assignments. Attrition Bias: High. More patients dropped out due to lack of efficacy in MTX group and development of an AE led to more dropouts in combo MTX/baricitinib group. Subjects who dropped out were defined as non-responders and their data was imputed as LOCF. Reporting Bias: High. Protocol unavailable. Funded by Eli Lilly and Incyte who had a role in the study design, data collection, data analysis, data interpretation, and writing of the manuscript. Other Bias: High. A large percent of the authors have served as consultants or paid speakers for many clinical trials sponsored by other manufacturers. **Applicability**: Patient: ~90% of patients did not have prior exposure to a DMARD, which affects applicability. Screening failure rate was approximately 50% due to inclusion criteria requiring an elevated hsCRP, resulting in reduced external validity. Intervention: Dosing for BARI was assessed in phase 2 trials. Comparator: Limited to MTX 20mg/week. Weekly MTX was given in combination with all treatments, which reflects clinical practice with other biologics. Outcomes: Primary outcomes were an appropriate assessment for the treatment of RA, although ACR50 or ACR70 might be considered more clinically important. Setting: 198 centers in 18 countries: Central and South America: 29% United States and Canada: 21% Japan: 18%

				2. 95 (60%) 3. 136 (63%) p<0.05 for 1 vs. 2 p<0.05 for 1 vs. 3 95% CI NR	17%/6 20%/5			Europe: 14% Rest of the world: 19%
Taylor et al.[11] RA-BEAM Phase 3 RCT, DB, PC, MC Efficacy and safety of baricitinib in RA patients who had an IR to MTX therapy N=1305 Duration: 52 weeks	1. PBO + MTX 10mg titrated up to 20mg once weekly over 8 wks* 2. BARI 4mg once daily + MTX 10mg titrated up to 20mg once weekly over 8 wks 3. ADA 40mg every other week + MTX 10mg titrated up to 20mg once weekly over 8 wks N=1307 52 weeks *Starting at week 24, non-responders in Arm # 1 were rescued with BARI 4mg po once daily + MTX once weekly	Demographics: 1. Mean age: 53yo 2. Female >75% 3. Mean RA duration: 10 ± 9 yrs 4. Treated with MTX + csDMARD: 17% Key Inclusion Criteria: 1. Inadequate response to MTX after 12 wks of tx (≥3 erosions, ≥6/68 tender joints, ≥6/66 swollen joints, hsCRP ≥6 mg/l) Key Exclusion Criteria: 1. prior bDMARD use 2. concurrently receiving MTX, HCQ and SSZ or combination of any 3 csDMARDS 3. Use of >10 mg/day of prednisone or equivalent	ITT: 1. 488 2. 487 3. 330 PP: 1. 407 2. 427 3. 286 Attrition: 1. 81 (17%) 2. 60 (12%) 3. 44 (13%)	Primary Endpoint: ACR 20 response at week 12 for BARI vs. PBO 1. 196 (40%) 2. 339 (70%) 3. 202 (61%) p≤0.001 for 1 vs. 2 p≤0.05 for 2 vs. 3 95% CI NR Secondary Endpoints: Non-inferiority comparison of BARI to ADA based on ACR 20 response at week 12 1. 196 (40%) 3. 202 (61%) p≤0.05 95% CI 2 to 15 ACR 20 at week 24 1. 179 (37%) 2. 360 (74%) 3. 219 (66%) p≤0.001 for 1 vs. 2 p≤0.05 for 2 vs. 3 95% CI NR ACR50 at week 24 1. 94 (19%) 2. 246 (51%) 3. 150 (45%) p≤0.001 for 1 vs. 2 p≤0.05 for 2 vs. 3 95% CI NR	30%/4 21%/5 37%/3 8%/13 32%/4 26%/4	SAEs at week 24 1. 22 (5%) 2. 23 (5%) 3. 6 (2%) TEAEs at week 24 1. 295 (60%) 2. 347 (71%) 3. 224 (68%) Infections at week 24 1. 134 (27%) 2. 176 (36%) 3. 110 (33%) SAEs at week 52 1. BARI 38 (8%) 2. ADA 13 (4%) TEAEs at week 52 1. BARI 384 (79%) 2. ADA 253 (77%) Infections at week 52 1. BARI 233 (48%) 2. ADA 145 (44%) CV events (CV death, MI, or stroke) 1. BARI 2 (<1%) 2. ADA 1 (<1%) p-values and 95% CI NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Patients randomized 3:3:2, stratified by geographic region and baseline joint erosion status. Baseline characteristics similar between groups. Not clear how randomization was achieved. Performance Bias: Low. Patients, investigators, and all other personnel involved in the conduct of the study remained blinded to the study data and to individual treatment assignments until the contribution of their sites to the studies was completed. Detection Bias: Low. Patients and investigators blinded to the study data and treatment assignments. Attrition Bias: Low. Attrition rates balanced between groups and primarily due to AE. The limitations of this analysis include the use of LOCF before rescue or discontinuation. This method assumes that the patient reported values do not change over time. Reporting Bias: High. Protocol available. Trial designed by Lilly, academic advisory board consisted of authors who were not employees of Lilly or Incyte. Other Bias: A large percent of the authors have served as consultants or paid speakers for many clinical trials sponsored by other manufacturers. **Applicability**: Patient: Generalizable to the population of adults with moderately to severely active disease who have IR to MTX and who are bDMARD naïve. The study has limited ability to assess the efficacy of baricitinib with other background csDMARDs due to the enrollment of MTX-refractory patients, of whom only 15% to 18% in each treatment arm were on other csDMARDs Intervention: Dosing for BARI was assessed in phase 2 trials. Comparator: Adalimumab is a reasonable comparator. Outcomes: Primary outcomes were an appropriate assessment for the treatment of RA, although ACR50 or ACR70 might be considered more clinically important. Setting: This study was conducted in 281 centers in 26 countries: US/Canada (8%); Eastern Europe (18%)

								Western Europe (6%); Central and South America/Mexico (29%); Asia (except Japan) (10%); Japan (19%); Rest of the world (11%)
Dougados et al.[12] RA-BUILD Phase 3 RCT, DB, PC, MC Evaluate the efficacy and safety of baricitinib in RA patients with IR to csDMARDs N=684 Duration: 24 weeks	1. PBO + background csDMARD 2. BARI 2mg po once daily + background csDMARD 3. BARI 4mg po once daily + background csDMARD	Demographics: 1. Mean age: 51 yrs 2. Female ≥80% 3. Mean RA duration: 7.5 yrs Key Inclusion Criteria: 1. Inadequate response to one or more csDMARDs (≥6/68 tender joints, ≥6/66 swollen joints, hsCRP ≥3.6 mg/l) 2. Stable background therapy with csDMARD Key Exclusion Criteria: 1. Prior bDMARD use 2. Currently receiving MTX, HCQ and SSZ or a combination of any 3 csDMARDs 3. Use of >10 mg/day of prednisone or equivalent	ITT: 1. 228 2. 229 3. 227 PP: 1. 199 2. 209 3. 203 Attrition: 1. 29 (13%) 2. 20 (9%) 3.24 (11%)	Primary Endpoint: The proportion of patients achieving ACR20 response at week 12 with BARI 4mg vs PBO 1. 90 (39%) 2. 151 (66%) 3. 140 (62%) p≤0.001 for 1 vs. 2 p≤0.001 for 1 vs. 3 95% CI NR Secondary Endpoints: ACR 20 at week 24 1. 96 (42%) 2. 140 (61%) 3. 148 (65%) p≤0.001 for 1 vs. 2 p≤0.001 for 1 vs. 3 95% CI NR ACR50 at week 24 1. 49 (21%) 2. 95 (41%) 3. 100 (44%) p≤0.001 for 1 vs. 2 p≤0.001 for 1 vs. 3 95% CI NR	27%/4 23%/5 19%/6 23%/5 20%/5 23%/5	SAEs at week 24 1. 11 (5%) 2. 6 (3%) 3. 12 (5%) TEAEs at week 24 1. 161 (71%) 2. 154 (67%) 3. 162 (71%) Infections 1. 79 (35%) 2. 70 (31%) 3. 96 (42%) Serious Infections 1. 4 (2%) 2. 2 (1%) 3. 4 (2%) p-values and 95% CI NR for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1:1:1. Method of randomization not clear. Performance Bias: Double blinded. All study personnel remained blinded through the completion of the study. Noted a protocol was approved but did not specify that it was standardized across all sites and followed consistently. Detection Bias: Method for blinding primary endpoint of ACR20 assessment not mentioned. Attrition Bias: The percentages of patients who discontinued due to an AE were similar across the treatment groups Reporting Bias: Trial designed by Lilly, academic advisory board consisted of authors who were not employees of Lilly or Incyte Other Bias: High. A large percent of the authors have served as consultants or paid speakers for many clinical trials sponsored by other manufacturers. **Applicability**: Patient: Results of this study are generalizable to the population of adult patients with moderately to severely active RA who have had an insufficient response or are intolerant to csDMARDs and are bDMARD naive. Intervention: Dosing for BARI was assessed in phase 2 trials. Comparator: Two active baricitinib dose regimens, and a comparison of the different doses for statistically significant differences was not performed. Outcomes: Short duration of trial (24 wks). Primary outcomes were an appropriate assessment for the treatment of RA, although ACR50 or ACR70 might be considered more clinically important. Setting: 182 centers in 22 countries: US, Argentina, Australia, Belgium, Canada, Croatia, the Czech Republic, Germany, Hungary, India, Italy, Japan, Mexico, Poland, Portugal, Puerto Rico, Romania, Russia, Slovakia, South Korea, Spain, Taiwan, and the UK

Genovese et al.[13] RA-BEACON Phase 3 RCT, DB, PC, MC Efficacy and safety of baricitinib in RA patients who had an inadequate response to a TNFi or bDMARD. N = 527 Duration: 24 weeks	1.PBO + stable background csDMARD* 2. BARI 2mg po once daily + stable background csDMARD** 3. BARI 4mg po once daily + stable background csDMARD N=527 24 weeks 178 centers in 24 countries *Starting at week 16, non-responders were rescued with BARI 4 mg daily **Patients with renal impairment, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, received 2 mg baricitinib once daily if assigned to active treatment.	Demographics: 1. Mean age: 55 yrs 2. Female ≥79% 3. Mean RA duration: 14 ± 9 yrs Key Inclusion Criteria: 1. Adults ≥18 yo with inadequate response or intolerance to one or more prior TNFis (≥6/68 tender joints, ≥6/66 swollen joints, hsCRP ≥3 mg/l) 2. Stable background therapy with csDMARD Key Exclusion Criteria: 1. bDMARD within 28 day of randomization or rituximab within 6 mos of randomization 2. Use of >10 mg/day of prednisone or equivalent 3. Currently receiving MTX, HCQ and SSZ or a combination of any 3 csDMARDs 4. Started a new NSAID within 2 weeks of randomization 5. GFR<40 mL/min/17.3 m^2 or Alt>1.5 ULN	ITT: 1.176 2.174 3.177 PP: 1.144 2.157 3.158 Attrition: 1.32 (18%) 2.17 (10%) 3.19 (11%)	Primary Endpoint: The proportion of patients with an ACR 20 response at week 12 for BARI 4mg vs. PBO 1. 48 (27%) 2. 85 (49%) 3. 98 (55%) P<0.001 for 1 vs. 2 P<0.001 for 1 vs. 3 95% CI NR Secondary Endpoints: Proportion of patients with ACR 20 response at week 24 1. 48 (27%) 2. 78 (45%) 3. 82 (46%) P≤0.001 for 1 vs. 2 P≤0.001 for 1 vs. 3 95% CI NR Proportion of patients with ACR 50 response at week 24 1. 23 (13%) 2. 40 (23%) 3. 52 (29%) p≤0.01 for 1 vs. 2 p≤0.001 for 1 vs. 3 95% CI NR Proportion of patients with ACR 70 response at week 24 1. 6 (3%) 2. 23 (13%) 3. 30 (17%) p≤0.001 for 1 vs. 2 p≤0.001 for 1 vs. 3 95% CI NR	 22%/5 28%/4 18%/6 19%/6 10%/10 16%/7 10%/10 14%/8	TEAEs at week 24 1. 112 (64%) 2. 123 (71%) 3. 137 (77%) TEAEs in patients with prior exposure to 1 or 2 bDMARDs 1. 61% 2. 65% 3. 74% SAEs at week 24 1. 13 (7%) 2. 7 (4%) 3. 18 (10%) Withdrawals due to AEs 1. 7 (4%) 2. 7 (4%) 3. 11 (6%) Infections 1. 55 (31%) 2. 76 (44%) 3. 70 (40%) Serious Infection 1. 5 (3%) 2. 4 (2%) 3. 6 (3%) Nonmelanoma Skin Cancer 1. 0 2. 0 3. 2 (1%) MACE 1. 0 2. 0 3. 2 (1%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1:1 and stratified by region and history of bDMARD use. Method of randomization not described. Performance Bias: Low. Placebo tablets matched active treatment. Detection Bias: Low. All patients and study personnel were blinded to individual treatment assignments and remained blinded through the completion of the study. Two investigators evaluated each patient's joint counts but were blinded to other efficacy assessments. Attrition Bias: High. Higher percentage of attrition in the PBO group due to lack of efficacy. Attrition in BARI group was primarily due to AEs. Reporting Bias: Low. Protocol available in supplemental materials. Sponsored by Eli Lilly and Incyte Other Bias: A large majority of the authors were employees and stockholders of Lilly or received grant funding from the manufacturer. **Applicability**: Patient: Results are generalizable to adult patients with moderately to severely active RA who have received treatment with at least one TNFi and had an IR to therapy. Intervention: BARI dosing derived from Phase 2 trials that assessed efficacy via ACR 20 response and safety. Comparator: Placebo used a comparator for the first 16 weeks, afterwards non-responders were started on active therapy for duration of trial. Outcomes: The time frame for interpretation of safety data and durability of treatment effectiveness is limited to 24 weeks. Setting: Study was conducted at 178 centers in 24 countries: US, Argentina, Australia, Austria, Belgium, Canada, Denmark, France, Germany, Greece, Israel, Italy, Japan, Mexico, Poland, Puerto Rico, South Korea, Spain, Switzerland, Turkey, and the UK.

						p-values and 95% CI NR for all		

Abbreviations [alphabetical order]: ACPA = anticitrullinated protein antibody; ACR = American College of Rheumatology; ACR 20/50/70 = 20/50/70% improvement in American College of Rheumatology Criteria; ADA = adalimumab; AE = adverse event; ALT = alanine transaminase: ARR = absolute risk reduction; BARI= baricitinib; bDMARD = biologic DMARD; CI = confidence interval; csDMARD = conventional synthetic DMARD; CV = cardiovascular; DB = double blind; DAS28-CRP =28 Joint Disease Activity Score based on C-reactive protein level; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire-Disability Index; HCQ = hydroxychloroquine; hsCRP = high-sensitivity C-reactive protein; IR = inadequate response; ITT = intention to treat; IVRS = interactive voice response system; LOCF = last observation carried forward; MACE = major adverse cardiovascular event; MC = multi-center; MCID = minimum clinically important difference; MI = myocardial infarction; MOS = months; MTX = methotrexate; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NSAID = non-steroidal anti-inflammatory drug; PBO = placebo; PO = oral; PP = per protocol; RA = rheumatoid arthritis; RCT = randomized controlled trial; RF = rheumatoid factor; SAE = serious adverse effect; SDAI = Simplified Disease Activity Index; SSZ = sulfasalazine; TEAE = treatment-emergent adverse event; TNFi = tumor necrosis factor inhibitor; tsDMARD = targeted synthetic DMARD; ULN = upper limit normal; WKS = weeks; YRS = years

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Appendix 1: Current Preferred Drug List

Route	Formulation	Brand	Generic	PDL
SUB-Q	SYRINGEKIT	HUMIRA	adalimumab	Y
SUB-Q	SYRINGEKIT	HUMIRA PEDIATRIC CROHN'S	adalimumab	Y
SUB-Q	PEN IJ KIT	HUMIRA PEN	adalimumab	Y
SUB-Q	PEN IJ KIT	HUMIRA PEN CROHN-UC-HS STARTER	adalimumab	Y
SUB-Q	PEN IJ KIT	HUMIRA PEN PSORIASIS-UVEITIS	adalimumab	Y
SUB-Q	VIAL	ENBREL	etanercept	Y
SUB-Q	SYRINGE	ENBREL	etanercept	Y
SUB-Q	CARTRIDGE	ENBREL MINI	etanercept	Y
SUB-Q	PEN INJCTR	ENBREL SURECLICK	etanercept	Y
SUB-Q	SYRINGE	ORENCIA	abatacept	N
SUB-Q	AUTO INJCT	ORENCIA CLICKJECT	abatacept	N
INTRAVEN	VIAL	ORENCIA	abatacept/maltose	N
SUB-Q	SYRINGE	KINERET	anakinra	N
ORAL	TABLET	OTEZLA	apremilast	N
ORAL	TAB DS PK	OTEZLA	apremilast	N
ORAL	TABLET	OLUMIANT	baricitinib	N
SUB-Q	AUTO INJCT	BENLYSTA	belimumab	N
SUB-Q	SYRINGE	BENLYSTA	belimumab	N
INTRAVEN	VIAL	BENLYSTA	belimumab	N
SUB-Q	SYRINGE	SILIQ	brodalumab	N
SUB-Q	VIAL	ILARIS	canakinumab/PF	N
SUB-Q	KIT	CIMZIA	certolizumab pegol	N
SUB-Q	SYRINGEKIT	CIMZIA	certolizumab pegol	N
SUB-Q	PEN INJCTR	SIMPONI	golimumab	N
SUB-Q	SYRINGE	SIMPONI	golimumab	N
INTRAVEN	VIAL	SIMPONI ARIA	golimumab	N
SUB-Q	SYRINGE	TREMFYA	guselkumab	N
INTRAVEN	VIAL	REMICADE	infliximab	N
INTRAVEN	VIAL	RENFLEXIS	infliximab-abda	N
INTRAVEN	VIAL	INFLECTRA	infliximab-dyyb	N
SUB-Q	AUTO INJCT	TALTZ AUTOINJECTOR	ixekizumab	N
SUB-Q	AUTO INJCT	TALTZ AUTOINJECTOR (2 PACK)	ixekizumab	N

SUB-Q	AUTO INJCT	TALTZ AUTOINJECTOR (3 PACK)	ixekizumab	N
SUB-Q	SYRINGE	TALTZ SYRINGE	ixekizumab	N
INTRAVEN	VIAL	TYSABRI	natalizumab	N
INTRAVEN	VIAL	RITUXAN	rituximab	N
SUB-Q	SYRINGE	KEVZARA	sarilumab	N
SUB-Q	SYRINGE	COSENTYX (2 SYRINGES)	secukinumab	N
SUB-Q	PEN INJCTR	COSENTYX PEN	secukinumab	N
SUB-Q	PEN INJCTR	COSENTYX PEN (2 PENS)	secukinumab	N
SUB-Q	SYRINGE	COSENTYX SYRINGE	secukinumab	N
SUB-Q	SYRINGE	ILUMYA	tildrakizumab-asmn	N
INTRAVEN	VIAL	ACTEMRA	tocilizumab	N
SUB-Q	SYRINGE	ACTEMRA	tocilizumab	N
ORAL	TABLET	XELJANZ	tofacitinib citrate	N
ORAL	TAB ER 24H	XELJANZ XR	tofacitinib citrate	N
SUB-Q	SYRINGE	STELARA	ustekinumab	N
INTRAVEN	VIAL	STELARA	ustekinumab	N
INTRAVEN	VIAL	ENTYVIO	vedolizumab	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to October Week 2 2018, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 17, 2018

1	Adalimumab/	4071
2	Etanercept/	5149
3	tocilizumab.mp.	2093
4	Abatacept/	2337
5	Infliximab/	8455
6	Rituximab/	11334
7	golimumab.mp.	838
8	apremilast.mp.	344
9	tofacitinib.mp.	725
10	certolizumab.mp.	921
11	Certolizumab Pegol/	427
12	secukinumab.mp.	487
13	Abatacept/	2337
14	ixekizumab.mp.	238
15	Ustekinumab/	649
16	Natalizumab/	1255
17	vedolizumab.mp.	462
18	brodalumab.mp.	155
19	guselkumab.mp.	70
20	anakinra.mp.	1312
21	canakinumab.mp.	429
22	sarilumab.mp.	46
23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	34167
24	Arthritis, Rheumatoid/	46038
25	PSORIASIS/	17007
26	Arthritis, Psoriatic/	4397
27	Spondylitis, Ankylosing/	6619
28	Crohn Disease/	20017
29	Colitis, Ulcerative/	15514
30	Arthritis, Juvenile/	5065
31	24 or 25 or 26 or 27 or 28 or 29 or 30	104667
32	23 and 31	12996
33	limit 32 to (yr="2017 - 2018" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	418

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

ILUMYA™ (tildrakizumab-asmn) injection, for subcutaneous use
Initial U.S. Approval: 2018

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

---------- DOSAGE AND ADMINISTRATION ----------
- Administer by subcutaneous injection. (2.1)
- Recommended dose is 100 mg at Weeks 0, 4, and every twelve weeks thereafter. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Injection: 100 mg/mL solution in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------
Serious hypersensitivity reaction to tildrakizumab or to any of the excipients. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- *Hypersensitivity:* If a serious allergic reaction occurs, discontinue ILUMYA immediately and initiate appropriate therapy. (5.1)
- *Infections:* ILUMYA 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, consider discontinuing ILUMYA until the infection resolves. (5.2)
- *Tuberculosis (TB):* Evaluate for TB prior to initiating treatment. (5.3)

---------- ADVERSE REACTIONS ----------
Most common (≥1%) adverse reactions associated with ILUMYA treatment are upper respiratory infections, injection site reactions, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Live Vaccines: Avoid use of live vaccines in patients treated with ILUMYA. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2018

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

OLUMIANT (baricitinib) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving OLUMIANT. (5.1)**
- **If a serious infection develops, interrupt OLUMIANT until the infection is controlled. (5.1)**
- **Prior to starting OLUMIANT, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting OLUMIANT. (5.1)**
- **Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)**
- **Lymphoma and other malignancies have been observed in patients treated with OLUMIANT. (5.2)**
- **Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with OLUMIANT. Patients with symptoms of thrombosis should be evaluated promptly. (5.3)**

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

OLUMIANT® is a Janus kinase (JAK) inhibitor indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. (1.1)

Limitation of Use: Use of OLUMIANT in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1.1)

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

The recommended dose of OLUMIANT is 2 mg once daily. (2.1)

OLUMIANT may be used as monotherapy or in combination with methotrexate or other DMARDs. (2.1)

Anemia: Avoid initiation or interrupt OLUMIANT in patients with hemoglobin less than 8 g/dL. (2.2, 2.3, 5.5)

Lymphopenia: Avoid initiation or interrupt OLUMIANT in patients with an Absolute Lymphocyte Count less than 500 cells/mm^3. (2.2, 2.3, 5.5)

Neutropenia: Avoid initiation or interrupt OLUMIANT in patients with an Absolute Neutrophil Count less than 1000 cells/mm^3. (2.2, 2.3, 5.5)

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

Tablets (not scored): 2 mg (3)

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

None.

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

- Serious Infections: Avoid use of OLUMIANT in patients with active, serious infection, including localized infections. If a serious infection develops, interrupt OLUMIANT therapy until the infection is controlled. Do not give OLUMIANT to patients with active tuberculosis. (5.1)
- Thrombosis: Use with caution in patients who may be at increased risk. (5.3)
- Gastrointestinal Perforations: Use with caution in patients who may be at increased risk. (5.4)
- Laboratory Assessment: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids. (5.5)
- Vaccinations: Avoid use of OLUMIANT with live vaccines. (5.6)

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

Adverse reactions (greater than or equal to 1%) include: upper respiratory tract infections, nausea, herpes simplex, and herpes zoster. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

OLUMIANT is not recommended in patients taking strong Organic Anion Transporter 3 (OAT3) inhibitors (e.g., probenecid). (2.5, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic Impairment: OLUMIANT is not recommended in patients with severe hepatic impairment. (2.4, 8.6)
- Renal Impairment: OLUMIANT is not recommended in patients with moderate or severe renal impairment. (2.4, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 05/2018

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 (both pharmacy and physician-administered claims)

Covered Alternatives:

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

Table 1. Approved and Funded Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo		
Adalimumab (HUMIRA) and biosimilars	≥18 yo	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo(Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥2 yo (Humira)
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			
Baricitinib (OLUMIANT)						≥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	≥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 Pemphigus Vulgaris ≥18 yo
Sarilumab (KEVZARA)						≥18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			
Tildrakizumab-asmn (ILUMYA)				≥18 yo				
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo
Tofacitinib (XELJANZ)					≥18 yo	≥18 yo	≥18 yo	
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.

Approval Criteria		
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? 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. If the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® product or an Enbrel® product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to #10	**No**: Go to #12
10. Is the plaque psoriasis severe in nature, which has resulted in functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.
11. Has the patient failed to respond or had inadequate response to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; and • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #13	**No:** Go to #17

Approval Criteria		
13. Has the patient failed to respond or had inadequate response to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; or • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira® product or an Enbrel® product for at least 3 months?	**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 #16	**No:** Go to #15
15. Is the patient on concurrent DMARD therapy with plans to continue concomitant use OR does the patient have documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.
16. 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.
17. 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 #18	**No:** Go to #19

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

Renewal Criteria		
1. Is the request for treatment of psoriatic arthritis or rheumatoid arthritis?	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient been adherent to both biologic and DMARD therapy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
3. 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: *1/19 (DM); 1/18; 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/21/13*