Cytokine and CAM Antagonists and Related Agents Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Rheumatoid Arthritis (RA)	Juvenile Idiopathic Arthritis (JIA)	Ankylosing Spondylitis (AS)	Plaque Psoriasis (PSO) Moderate to severe in candidates for systemic therapy or phototherapy	Psoriatic Arthritis (PsA)	Crohn's Disease (CD) Reduce signs and symptoms and inducing and maintaining clinical response in patients with moderately to severely active CD	Ulcerative Colitis (UC)	Select Periodic Fever Syndromes
Anti-Tumor Necrosis Factor (TNF) Biologics									
adalimumab[a] (Humira®)[1]	Abbvie	X	X (≥ 2 years)	X	X	X	X (≥ 6 years)	X (≥ 5 years)	--
adalimumab-atto[a] (Amjevita™)[2]	Amgen	X	X (≥ 2 years)	X	X	X	X (≥ 6 years)	X	--
certolizumab pegol[b] (Cimzia®)[3]	UCB	X	--	X	X	X	X	--	--
etanercept[c] (Enbrel®)[4]	Amgen	X	X (≥ 2 years)	X	X (≥ 4 years)	X	--	--	--
golimumab SC[d] (Simponi®)[5]	Janssen Biotech	X	--	X	--	X	--	X	--
golimumab IV[d] (Simponi® Aria®)[6]	Janssen Biotech	X	X (≥ 2 years)	X	--	X (≥ 2 years)	--	--	--
infliximab[e] (Remicade®)[7]	generic, Janssen Biotech	X	--	X	X	X	X (≥ 6 years)	X (≥ 6 years)	--
infliximab-abda[e] (Renflexis®)[8]	Merck/ Organon	X	--	X	X	X	X (≥ 6 years)	X (≥ 6 years)	--
infliximab-axxq[e] (Avsola®)[9]	Amgen	X	--	X	X	X	X (≥ 6 years)	X (≥ 6 years)	--
infliximab-dyyb[e] (Inflectra®)[10]	Pfizer	X	--	X	X	X	X (≥ 6 years)	X (≥ 6 years)	--

IV = intravenous; SC = subcutaneous

FDA-Approved Indications (continued)

Drug	Manufacturer	Rheumatoid Arthritis (RA)	Juvenile Idiopathic Arthritis (JIA)	Ankylosing Spondylitis (AS)	Plaque Psoriasis (PSO) Moderate to severe in candidates for systemic therapy or phototherapy	Psoriatic Arthritis (PsA)	Crohn's Disease (CD) Reduce signs and symptoms and inducing and maintaining clinical response in patients with moderately to severely active CD	Ulcerative Colitis (UC)	Select Periodic Fever Syndromes
Other Biologic Agents									
abatacept[f] (Orencia®)[11]	Bristol-Myers Squibb	X	X (≥ 6 years: IV) (≥ 2 years: SC)	--	--	X	--	--	--
anakinra[g] (Kineret®)[12]	Sobi	X	--	--	--	--	--	--	X (pediatrics)
brodalumab (Siliq®)[13]	Bausch	--	--	--	X	--	--	--	--
canakinumab[h] (Ilaris®)[14]	Novartis	--	X (≥ 2 years)	--	--	--	--	--	X (≥ 4 years)
guselkumab (Tremfya®)[15]	Janssen Biotech	--	--	--	X	X	--	--	--
inebilizumab-cdon[i] (Uplizna®)[16]	Viela Bio	--	--	--	--	--	--	--	--
ixekizumab[j] (Taltz®)[17]	Eli Lilly	--	--	X	X (≥ 6 years)	X	--	--	--
rilonacept[k] (Arcalyst®)[18]	Regeneron/ Kiniksa	--	--	--	--	--	--	--	X (≥ 12 years)
risankizumab-rzaa (Skyrizi®)[19]	Abbvie	--	--	--	X	X	X	--	--
sarilumab[l] (Kevzara®)[20]	Sanofi-Aventis	X	--	--	--	--	--	--	--

IV = intravenous; SC = subcutaneous

FDA-Approved Indications (continued)

Drug	Manufacturer	Rheumatoid Arthritis (RA)	Juvenile Idiopathic Arthritis (JIA)	Ankylosing Spondylitis (AS)	Plaque Psoriasis (PSO) Moderate to severe in candidates for systemic therapy or phototherapy	Psoriatic Arthritis (PsA)	Crohn's Disease (CD) Reduce signs and symptoms and inducing and maintaining clinical response in patients with moderately to severely active CD	Ulcerative Colitis (UC)	Select Periodic Fever Syndromes
Other Biologic Agents *(continued)*									
satralizumab-mwge[m] (Enspryng™)[21]	Genentech	--	--	--	--	--	--	--	--
secukinumab[n] (Cosentyx®)[22]	Novartis	--	--	X	X (≥ 6 years)	X (≥ 2 years)	--	--	--
tildrakizumab-asmn (Ilumya®)[23]	Sun	--	--	--	X	--	--	--	--
tocilizumab[o] (Actemra®)[24]	Genentech	X	X (≥ 2 years)	--	--	--	--	--	--
ustekinumab[p] (Stelara®)[25]	Janssen Biotech	--	--	--	X (≥ 6 years)	X (≥ 6 years)	X	X	--
vedolizumab[q] (Entyvio®)[26]	Takeda	--	--	--	--	--	X	X	--
Non-biologic Agents									
abrocitinib[r] (Cibinqo™)[27]	Pfizer	--	--	--	--	--	--	--	--
apremilast[s] (Otezla®)[28]	Amgen	--	--	--	X	X	--	--	--
baricitinib[t] (Olumiant®)[29]	Eli Lilly	X	--	--	--	--	--	--	--
tofacitinib[u] (Xeljanz®, Xeljanz XR)[30]	Pfizer	X	X (≥ 2 years)	X	--	X	--	X	--
upadacitinib[v] (Rinvoq®)[31]	Abbvie	X	--	X	--	X	--	X	--

IV = intravenous; SC = subcutaneous

a. Adalimumab-atto is considered a biosimilar to adalimumab (Humira) for its indications. Biosimilar, a term used for biologic products, means that approval is based on data demonstrating that it is highly similar to another FDA-approved biological product (a reference product) and there are no clinically meaningful differences between the 2 products. For RA and PsA, adalimumab and adalimumab-atto may be used alone or in combination with methotrexate (MTX) or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs). For PSO, adalimumab and adalimumab-atto are indicated in patients who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. Adalimumab and adalimumab-atto are indicated for the treatment of moderately to severely active UC; effectiveness of adalimumab has not been established in patients who have lost response to or were intolerant to TNF antagonists. Adalimumab and adalimumab-atto are approved for the treatment of polyarticular JIA (pJIA) in children in children ≥ 2 years old when used alone or in combination with MTX. Adalimumab is also indicated for the treatment of moderate to severe hidradenitis suppurativa (HS) in adolescents and adults and non-infectious intermediate, posterior, and panuveitis in patients ≥ 2 years of age.

b. Certolizumab pegol is approved for the treatment of adults with active nonradiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

c. In psoriatic arthritis and RA, etanercept may be used with or without methotrexate. Etanercept is approved for the treatment of pJIA in children ≥ 2 years old.

d. In RA, golimumab is indicated only in combination with methotrexate. For PsA and AS, golimumab may be used alone or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drug (DMARD). Subcutaneous (SC) golimumab is indicated in adult patients with moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine (6-MP) for inducing and maintaining clinical response, improving endoscopic appearance of the mucosa during induction, inducing clinical remission, or achieving and sustaining clinical remission in induction responders. Intravenous (IV) golimumab (Simponi Aria) is approved for the treatment of pJIA in children ≥ 2 years old.

e. Infliximab-abda, infliximab-axxq, and infliximab-dyyb are considered biosimilar to infliximab (Remicade) for their indications. In RA, infliximab and its biosimilars are indicated only in combination with methotrexate. In CD, infliximab and its biosimilars are indicated for patients who have had an inadequate response to conventional therapy; reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing CD. Likewise, in UC, they are indicated for those with an inadequate response to conventional therapy. The generic product for infliximab (Remicade) is an authorized generic.

f. Abatacept should not be administered concomitantly with TNF antagonists or with anakinra. Abatacept may be used as monotherapy or concomitantly with methotrexate. In RA, abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists. Abatacept SC is approved for the treatment of pJIA in children ≥ 2 years old. Abatacept IV is approved for the treatment of pJIA in children ≥ 6 years of age and the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients ≥ 2 years old undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor.

g. In RA, anakinra is indicated only for patients ≥ 18 years of age who have had an inadequate response to one or more DMARDs; it may be used alone or in combination with DMARDs, except TNF antagonists. Anakinra is approved for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) associated with Neonatal Onset Multisystem Inflammatory Disease (NOMID). It is also approved to treat Deficiency of Interleukin-1 Receptor Antagonist (DIRA).

h. Canakinumab is approved for the treatment of CAPS, including familiar cold autoinflammatory syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and pediatrics ≥ 4 years of age. It is also approved for the following other periodic fever syndromes in adults and pediatric patients ≥ 2 years of age: Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF). It is also indicated for active Still's disease, including adult-onset Still's disease (AOSD) and systemic JIA in patients ≥ 2 years old.

i. Inebilizumab-cdon is indicated to treat adults with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

j. For PsA, ixekizumab may be administered alone or in combination with a conventional DMARD (e.g., methotrexate). For ankylosing spondylitis, ixekizumab may be used with conventional DMARDs (e.g., sulfasalazine), corticosteroids, NSAIDs, and/or analgesics. Ixekizumab also is approved for the treatment of adults with active nr-axSpA with objective signs of inflammation.

k. Rilonacept is approved for patients with CAPS in patients ≥ 12 years of age, including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS). It is also approved for the maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and pediatric patients weighing ≥ 10 kg and the treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and pediatric patients ≥ 12 years old.

l. Sarilumab is indicated for the treatment of adults with moderately to severely active RA who have had an inadequate response to one or more DMARDs.

m. Satralizumab-mxge is approved for the treatment of NMOSD in adult patients who are AQP4 antibody positive.

n. Secukinumab is also approved for the treatment of active nr-axSpA with objective signs of inflammation. It is also approved for the treatment of active enthesitis-related arthritis (ERA) in patients ≥ 4 years old.

o. In RA, tocilizumab is indicated for the treatment of adults with moderately to severely active RA who have had an inadequate response to one or more DMARDs. In RA, tocilizumab may be used alone or in combination with methotrexate or other DMARDs. IV and SC tocilizumab are indicated for both systemic and pJIA in children ≥ 2 years of age. Tocilizumab prefilled syringes for SC injection are not approved for JIA. Tocilizumab is also approved for use in adult patients with giant cell arteritis (GCA) and for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and pediatric patients ≥ 2 years of age. Tocilizumab is also approved to slow the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

p. In PsA, ustekinumab may be used alone or in combination with methotrexate. Approval of ustekinumab in UC is for those with moderate to severe disease.

q. Vedolizumab is approved for treatment of moderately to severely active UC, as well as treatment of moderately to severely active CD.

r. Abrocitinib is indicated for the treatment of adults with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Abrocitinib is not recommended for use in combination with other Janus kinase (JAK) inhibitors, biologic immunomodulators, or other immunosuppressants.

s. Apremilast is also indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease. For plaque psoriasis, it is indicated for patients who are candidates for phototherapy or systemic therapy, regardless of severity.

t. Baricitinib is indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response ≥ 1 TNF antagonist. It is also indicated in adults with severe alopecia areata. It carries a limitation for use that it is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants, (e.g., azathioprine, cyclosporine). Baricitinib is also indicated for the treatment of coronavirus disease 2019 (COVID-19) in select hospitalized adults requiring ventilation assistance; this indication will not be addressed in this Therapeutic Class Review.

u. In RA, tofacitinib is indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to ≥ 1 TNF antagonist. It may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs. In PsA, tofacitinib is indicated for the treatment of adult patients with active PsA who have had an inadequate response or intolerance to ≥ 1 TNF antagonist. In UC, tofacitinib is indicated for patients with moderate to severely active disease who have an inadequate response or intolerance to ≥ 1 TNF antagonist. For AS, tofacitinib tablets (Xeljanz, Xeljanz ER) are indicated for the treatment of adults with active AS who have had an inadequate response or intolerance to ≥ 1 TNF antagonists. Tofacitinib (Xeljanz) is approved for the treatment of pJIA in children ≥ 2 years of age who have had an inadequate response or intolerance to ≥ 1 TNF antagonist. The oral solution is only approved for pJIA, and the XR formulation is not approved for pJIA. For any indication, tofacitinib should not be used in combination with biologic DMARDs or with potent immunosuppressants (e.g., azathioprine, cyclosporine).

v. Upadacitinib is indicated for the treatment of adult patients with moderately to severely active RA, active PsA, active AS, or active nr-axSpA with objective signs of inflammation in which it should only be used in those with an inadequate response or intolerance to ≥ 1 TNF antagonist. It may be used alone or in combination with methotrexate or other nonbiologic DMARDs for these indications. It is also approved for the treatment of adults with moderately to severely active UC in those with an inadequate response or intolerance to ≥ 1 TNF antagonist. Upadacitinib is also approved for the treatment of patients ≥ 12 years of age with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use

of those therapies is inadvisable. The use of upadacitinib in combination with other JAK inhibitors, biologic DMARDs, or potent immunosuppressants (e.g., azathioprine, cyclosporine) is not recommended.

OVERVIEW

Cytokines and cell-adhesion molecules (CAMs) are chemical mediators involved in inflammatory processes throughout the body.

Cytokines

Cytokines are small proteins secreted in response to an immune stimulus for the purpose of mediating and regulating immunity, inflammation, and hematopoiesis. Cytokines are derived from monocytes and macrophages and induce gene expression of a number of proteins that contribute to the inflammatory response. The actions of the individual cytokines are widely varied, including stimulating production of other cytokines and increased adhesion molecule expression and activate B cells, T cells, and natural killer cells. They contribute to fibrosis and tissue degeneration associated with chronic inflammation, primarily by inducing the proliferation of fibroblasts and collagenase. The pro-inflammatory cytokines, tumor necrosis factor (TNF), and interleukin (IL)-1, are involved in tissue destruction in many chronic inflammatory diseases affecting various organs.[32]

TNFα and TNFß are closely related proteins recognized by the same cell surface receptor. TNFα is overproduced in the joints of patients with rheumatoid arthritis (RA) and is increased in the synovial fluid and synovium in patients with psoriatic arthritis (PsA) and in the skin of psoriatic lesions.[33,34,35,36,37] Increased expression of TNFα has been reported in the serum, synovium, and sacroiliac joints in patients with ankylosing spondylitis (AS).[38,39,40,41,42] TNFα also has a role in Crohn's disease in stimulation of inflammation.[43]

IL-1 plays a major role in the promotion of rheumatic inflammation.[44,45] It promotes inflammation, as well as bone and cartilage resorption, and is present in increased concentrations in the synovia of patients with RA.[46] Over-expression of IL-12 and IL-23 have been implicated in the pathogenesis of psoriasis.[47] IL-12 induces and sustains type 1 T helper (Th1) immune responses leading to the secretion of interferon and the homing of T cells to the skin. IL-23 maintains chronic autoimmune inflammation via the induction of IL-17, regulation of T memory cells, and direct activation of macrophages. The human monoclonal IgG2 antibody inhibits IL-17 cytokine-induced responses including the release of pro-inflammatory cytokines and chemokines. IL-6 has a wide range of biological activities in immune regulation, hematopoiesis, inflammation, and oncogenesis.[48] Overproduction of IL-6 has been linked to various inflammatory, auto-immune, and malignant diseases.

Cell Adhesion Molecules

Cell adhesion molecules (CAMs) are cell surface proteins involved in the binding of cells, usually leukocytes, to each other, endothelial cells, or the extracellular matrix.[49] Specific signals produced in response to wounds and infection control the expression and activation of these molecules. The interactions and responses initiated by binding of these CAMs to their receptors/ligands play important roles in the mediation of the inflammatory and immune reactions that constitute one line of the body's defense against these insults.

Most of the CAMs characterized so far fall into 3 general families of proteins: the immunoglobulin (Ig) superfamily, the integrin family, and the selectin family.[50] The Ig superfamily of adhesion molecules bind to integrins on leukocytes and mediate their flattening onto the blood vessel wall with their subsequent extravasation into surrounding tissue. The integrin family of CAMs consists of an α chain and a ß chain that mediate cell-to-cell interactions, such as leukocyte adherence to the vascular endothelium. Different

sets of integrins are expressed by different populations of leukocytes to provide specificity for binding to different types of CAMs expressed along the vascular endothelium. The selectin family is involved in the adhesion of leukocytes to activated endothelium followed by extravasation through the blood vessel walls into lymphoid tissues and sites of inflammation. Other proteins that are functionally classified as CAMs are involved in strengthening the association of T cells with antigen-presenting cells or target cells, in T cell activation, and in recirculating lymphocytes back to the circulation via the lymphatic system.

Different CAMs have been implicated in inflammatory diseases (e.g., psoriasis), fibrotic diseases (e.g., degenerative diseases of the lung, liver, and kidney), and autoimmune diseases (e.g., RA).[51] Vascular CAM-1 has been implicated in interactions between leukocytes and connective tissue, including RA synovial tissue fibroblasts. Such interactions within the synovium contribute to RA inflammation.[52] In psoriatic skin, intercellular CAM-1 (ICAM-1) cell surface expression is upregulated on endothelium and keratinocytes. Activation of T lymphocytes involves the interaction between lymphocyte function-associated antigen type 3 (LFA-3) on antigen-presenting cells and CD2 on T lymphocytes. This lymphocyte activation and trafficking to skin play a role in the pathophysiology of chronic plaque psoriasis.

Role in Therapy

Ankylosing Spondylitis (AS) and nonradiographic axial spondyloarthritis (nr-axSpA)

Axial spondyloarthritis (axSpA) is an inflammatory condition generally affecting the spine and can be furthered subdivided into ankylosing spondylitis (AS; radiographic axSpA) and nonradiographic axSpA (nr-axSpA).[53,54] In 2019, the American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) published an update to their 2015 guidelines on the treatment of ankylosing spondylitis (AS) and nr-axSpA.[55,56] For active AS and nr-axSpA, the guidelines recommend continuous therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) as a primary treatment with TNF antagonists as alternatives in patients with persistent activity despite NSAID treatment. No particular TNF antagonist is preferred over another, except in patients with comorbid inflammatory bowel disease (IBD) or recurrent iritis, in which monoclonal antibodies should be used (e.g., infliximab or adalimumab) over other biologics (e.g., etanercept). Alternatives include ixekizumab and secukinumab, both preferred over an alternative TNF antagonist in primary nonresponse and over tofacitinib, as well as tofacitinib; however, an alternative TNF antagonist is preferred over ixekizumab and secukinumab in secondary nonresponse and over tofacitinib. Sulfasalazine or methotrexate is recommended in patients with active AS and with prominent peripheral arthritis despite treatment with NSAIDS when a TNF antagonist is not available. Switching from one agent to its biosimilar is not recommended in patients with nonresponse. Use of systemic glucocorticoids is not recommended, although local glucocorticoids are recommended conditionally in select patients. For stable AS and nr-axSpA, ACR recommends on-demand NSAID use over continuous NSAID use. They also recommend TNF antagonist monotherapy over use in combination with NSAIDs or a conventional DMARD when combination therapy was previously received. They further recommend continuing treatment with the biologic agent over discontinuation, taper, or biosimilar switch. For both active and stable AS and nr-axSpA, ACR conditionally recommends against co-treatment with low-dose methotrexate. Additional recommendations, as well as levels of recommendation and supporting evidence are further detailed in the guidelines. Upadacitinib was not approved for AS or nr-axSpA at the time these guidelines were developed.

Crohn's Disease (CD)

In 2021, the American Gastroenterological Association (AGA) issued a guideline on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease and notable recommendations regarding agents within this class are described below.[57] In adult outpatients with moderate to severe Crohn's disease, the AGA recommends the use of a TNF antagonist (moderate evidence) or ustekinumab (moderate evidence) over no treatment for induction and maintenance of remission, and the AGA suggests the use of vedolizumab over no treatment for induction and maintenance of remission (low/moderate evidence). In biologic treatment-naïve adult outpatients with moderate to severe Crohn's disease, the AGA recommends the use of infliximab, adalimumab, or ustekinumab (moderate evidence) over certolizumab pegol (low evidence) and suggests the use of vedolizumab over certolizumab pegol for the induction of remission. In adult outpatients with moderate to severe Crohn's disease who never responded to TNF antagonists, the AGA recommends ustekinumab (moderate evidence) and suggests vedolizumab (low evidence) over no treatment of the induction of remission. If patients had previously responded to infliximab, the AGA recommends adalimumab or ustekinumab (moderate evidence for both) and suggests vedolizumab (low evidence) over no treatment for the induction of remission. The group also recommends the use of biologic drug monotherapy over thiopurine monotherapy for the induction of remission (moderate evidence). In adult outpatients with moderate to severe Crohn's disease who are treatment-naïve to biologics and immunomodulators, the AGA suggests infliximab plus thiopurines over infliximab monotherapy (moderate evidence) and adalimumab plus thiopurines over adalimumab monotherapy (very low evidence) for induction and maintenance of remission. The AGA do not make recommendations regarding the use of ustekinumab or vedolizumab as monotherapy or in combination with another agent. The AGA does suggest the early introduction of a biologic over waiting until failure of 5-aminosalicylates and/or corticosteroids (low evidence). For those with an active perianal fistula, the AGA recommends infliximab over no treatment for the induction and maintenance of fistula remission (moderate evidence) and suggests adalimumab, ustekinumab, or vedolizumab over no treatment for the induction or maintenance of fistula remission (low evidence). Risankizumab-rzaa was not approved for Crohn's disease at the time these guidelines were developed. The role of natalizumab (Tysabri®) and other agents not in this therapeutic class are also addressed in the guidance.

The 2018 American College of Gastroenterology (ACG) guidelines for Crohn's disease recommend the use of TNF antagonists (e.g., infliximab, certolizumab pegol, adalimumab) for the treatment of moderate to severe disease in patients who have not responded to corticosteroids or immunosuppressive agents or for severely active disease (strong recommendation).[58] Ustekinumab should be given for patients who failed previous treatment with corticosteroids, traditional agents, or TNF antagonists or who are naïve to TNF antagonists (strong recommendation). Further, combination therapy of infliximab with immunomodulators is more effective than treatment with either agent alone in patients who are naïve to those agents (strong recommendation). For patients with objective evidence of active disease and moderate to severe disease, vedolizumab with or without an immunomodulator should be considered for induction of symptomatic remission (strong recommendation). Natalizumab should be considered for induction of symptomatic response and remission in patients with active disease (strong recommendation). Infliximab may be administered to treat fulminant disease (conditional recommendation). Risankizumab-rzaa was not approved for Crohn's disease at the time these guidelines were developed. Additional information on diagnosis, treatment of mild to moderate disease/low-risk disease, fistulizing disease, and other treatment agents are further detailed in the guidelines.

Juvenile Idiopathic Arthritis (JIA) and Adult Onset Still's Disease (AOSD)

The 2019 ACR/Arthritis Foundation guideline for the therapeutic approach for non-systemic polyarthritis (polyarticular JIA [pJIA]), sacroiliitis, and enthesitis provides strong and conditional recommendations; conditional recommendations apply to the majority of patients but are preference-sensitive.[59] The organization recommends NSAIDs conditionally as adjunctive therapy (very low level of evidence). Regarding traditional disease modifying antirheumatic drugs (DMARDs) for polyarthritis, methotrexate is conditionally recommended over leflunomide or sulfasalazine (moderate and very low evidence, respectively) and subcutaneous (SC) methotrexate is conditionally recommended over oral methotrexate (very low evidence). In patients with polyarthritis, combination therapy with a biologic DMARD is conditionally recommended over biologic monotherapy when initiating treatment with a biologic (etanercept [very low evidence], adalimumab [moderate evidence], golimumab [very low evidence], abatacept [low evidence], or tocilizumab [low evidence]). Combination therapy with a DMARD is strongly recommended for infliximab (low evidence). Intraarticular glucocorticoids are conditionally recommended as adjunct therapy (very low evidence), and oral corticosteroids as a bridge therapy are conditionally recommended in patients with moderate or high disease activity (very low evidence); however, bridge therapy is not recommended in patients with low disease activity (very low evidence). In addition, the group strongly recommends against adding chronic low-dose glucocorticoids, regardless of disease activity (very low evidence) in polyarthritis patients. For initial therapy in polyarthritis patients, the group strongly recommends all patients have initial therapy with DMARD over NSAID monotherapy (moderate evidence), with methotrexate monotherapy conditionally recommended over triple DMARD therapy (low evidence). In patients without risk factors (e.g., positive anti-cyclic citrullinated peptide antibodies, positive rheumatoid factor, or presence of joint damage), the group recommends initial therapy with a DMARD conditionally over a biologic (low evidence); however, in those with risk factors, the group recognizes that there are situations in which a biologic may be preferred (low evidence; e.g., involvement of high risk joints [cervical spine, wrist, or hip], high disease activity, and/or those judged to be high risk of disabling joint damage). For subsequent therapy in low disease activity patients, defined as clinical Juvenile Disease Activity Score based on 10 joints (cJADAS-10) ≤ 2.5 and ≥ 1 active joint, escalation of therapy (e.g., intraarticular glucocorticoid injection, DMARD dose optimization, methotrexate trial, and adding or changing biologic) is recommended over no escalation (very low evidence). For subsequent therapy in moderate or high disease activity (cJADAS-10 > 2.5) patients receiving DMARD monotherapy, the group conditionally recommends adding a biologic to the original DMARD over changing to a second DMARD (low evidence) or triple DMARD therapy (low evidence). For subsequent therapy in moderate or high disease activity polyarthritis patients receiving a TNF antagonist with or without a DMARD, the group conditionally recommends switching to a non-TNF antagonist (e.g., tocilizumab, abatacept) over switching to a second TNF antagonist (very low evidence); however, a second TNF antagonist may be appropriate in patients with good initial response to a TNF antagonist who have experienced secondary failure. If the patient is receiving their second biologic, use of a TNF antagonist, abatacept, or tocilizumab is conditionally recommended over rituximab (very low evidence). Tofacitinib was not FDA approved for JIA at the time these guidelines were developed.

For patients with JIA and sacroiliitis, the 2019 ACR/Arthritis Foundation guideline strongly recommends treatment with an NSAID over no NSAID treatment (very low evidence).[60] In those who are already on NSAIDs with continued active disease, the group strongly recommends a TNF antagonist over NSAID monotherapy (low evidence), with a conditional recommendation (low evidence) for sulfasalazine in those who have contraindications or have failed a TNF antagonist. The group strongly recommends against the use of methotrexate monotherapy (very low evidence). Bridging therapy with a limited

duration oral corticosteroid in select conditions and adjunct use of intraarticular glucocorticoid are conditionally recommended (both very low evidence). For those with JIA and enthesitis, the group strongly recommends NSAID treatment over no NSAID treatment (very low evidence), with a TNF antagonist conditionally recommended over methotrexate or sulfasalazine if disease activity continues (low evidence). Bridging therapy with a limited duration oral corticosteroid in select conditions also is conditionally recommended (very low evidence). The group provides additional recommendations on specific glucocorticoids, treatment of patients who also have sacroiliitis and physical and occupational therapy.

The 2021 update of the ACR guidelines for the treatment of JIA includes oligoarthritis and systemic JIA.[61] First-line treatment for oligoarthritis (JIA involving ≤ 4 joints without systemic manifestations) includes intra-articular glucocorticoids and/or NSAIDs (very low evidence). If there is an inadequate response, then non-biologic DMARDS (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, calcineurin inhibitors) are strongly recommended, with methotrexate conditionally recommended as the preferred agent. If an adequate response is not achieved with a non-biologic DMARD, then ACR strongly recommends a biologic DMARD (TNF inhibitor, abatacept, tocilizumab, anakinra, canakinumab) with no preference of one agent over another (very low evidence). For treatment of systemic JIA (sJIA), a brief trial of NSAIDs is conditionally recommended as initial monotherapy in patients without macrophage activation syndrome (very low evidence). Biologic DMARDs (IL-1 and IL-6 inhibitors) are recommended as initial monotherapy in patients with macrophage activation syndrome (very low evidence), with no preference of one agent over another.

Systemic JIA is also known as pediatric-onset Still's disease.[62] Adult-onset Still's disease (AOSD), also known as Wissler-Fanconi syndrome, is a rare inflammatory disorder that is an adult-onset counterpart to sJIA.[63] It is unpredictable, sometimes appearing and disappearing suddenly, idiopathic, and affected individuals may develop high fevers, rash, joint or muscle pain, sore throat, and other systemic symptoms of inflammatory disease. It is most commonly treated with NSAIDs for inflammation and antipyretics, such as acetaminophen. Select traditional DMARDs, such as methotrexate, and corticosteroids also may also be used for systemic symptoms. Currently, only canakinumab is FDA-approved for the treatment of AOSD in the United States (US).

Plaque Psoriasis

Systemic therapy for plaque psoriasis may include apremilast, methotrexate, cyclosporine, acitretin, methoxsalen, and several biologic agents. The evidence-based clinical practice guidelines of the American Academy of Dermatology (AAD) published in sections from 2008 to 2011 have undergone a gradual update in 2019 and 2020 in collaboration with the National Psoriasis Foundation (NPF).[64,65,66,67,68,69] The group provides several recommendations on non-biologic systemic therapy, including guidance regarding the use of methotrexate, apremilast, tofacitinib, cyclosporine, acitretin, hydroxyurea, leflunomide, mycophenolate mofetil, thioguanine, and tacrolimus. The notable recommendations most applicable to this class are included here. The group recommends methotrexate for the treatment of moderate to severe psoriasis in adults, although it is less effective than adalimumab and infliximab for cutaneous psoriasis (strength of recommendation A). It is also effective for psoriatic arthritis (peripheral, not axial) but is less effective than TNF antagonists (strength of recommendation B). The group recommends apremilast for the treatment of moderate to severe psoriasis in adults (strength of recommendation A). No recommendations regarding overall appropriateness recommendation for the use of tofacitinib was included; it is not approved for the treatment of psoriasis. The group recommends adalimumab, etanercept, and infliximab (strength of recommendation A for all) for moderate to severe psoriasis. Due

to limited evidence, certolizumab pegol does not have a recommendation, but they state that it is likely to have class characteristics similar to other TNF antagonists. Treatment response with TNF antagonists is best ascertained at 12 to 16 weeks following initiation (infliximab at 8 to 10 weeks). Brodalumab, guselkumab, ixekizumab, secukinumab, tildrakizumab, and ustekinumab, with a response ascertained after 12 weeks, are also recommended for moderate to severe psoriasis (strength of recommendation A for all). The group also stated that risankizumab is recommended for moderate to severe psoriasis (response ascertained after 12 weeks); however, they assigned this a strength of recommendation B as this was not FDA-approved at the time of guideline publication. They also state that while there is no evidence to support combining risankizumab with adjunct topical or systemic therapies, there is no reason that combination therapy should be considered unsafe. Based on limited data from a retrospective case series, apremilast may be combined with TNF antagonists (adalimumab, etanercept, infliximab) or ustekinumab to augment efficacy to treat moderate to severe cases (recommendation C for all). In general, the group recommends that efficacy and safety data be discussed with the patient for treatment initiation and switching. In addition, a quality of life discussion should occur with the patient. Other factors affecting patient preference (e.g., dosing, cost, route) should also be discussed. Notably, they state that biologics with less frequent dosing (e.g., 8 to 12 weeks) may be preferred in some patients. Regarding treatment switching, all other biologic therapies for psoriasis may be switched with another with the possibility for improved efficacy, safety, and/or tolerability; however, there are insufficient data to make more specific recommendations. Primary failure to respond to a TNF antagonist does not prevent a response to an alternative TNF antagonist, although reduced efficacy could occur. In addition, all products can lose efficacy over time (secondary failure). Rigorous data to guide therapy at that time are limited, but there are various treatment strategies that can be employed on a case-by-case basis. Augmentation using a combination of a biologic with select small molecule systemic agents, phototherapy, or topical agents is recommended in select patients with continued disease severity. For pediatric patients, AAD/NPF provides recommendations for topical and conventional systemic agents. Regarding biologics in pediatric patients, AAD/NPF recommends the use of etanercept for patients ≥ 6 years of age with moderate to severe psoriasis. Adalimumab, infliximab, and ustekinumab are also alternatives in select pediatric patients. Extensive recommendations by medication, class, and/or group, including dosing (initial, maintenance, escalation, and optimal intervals), monitoring, treatment discontinuation and reinitiation, antibody development, comorbidities, adverse effects, timeline, and augmentation strategies, are detailed in the guidelines. The group states that topical steroid therapies may be combined with biologics for moderate to severe psoriasis. They also recommend the addition of calcipotriene/betamethasone to adalimumab for 16 weeks for the treatment of moderate to severe psoriasis to accelerate clearance of psoriatic plaques and the addition of an ultra-high potency topical corticosteroid to standard dose etanercept for 12 weeks for the treatment of moderate to severe psoriasis.

Psoriatic Arthritis (PsA)

In 2018, ACR, in collaboration with NPF, published a guideline on the treatment of PsA and emphasize a treat-to-target approach.[70] For initial treatment in treatment-naïve patients with active PsA, the group recommends treatment with a TNF antagonist over an oral small molecule (e.g., methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast), an IL-17 inhibitor (brodalumab, ixekizumab, secukinumab), or an IL-12/23 inhibitor (e.g., ustekinumab) (conditional recommendations based on low or very low levels of evidence). In addition, an oral small molecule is recommended over an IL-17 inhibitor or IL-12/23 inhibitor, and methotrexate, specifically, is recommended over an NSAID (conditional

recommendations, all very low evidence). Use of an IL-17 antagonist is recommended over an IL-12/23 antagonist (conditional recommendation, very low evidence). In patients with active PsA despite treatment with an oral small molecule, the group recommends switching to a TNF antagonist over a different oral small molecule, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, tofacitinib, or a TNF antagonist in combination with methotrexate (conditional recommendations, low to moderate evidence). They also recommend switching to an IL-17 antagonist, over a different oral small molecule, an IL-12/23 inhibitor, abatacept, tofacitinib, or an IL-17 antagonist in combination with methotrexate, and to an IL-12/23 inhibitor over a different oral small molecule, abatacept, tofacitinib, or an IL-12/23 inhibitor in combination with methotrexate (conditional recommendations, very low to moderate evidence). The ACR also recommends adding apremilast to an oral small molecule rather than switching to apremilast and recommend switching to another oral small molecule rather than adding another non-apremilast small molecule (conditional recommendations, low evidence). In adults with active PsA despite treatment with TNF antagonist monotherapy, the group recommends switching to a different TNF antagonist over switching to an IL-17 or IL-12/23 inhibitor, abatacept, or tofacitinib, or adding methotrexate, although adding methotrexate to a different TNF antagonist is an option (conditional recommendations, very low or low evidence). Likewise, they recommend switching to an IL-17 inhibitor (without methotrexate) over switching to an IL-12/23 inhibitor (without methotrexate), abatacept, or tofacitinib and switching to an IL-12/23 inhibitor over switching to abatacept or tofacitinib (conditional recommendations, very low or low evidence). In adults with active PsA despite treatment with TNF antagonist and methotrexate therapy, the group recommends switching to a different TNF antagonist plus methotrexate over a different TNF antagonist but recommends switching to IL-17 or -12/23 inhibitor monotherapy (over IL-17 or -12/23 inhibitor in combination with methotrexate) (conditional recommendations, very low evidence). Several other conditional recommendations are included in the guidelines based on patients with active disease despite treatment, and, in general, the recommendations prefer alternative treatments in the following order: TNF antagonist, IL-17 inhibitor, IL-12/23 inhibitor, and addition of methotrexate. A notably strong recommendation in these guidelines is that in adult patients with active PsA and frequent serious infections who are both oral small molecule- and biologic treatment–naïve, an oral small molecule should be started over a TNF antagonist.

ACR's guidance also provided recommendations for patients who have PsA and other related disorders, such as active axial disease IBD.[71] Generally, these recommendations are similar to others in order of treatment preference; however, the group did include some notable strong recommendations for patients with active PsA and concomitant active IBD despite treatment with an oral small molecule, including recommendations to switch to a monoclonal antibody TNF antagonist over a TNF soluble receptor biologic (e.g., etanercept) or IL-17 inhibitor and that an IL-12/23 inhibitor is preferred over switching to an IL-17 antagonist (moderate evidence). A monoclonal antibody TNF antagonist is also preferred over an IL-12/23 inhibitor in this population, but this is a conditional recommendation (very low evidence).

Enthesitis is inflammation localized to the area at which ligaments, tendons, and other fibrous structures meet the bone. Enthesitis is a hallmark of PsA in adults and can occur in children as well, including in children with JIA.[72] Most commonly, signs and symptoms of enthesitis-related arthritis (ERA) in pediatric patients develop later in childhood or early adolescence, and the knee and back of the ankle are areas most commonly affected.[73] The International League of Associations for Rheumatology has developed criteria for the diagnosis of children with ERA.[74] Secukinumab is indicated for the treatment of active enthesitis-related arthritis (ERA) in patients 4 years of age and older. Secukinumab, ustekinumab, and IV

golimumab are FDA approved for the treatment of active juvenile psoriatic arthritis (secukinumab and golimumab in ≥ 2 years of age, ustekinumab in ≥ 6 years of age).

Rheumatoid Arthritis (RA)

The ACR updated the guidelines for the management of RA in 2021.[75] The guidelines address treatment with DMARDs, including both conventional and targeted small molecule DMARDs and biologics. The guidelines also address the role of glucocorticoids and the use of pharmacotherapy in select high-risk populations. The 2021 guidelines continue to focus on a treat-to-target approach based on mutual determination of a target between the patient and clinician.

Regarding DMARD initiation addressing agents within this therapeutic class, the ACR strongly recommends methotrexate monotherapy as the initial treatment in DMARD-naïve patients with moderate to high disease activity over biologic or targeted small molecule DMARD monotherapy (very low/moderate evidence), hydroxychloroquine or sulfasalazine (very low/low evidence), and the combination of methotrexate and a non-TNF antagonist biologic or targeted small molecule DMARD (low/very low evidence).[76] Methotrexate monotherapy is conditionally recommended over leflunomide (low evidence), dual or triple conventional DMARD treatment (moderate evidence), or the combination of methotrexate plus a TNF antagonist (low evidence). In general, select conventional small molecule DMARDs are preferred by ACR in low disease activity, and monotherapy with methotrexate is conditionally recommended over its use in combination with a biologic or targeted small molecule DMARD in patients with prior conventional DMARD treatment with moderate to high disease activity who are methotrexate-naïve.

Regarding treatment modification, ACR conditionally recommends the addition of a biologic or targeted small molecule DMARD over triple therapy in patients taking methotrexate (maximum tolerated dose) who have not achieved the clinical target (very low evidence).[77] In addition, ACR conditionally recommends switching to a biologic or targeted small molecule DMARD of a different class over to one of the same class in patients not at clinical target (very low evidence). ACR also addresses tapering of DMARDs, stating they conditionally recommend continuation of a DMARD at the current dose rather than a dose reduction (low evidence), although a dose reduction is conditionally recommended over gradual discontinuation (low evidence) and gradual discontinuation is conditionally recommended over abrupt discontinuation (low evidence). In patients taking methotrexate plus a biologic or targeted small molecule DMARD, ACR conditionally recommends gradual discontinuation of methotrexate over discontinuation of the other DMARD (very low evidence). ACR provides further guidance regarding the treatment of select patient populations, such as in patients with lung, heart, or liver disease or those with select infections or infection history. For instance, the group conditionally recommends the use of a non-TNF antagonist or targeted small molecule DMARD over a TNF antagonist in patients with New York Heart Association (NYHA) class III or IV heart failure and an inadequate response to conventional DMARDs (very low evidence).

Ulcerative Colitis (UC)

The updated 2019 ACG guidelines for UC provide extensive guidance on diagnosis, assessment, treatment goals, and treatment recommendations in adults.[78] Agents in this class are not addressed in their recommendations for induction and maintenance of mildly active disease. For induction of remission in moderately to severely active UC, the group recommends oral systemic corticosteroids (strong recommendation, high quality evidence). TNF antagonists (adalimumab, golimumab, infliximab; strong recommendation, high quality evidence) and vedolizumab (strong recommendation, moderate evidence)

are also recommended (strong recommendation, high quality evidence), and if infliximab is used, it should be used with a thiopurine (strong recommendation, moderate evidence). Vedolizumab or tofacitinib is recommended in patients who have previously failed TNF antagonist therapy (strong recommendation, moderate evidence for both). In patients who were previously TNF antagonist responders but are subsequently having an inadequate response, the group recommends monitoring of serum drug levels. To maintain remission in patients with previously moderately to severely active UC, regarding agents in this class review, they recommend the following: (1) against the addition of 5-aminosalicylic acid (5-ASA) in patients on TNF antagonists in those who had previously failed 5-ASA (conditional recommendations; very low evidence); (2) continuing adalimumab, golimumab, or infliximab if used to achieve remission (strong recommendation, moderate evidence); (3) continuing vedolizumab if used to achieve remission (strong recommendation, moderate evidence); and (4) continuing tofacitinib if used to achieve remission (strong recommendation, moderate evidence). Notably, the ACG states that robust data on combining TNF antagonists and immunomodulator therapy in moderately to severely active UC exist only for infliximab and thiopurines. In addition, the group states that patients who are primary nonresponders to TNF antagonists should be considered for an alternative mechanism of diseases control rather than a switch to another TNF antagonist; however, for secondary failure (initial response to TNF antagonist with later loss of efficacy), another TNF antagonist may be used. Several other specific recommendations are detailed in the guidelines, including the role of medications not within this class and nonpharmacologic guidance. Upadacitinib was not FDA approved for ulcerative colitis at the time the ACG guidelines were in development.

The AGA's 2019 guideline on the management of mild to moderate ulcerative colitis do not address the agents included in this review; however, the group notes that studies to identify the appropriate patient and timing for escalation could help with targeting therapy.[79] The AGA's 2020 guidelines on the management of moderate to severe ulcerative colitis provide specific recommendations on the role of these agents in the treatment of UC. They provide several recommendations for adult outpatients.[80] They recommend the use of infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment (strong recommendation, moderate evidence), with infliximab or vedolizumab suggested over adalimumab in biologic treatment-naïve patients for induction of remission (conditional recommendation, moderate evidence) unless the patient places a higher emphasis on convenience rather than efficacy and tofacitinib only recommended in the setting of a clinical or registry study (no recommendation, knowledge gap). They further suggest that those previously exposed to infliximab, particularly with nonresponse, should use ustekinumab or tofacitinib instead of vedolizumab or adalimumab for induction of remission (conditional recommendation, low evidence). They also suggest against using thiopurine monotherapy for induction of remission (conditional recommendation, very low evidence), but suggest it over no treatment for maintenance of remission (conditional recommendation, low evidence). They also suggest against the use of methotrexate monotherapy for induction or maintenance of remission (conditional recommendation, low evidence). The AGA suggests combining TNF antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate rather than biologic monotherapy (conditional recommendation, low evidence), although patients with less severe disease and a higher value of safety and lower value of efficacy may prefer biologic monotherapy. They also suggest early use of biologic agents with or without immunomodulator therapy rather than gradual step up after failure of 5-ASA (conditional recommendation, very low evidence), although patients with less severe disease and a higher value of safety and lower value of efficacy may prefer gradual step-up therapy. The AGA suggests against continuing 5-ASA for induction and maintenance of remission in those who have achieved remission with biologic agents and/or immunomodulators or tofacitinib (conditional

recommendation, very low evidence). The AGA also makes recommendations for hospitalized patients regarding intravenous (IV) corticosteroids, antibiotics, infliximab, and cyclosporine. Upadacitinib was not FDA approved for ulcerative colitis at the time the AGA guidelines were in development.

Other Disease States

Alopecia Areata

Alopecia areata is an autoimmune condition that attacks hair follicles causing hair loss.[81,82] Patchy baldness can develop anywhere on the scalp, face, and body. Onset can occur at any age, but most patients develop it during childhood, adolescence, or during their 20s or 30s. Approximately half of individuals experience hair regrowth within a few months without treatment. Alopecia may reoccur with unpredictable cycles. Baricitinib is the only medication FDA-approved for the treatment of alopecia areata in adults. Other medications have been used including corticosteroids, immunosuppressants, and agents that stimulate hair regrowth.

Atopic Dermatitis (AD)

Atopic dermatitis (AD) is a chronic, pruritic inflammatory disease of the skin resulting from a combination of genetic and environmental factors.[83] Often referred to as "eczema," AD affects up to 13% of children and about 7.3% of adults in the US.[84,85] AD commonly occurs in patients affected by asthma and other allergic conditions and is associated with elevated serum immunoglobulin E (IgE) levels.[86] AD is characterized by extremely dry, itchy skin on the insides of the elbows, behind the knees, and on the face, hands, and feet.[87] Abrocitinib and upadacitinib have not been addressed in the American Academy of Dermatology (AAD) guidelines from 2014.[88] These guidelines state that emollients, topical corticosteroids, and topical calcineurin inhibitors are the standard of care for the treatment of AD. Systemic immunomodulating agents are indicated for patients whose AD is not adequately controlled by topical regimens and/or phototherapy. Like the AAD guidelines, the American Academy of Allergy, Asthma, and Immunology (AAAAI) 2012 guidelines state first-line options include hydration (emollients), moisturizers, and topical corticosteroids.[89] AAAAI also recommends careful consideration of risks and benefits of systemic agents in patients who do not respond to topical agents or phototherapy; abrocitinib and upadacitinib are also not addressed in these guidelines.

Dupilumab (Dupixent®), an IL-4 receptor alpha antagonist, and tralokinumab-ldrm (Adbry™), an IL-13 antagonist, are indicated for the treatment of moderate to severe atopic dermatitis in patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[90,91] Both can be used with or without topical corticosteroids. Dupilumab is approved for use in those 6 months and older, while tralokinumab-ldrm is approved for use only in adults. Neither product is discussed in this Therapeutic Class Review.

Cytokine Release Syndrome (CRS)

CRS can occur following select immunotherapies and can result in a large, rapid release of cytokines into the blood.[92] This can manifest as fever, nausea, headache, rash, tachycardia, hypotension, and dyspnea and can be life-threatening. Tocilizumab (Actemra) is approved for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening CRS in adults and pediatric patients 2 years of age and older.

Deficiency of Interleukin-1 Receptor Antagonist (DIRA)

DIRA is a rare, life-threatening, autosomal recessive autoinflammatory disorder.[93,94] Interleukin-1 receptor antagonist (IL-1RA) helps to regulate inflammation, particularly IL-1; thus, DIRA results in an inability to properly regulate inflammation. DIRA most commonly presents with severe skin (e.g., pustulosis) and bone inflammation (e.g., multifocal osteomyelitis). While very rare, 2.5% of those from the northwest portion of Puerto Rico carry the mutation causing DIRA, and it is estimated that 1 in 6,300 patients in that region of the world could have this mutation. It may be more common in those of Dutch ancestry as well. DIRA can be treated with IL-1 blockade; the FDA approved anakinra (Kineret) and rilonacept (Arcalyst) for this use in December 2020.[95,96]

Giant Cell Arteritis (GCA)

GCA, or temporal arteritis, is a systemic inflammatory vasculitis of unknown etiology that is classified as a large-vessel vasculitis, but typically also involves small and medium arteries.[97] It occurs in older persons and can result in a wide variety of neurologic, ophthalmologic, and systemic complications. Most commonly, it affects the occipital, ophthalmic, posterior ciliary, proximal vertebral, and vertebral arteries. While the incidence of GCA ranges from 0.5 to 27 cases per 100,000 people in those ≥ 50 years old, the incidence is higher in the northern areas of the US. The primary treatment for GCA is high-dose corticosteroids, although clinical studies on various dosing protocols are limited. Steroids are generally continued until the resolution of symptoms and then may be tapered slowly to the lowest dose that adequately suppresses symptoms. Tocilizumab is the only non-corticosteroid drug FDA approved for the treatment of GCA. In 2021, the ACR published joint guidelines regarding the treatment of GCA. For medical management of newly diagnosed GCA, the group generally recommends the use of oral glucocorticoids.[98] They conditionally recommend the addition of tocilizumab to oral glucocorticoids over oral glucocorticoids alone (low to high level of evidence). Once clinical remission is reached, the dose of the oral glucocorticoid may be tapered. In patients with active extracranial large vessel involvement, ACR conditionally recommends the addition of a non-glucocorticoid immunosuppressive (e.g., methotrexate, tocilizumab) over glucocorticoids alone (very low to low evidence). Agents that can be considered non-glucocorticoid immunosuppressives include abatacept, azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, TNF antagonists, and tocilizumab, although the group recognizes that data are limited for several of these in this patient group. For patients who relapse while receiving moderate to high dose glucocorticoids, ACR conditionally recommends the addition of a non-glucocorticoid immunosuppressive agent (for glucocorticoid sparing). For patients with GCA who relapse with symptoms of cranial ischemia, ACR conditionally recommends adding a non-glucocorticoid immunosuppressive agent (e.g., methotrexate, tocilizumab; in addition to increasing the dose of glucocorticoids), further clarifying that ACR conditionally recommends adding tocilizumab over adding methotrexate. Recommendations for relapse described above are based on limited evidence and expert opinion (no dedicated literature review).

Hidradenitis Suppurativa (HS)

HS is an insidious chronic condition that affects the terminal follicular epithelium in apocrine gland-bearing skin, such as the armpits or perianal area.[99] It typically occurs in adolescents (generally after puberty) and adults, is generally diagnosed clinically, and affects approximately 1% to 2% of the US population. Select signs and symptoms include erythema, raised bumps or lesions, painful lesions, and local arthritis or arthralgia. In addition to nonpharmacologic treatments, pharmacologic treatment includes anti-inflammatories, antibiotics, antiandrogens, and biologics, such as infliximab. Surgery may

also be considered in some patients. Within this class, only adalimumab is approved by the FDA for this use. The 2019 guidelines from the US and Canadian Hidradenitis Suppurativa Foundation provide recommendations on the diagnosis, evaluation, and treatment of HS.[100,101] Regarding agents in this class, adalimumab is recommended in patients with moderate to severe disease. Infliximab, anakinra, and ustekinumab may also be effective; however, the optimal dosing of this agents has not been established. Limited evidence does not support the use of etanercept for HS.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

NMOSD is a rare autoimmune, inflammatory CNS syndrome involving the optic nerve, spinal cord, and brain stem, with an estimated prevalence of 0.37 to 10 cases per 100,000 persons.[102] NMOSD is proposed to primarily be mediated by B cells, and aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) are likely involved in the pathogenesis of NMOSD because they bind to astrocytes in the CNS. This binding can trigger attacks, such as loss of vision, paralysis, nerve pain, and respiratory failure. NMOSD is more common in women than in men.

There are currently no clinical practice guidelines for the treatment of NMOSD in the US.[103] In practice, the standard treatment for acute attacks involves steroids, such as high-dose IV methylprednisolone or plasma exchange for patients with severe symptoms. The chances of relapse and permanent disability are approximately 90%.[104] The agents FDA-approved for NMOSD in this class are used to prevent attacks in adults who are seropositive for AQP4-IgG antibodies; these include inebilizumab-cdon (Uplizna), satralizumab-mwge (Enspryng), and eculizumab (Soliris®) which is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.[105]

Oral Ulcers Associated with Behçet's Disease

Behçet's disease is a recurrent syndrome of aphthous ulcers, genital ulcerations, and uveitis or retinal vasculitis.[106] Most commonly presenting in the late third to early fourth decade of life, the oral ulcers are a hallmark symbol of this disease of unknown etiology, but thought to stem from vasculitis, although it can have several other manifestations (e.g., skin lesions, arthritis, gastrointestinal [GI] lesions, central nervous system [CNS] involvement, vascular lesions). Onset can also occur in childhood as well. The prevalence in the US is not fully known but is thought to range from 0.12 to 0.33 cases per 100,000 people and be more common in those of Turkish, Asian, and Middle Eastern descent. The oral ulcers of Behçet's disease are typically painful, nonscarring, and appear in crops. Apremilast (Otezla) is the only agent approved for the treatment of oral aphthae associated with Behçet's disease; however, several treatments have been used off-label for years, including topical and oral corticosteroids, other topical agents, colchicine, sulfasalazine, and azathioprine. The 2018 guidelines from the European League Agents Rheumatism (EULAR) on the management of Behçet's syndrome recommend topical corticosteroids for the treatment of oral ulcers, with a trial of colchicine for the prevention of recurrent mucocutaneous lesions especially when the dominant lesion is erythema nodosum or genital ulcer (IB, A). Additionally, azathioprine, thalidomide, interferon-alpha, TNF antagonists, or apremilast may be considered in select cases (IB, A).

Periodic Fever Syndrome

There are multiple disorders that may be considered periodic fever syndromes, which may be somewhat of a misleading description since most disorders within the group are often episodic and recurrent rather than truly periodic.[107] These rare, hereditary syndromes are characterized by short and recurrent severe localized inflammation and fever “attacks” that are not otherwise explained by routine childhood (or

adult) infections. Periodic fever syndrome is defined as 3 or more episodes of unexplained fever in a 6-month period, occurring at least 7 days apart. These can occur periodically or irregularly and undergo spontaneous remission. Cryopyrin-associated periodic syndromes (CAPS) is a family of syndromes associated with mutations in cryopyrin, now known as nucleotide-binding domain and leucine-rich repeat containing family, pyrin domain-containing 3 (NLRP2). CAPS includes Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), and chronic infantile neurologic cutaneous articular syndrome (CINCA), which is also known as neonatal-onset multisystem inflammatory disease (NOMID). Anakinra (Kineret), canakinumab (Ilaris), and rilonacept (Arcalyst) are approved for the treatment of CAPS in select ages. Anakinra is only approved for patients with CAPS associated with NOMID, and rilonacept and canakinumab are approved more generally for patients with CAPS, including FCAS and MWS. Canakinumab is also approved for the following other periodic fever syndromes: Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF). FMF is the most common monogenic periodic fever syndrome while TRAPS is the second most common.

Recurrent Pericarditis

Acute pericarditis is inflammation of the pericardium and symptoms can include chest pain, electrocardiogram (ECG) changes, pericardial effusion, and pericardial friction rub.[108,109] It typically lasts up to 6 weeks, although symptoms may recur, and recurrence may be as high as 15% to 30% in select patients with idiopathic pericarditis. In recurrent pericarditis, these symptoms return after a symptom-free period of at least 4 to 6 weeks. Symptoms of recurrent pericarditis include pleuritic chest pain with fever, pericardial rub, ECG changes, new or worsening pericardial effusion, and/or elevation of markers of inflammation; patients may feel well in between attacks and others may have a more persistent disease course. Studies have suggested that many cases of recurrent pericarditis are caused by an autoimmune disorder, although other causes are possible (e.g., infection). There are no well-established predictors of recurrence. The pharmacologic treatment of recurrent pericarditis is similar to treatment of acute pericarditis, and includes NSAIDs or aspirin, plus colchicine as typical first-line agents. Steroids or combination therapy may also be considered. Other agents that may be used for treatment in late-line therapy include rilonacept and the off-label use of anakinra, azathioprine, or immune globulins. Pericardiectomy may also be considered in select patients.

Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

Systemic sclerosis (SSc), or scleroderma, is a systemic disease affecting the connective tissue in which skin and internal organs thicken due to excess collagen fibers.[110,111,112] There is pulmonary involvement in over 80% of those with SSc, most frequently interstitial lung disease (ILD) and pulmonary hypertension (PAH), and these patients tend to have a poorer prognosis. In most patients with SSc-ILD, lung injury is characterized by nonspecific interstitial pneumonia (NSIP), but it can also be due to usual interstitial pneumonia (UIP). Initiating treatment should be patient-specific, considering the patient's disease extent and severity. While there are no US-based guidelines for the treatment of SSc-ILD, agents that have been used for treatments include cyclophosphamide, mycophenolate mofetil, nintedanib (Ofev®), and tocilizumab. Tocilizumab was approved for SSc-ILD in 2021 and is the only agent in this class that is indicated for this use.

Uveitis

Non-infectious intermediate and posterior uveitis is inflammation of the intermediate and posterior uvea, while panuveitis is inflammation of the anterior chamber, vitreous humor, and choroid or retina simultaneously.[113,114,115,116] Together, these represent the most severe and highly recurrent forms of uveitis. The incidence of all cases of uveitis is approximately 25 to 52 cases per 100,000 patients per year, and anterior uveitis is the most common form of uveitis. Initial treatment is typically with topical corticosteroids. Adalimumab is generally reserved for patients with disease non-responsive to initial treatment. Other treatments include systemic glucocorticoids, immunosuppressives, and intraocular implants.

In 2019, the ACR and Arthritis Foundation published guidelines on the treatment of uveitis associated with JIA, one of the most common extraarticular manifestations of JIA.[117] The group recommends select topical glucocorticoids in patients with JIA and active chronic anterior uveitis for short-term control, but for those who are unable to control symptoms with short-term therapy, they recommend adding systemic therapy in order to taper topical glucocorticoids. Changing or escalating systemic therapy is recommended after ≥ 3 months if control is not achieved. For JIA patients who develop new chronic anterior uveitis despite stable systemic therapy, they recommend topical glucocorticoids prior to changing or escalating systemic therapy right away. Regarding specific agents, they group recommends SC methotrexate conditionally over oral methotrexate; however, use of a TNF antagonist with methotrexate in severe active disease and sight-threatening complications is conditionally recommended over methotrexate monotherapy. If starting a TNF antagonist, they conditionally recommend a monoclonal antibody over etanercept. The dose or frequency of the TNF antagonist should be escalated for an inadequate response prior to trying another biologic agent. Likewise, if a patient has failed a TNF antagonist following an escalated dose/frequency, changing to a different TNF antagonist is conditionally recommended over another biologic. Abatacept or tocilizumab as biologics and mycophenolate, leflunomide, or cyclosporine as nonbiologic options are conditionally recommended in patients who have failed methotrexate and 2 monoclonal antibody TNF antagonists. The disease should be well-controlled for 2 years on a DMARD and/or biologic therapy prior to tapering (conditional recommendation). For pediatric patients with spondyloarthritis who develop acute anterior uveitis, the group conditionally recommends topical glucocorticoids prior to a change in systemic therapy. Notably, the only agent approved for uveitis in this class is adalimumab.

Similarly, a committee of the American Uveitis Society states that infliximab and adalimumab may be considered as second-line immunomodulatory agents for the treatment of uveitis associated with juvenile arthritis.[118] Both agents may also be considered as second-line immunomodulatory agents for posterior uveitis and panuveitis. Notably, infliximab is not FDA-approved for uveitis.

An international group also provided guidance under their Fundamentals Of Care for UveitiS (FOCUS) Initiative in 2017.[119] The group supports the use of adalimumab for noninfectious uveitis (Grade A recommendation). Additional recommendations are made on other biologic agents, but only adalimumab is approved for this use and other agents did not receive as high of levels of recommendation.

Role of Biosimilars

In 2018, the ACR published a white paper regarding the use of biosimilars in the treatment of rheumatic diseases.[120] It provides a comprehensive overview of the scientific, clinical, economic, and prescribing issues pertaining to biosimilar use, including efficacy and competition. They note that available real-world studies have demonstrated efficacy for extrapolated indications and state that healthcare providers

should incorporate biosimilars, where appropriate, into treatment for patients with rheumatologic diseases.

An international multidisciplinary task force issued consensus-based recommendations on the use of biosimilars for rheumatologic diseases, focusing on multiple factors, including extrapolation of indications, and switching between originator products and biosimilars.[121] They state treatment is a shared decision between the patient and clinician, and patients and providers must be educated on biosimilars. In addition, biosimilars are not considered superior or inferior to the originator product, and biosimilars should be considered safe and effective for all the originator product's approved indications. Notably, ACR cautions against interchangeability without consulting a prescriber. Additional disease-specific recommendations for the use of biosimilars are included, when applicable, above.

Therapeutic Drug Monitoring (TDM)

While there are various assays available to provide insight for TDM within this class, the clinical role of TDM is not well-established. In 2017, the AGA published guidelines on the role of TDM for IBD, including both Crohn's disease and ulcerative colitis.[122] They note that the trough concentrations of these agents can vary due to disease severity, phenotype, degree of inflammation, immunomodulator use, gender, body mass index, and individual pharmacokinetics. TDM can be used to determine the drug's trough concentration and assess for the presence of anti-drug antibodies. They suggest reactive TDM to guide treatment changes in adults with active IBD that is treated with anti-TNF agents (conditional recommendation; low quality of evidence). Suggested target trough concentrations included ≥ 5 mcg/mL, ≥ 7.5 mcg/mL, and ≥ 20 mcg/mL for infliximab, adalimumab, and certolizumab pegol, respectively, based on limited available data. The target trough for golimumab is unknown due to lack of evidence. Due to lack of data, AGA did not make a recommendation for TDM for adults with quiescent IBD treated with anti-TNF agents. On the other hand, in 2019, a consensus panel published guidance on the role of TDM in IBD and agreed proactive TDM for anti-TNF therapies was found to be appropriate after induction and at least once during maintenance therapy; however, this was not the case for other biologics.[123]

TDM recommendations for other disease states are lacking at this time. Strategies based on TDM of TNF inhibitors seem promising for RA, but supporting trials are too limited, and even less data are available for non-TNF inhibitors.[124] Likewise, a growing body of evidence suggests that TDM in psoriasis patients can maximize their therapeutic potential. Evidence is greatest with adalimumab and infliximab, but there are also data, albeit limited, with ustekinumab, etanercept, and other biologics. Additional research is required to further investigate the potential of TDM in active psoriasis patients.[125] In addition, data in pediatric patients are extremely limited at this time.[126]

Not discussed in this class review

Intravenous abatacept (Orencia) is also approved for the treatment of acute graft versus host disease (aGVHD).[127] For this indication, it is dosed as an age-based (range, 10 mg/kg to 15 mg/kg) IV infusion over 1 hour on the day prior to transplantation and on days 5, 14, and 28 following transplantation. Use of abatacept for this indication is not detailed in this review.

PHARMACOLOGY[128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158]

Antagonists that bind cytokines or their receptors can block cytokine activity. Biologics, such as the IL-1 receptor antagonists, anakinra (Kineret), canakinumab (Ilaris), and rilonacept (Arcalyst), and the TNFα

antagonists, adalimumab (Humira), adalimumab-atto (Amjevita), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi, Simponi Aria), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), and infliximab-dyyb (Inflectra), exert their action by neutralizing the activities of the inflammatory agents IL-1 and TNFα, respectively. Ustekinumab (Stelara) is an IL-12 and IL-23 antagonist, and guselkumab (Tremfya), risankizumab-rzaa (Skyrizi), and tildrakizumab-asmn (Ilumya) are IL-23 antagonists, as the latter 3 bind to the p19 subunit of IL-23 and prevent its binding to the IL-23 receptor. Sarilumab (Kevzara) and tocilizumab (Actemra) are anti-human IL-6 receptor monoclonal antibodies.[159] Ixekizumab (Taltz) and secukinumab (Cosentyx) are human IgG1 monoclonal antibodies that selectively bind to the IL-17A cytokine and inhibit its interaction with the IL-17 receptor. Similarly, brodalumab (Siliq) is a human monoclonal IgG2 antibody that inhibits IL-17 cytokine induced responses including the release of pro-inflammatory cytokines and chemokines. Vedolizumab (Entyvio) is a humanized monoclonal antibody that binds to α4β7 integrin and blocks mucosal cell adhesion and inhibits the migration of T-lymphocytes into the GI tissue. Apremilast (Otezla) has a substantially different mechanism; it is an oral phosphodiesterase 4 (PDE4) inhibitor, specific for cyclic adenosine monophosphate (cAMP) PDE4 inhibition. The specific mechanism by which apremilast exerts its effect is unknown.

Despite their common ability to inhibit TNFα bioactivity, the molecular structures and mechanisms of action of TNF antagonists are significantly different. The TNF-binding moiety of etanercept, a fusion protein, is derived from soluble TNF receptor subunits. Infliximab, infliximab-abda, infliximab-axxq, and infliximab-dyyb are chimeric (mouse-human) monoclonal antibodies to TNF, and adalimumab, adalimumab-atto (Amjevita), golimumab, and certolizumab pegol are fully human anti-TNF monoclonal antibodies.[160]

Cytokines secreted in response to an immune stimulus bind to receptors on cell surfaces and activate intracellular Janus kinase (JAK) proteins, which in turn activate a signaling pathway within the cell.[161] In the signaling pathway, JAKs work by phosphorylating Signal Transducers and Activators of Transcription (STATs), which activates them to modulate intracellular activity including gene expression. JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK 1/JAK3, JAK1/TYK2, JAK2/JAK2, and JAK2/tyrosine kinase 2 [TYK2]). This leads to immune cell proliferation, and over-activation of JAK can lead to inflammation and tissue destruction. Abrocitinib has demonstrated selectivity for JAK1 over JAK2 (28-fold), JAK3 (>340-fold), and tyrosine kinase (TYK) 2 (43-fold). Baricitinib has greater inhibitor potency at JAK1, JAK2, and TYK2, where it prevents phosphorylation and the activation of STATs. Tofacitinib (Xeljanz, Xeljanz XR) selectively inhibits JAK1 and JAK3, thereby blocking signaling for several cytokines, including many interleukins that are integral to lymphocyte activation, proliferation, and function. In addition, inhibition of JAK1 results in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6. Upadacitinib (Rinvoq) is also a JAK inhibitor and has greater inhibitory potency at JAK1 and JAK2 relative to JAK3 and TYK2. The relevance of this JAK specificity to its efficacy is not fully known.

Satralizumab-mwge (Enspryng) is an interleukin-6 (IL-6) receptor antagonist. Its benefit in NMOSD is thought to be related to IL-6-mediated signaling via binding to soluble and membrane-bound IL-6 receptors.

As a humanized immunoglobulin G (IgG) monoclonal antibody, inebilizumab-cdon (Uplizna) is proposed to reduce the risk of attacks in patients with NMOSD by binding to CD19 surface antigens and depleting B cells through antibody-dependent cellular cytolysis.

PHARMACOKINETICS[162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192]

Drug	Half-life (days)	Bioavailability (%)
Anti-TNF Biologics		
adalimumab (Humira)[193]	10 to 20	64
adalimumab-atto (Amjevita)		
certolizumab pegol (Cimzia)	14	80
etanercept (Enbrel)	4.3 ± 1.3	60
golimumab SC (Simponi)	14	53
golimumab IV (Simponi Aria)	12 ±3	n/a
infliximab (Remicade)	7.7 to 9.5	n/a
infliximab-abda (Renflexis)		
infliximab-axxq (Avsola)		
infliximab-dyyb (Inflectra)		
Other Biologic Agents		
abatacept IV (Orencia)	13.1 to 14.3	n/a
abatacept SC (Orencia)	14.3	78.6 (SC)
anakinra (Kineret)	0.17 to 0.25	95
brodalumab (Siliq)	nd	55
canakinumab (Ilaris)	26	66
guselkumab (Tremfya)	15 to 18	49
inebilizumab-cdon (Uplizna)	18	n/a
ixekizumab (Taltz)	13	60 to 81
rilonacept (Arcalyst)	nd	nd
risankizumab-rzaa (Skyrizi)	21 (CD), 28 (PSO)	74 to 89
sarilumab (Kevzara)	up to 10	nd
satralizumab-mwge (Enspryng)	30	85
secukinumab (Cosentyx)	22 to 31	55 to 77
tildrakizumab-asmn (Ilumya)	23	73 to 80
tocilizumab (Actemra) adults*	up to 11 to 13.2 (IV); 4.2 to 18.9 (SC)	80 (SC)
tocilizumab (Actemra) pediatrics*	up to 16 to 17 (IV); up to 10 to 14 (SC)	95 to 96 (SC)
ustekinumab (Stelara)	14.9 to 45.6	nd
vedolizumab (Entyvio)	25	n/a
Non-biologic Agents		
abrocitinib (Cibinqo)	3 to 5 hours	60
apremilast (Otezla)	6 to 9 hours	73
baricitinib (Olumiant)	12 hours	80
tofacitinib (Xeljanz, Xeljanz XR)	3 hours (IR); 6 hours (ER)	74 (IR); nd (ER)
upadacitinib (Rinvoq)	8 to 14 hours	nd

n/a = not applicable; nd = no data; IV = intravenous; SC = subcutaneous; IR = immediate-release; ER = extended-release
*Nonlinear/ concentration dependent

CONTRAINDICATIONS/WARNINGS[194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224]

TNF antagonists – adalimumab (Humira), adalimumab-atto (Amjevita), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi, Simponi Aria), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), and infliximab-dyyb (Inflectra)

The TNF antagonists all have a warning stating serious and sometimes fatal infections, including bacterial, tuberculosis (TB), viral, and opportunistic invasive fungal infections, have been reported with their use. Among opportunistic infections, TB, including reactivation of latent TB, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, and pneumocystosis were the most commonly reported. Serious bacterial infections due to *Legionella* and *Listeria* have been reported. Cryptococcosis and salmonellosis also have been reported. Typically, patients present with disseminated disease rather than localized disease and are on concurrent immunosuppressants, such as methotrexate or corticosteroids plus an agent in this review. Treatment with a TNF antagonist should not be initiated in patients with an active infection, and the risk/benefit ratio should be evaluated for patients with chronic or recurrent infections, exposure to TB, underlying conditions which predispose them to infections, or who have resided or traveled in areas of endemic TB or endemic mycoses. As a result, these agents must be used with caution in patients on concomitant immunosuppressive therapy and/or active or predisposition to infections. It is recommended that patients be evaluated with a TB skin test and that latent TB infections be treated prior to therapy. Monitor all patients during therapy for TB even if the initial latent TB test was negative. Use of TNF antagonists should be discontinued if a patient develops a serious infection or sepsis. Data obtained from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) suggest that adalimumab and infliximab (and, therefore, any corresponding biosimilar agents) carry a higher risk of serious infections than etanercept.[225]

Etanercept is contraindicated in patients with sepsis.

Use caution when switching between one biologic DMARD to another as overlapping biologic activity may increase the risk of infection.

Other therapeutic infectious agents (e.g., Bacillus Calmette-Guerin [BCG] bladder instillation for the treatment of cancer) could result in infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with TNF antagonists.

Use of TNF antagonists has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF antagonist therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF antagonist therapy. Carriers of HBV who require treatment with a TNF antagonist should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of treatment. In patients who develop HBV reactivation, TNF antagonists should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF antagonist therapy after HBV reactivation is controlled is not known.

Serious infections were seen in clinical studies with concurrent use of anakinra and etanercept, with no added benefit. Due to the nature of the adverse reactions seen with this combination therapy, similar toxicities may result from combination of anakinra and other TNF antagonists.

Patients at greater risk of infection may include patients older than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants, such as corticosteroids or methotrexate. The risks and benefits of treatments with TNF antagonists should be considered prior to initiating therapy in patients with chronic or recurrent infection, with prior exposure to TB, with a history of an opportunistic infection, or patients who have resided or traveled to areas of endemic TB or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, or patients with underlying conditions that may predispose them to infection, such as poorly controlled diabetes.

The TNF antagonists also possess a warning concerning the increased incidence of lymphoma in patients receiving these agents, especially in patients with active RA. In the controlled portions of clinical trials of some TNF-blocking agents, more malignancies (excluding lymphoma and nonmelanoma skin cancer) have been observed in patients receiving those TNF antagonists compared with control patients. The potential role of TNF-blocking therapy in the development of malignancies is not known.

Hepatosplenic T cell lymphoma (HSTCL), a rare type of T cell lymphoma, has been reported in patients treated with TNF antagonists. Nearly all of the reported TNF antagonist-associated cases of HSTCL have occurred in patients with Crohn's disease, with some occurring in ulcerative colitis patients. The majority were in adolescent and young adult males. Almost all patients had received azathioprine (AZA) or 6-mercaptopurine (6–MP) concomitantly with a TNF antagonist at or prior to diagnosis.

In November 2009, the risk of lymphoma and other malignancies, some fatal, reported in children and adolescent patients treated with TNF antagonists was added to the boxed warning for TNF antagonists. Approximately half of the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. Cases of acute and chronic leukemia have been reported in association with postmarketing TNF antagonist use in RA and other indications. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Acute and chronic leukemia have also been reported with TNF antagonist use in RA and other indications. Even in the absence of TNF antagonist therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer. As of November 2011, the FDA required manufacturers of TNF antagonists to perform enhanced safety surveillance on these products.[226]

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF antagonists. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Patients with psoriasis should be monitored for non-melanoma skin cancers, especially in those patients with a history of prolonged phototherapy treatment. Non-melanoma skin cancers were more common in patients with previous phototherapy in the maintenance trials of infliximab for the treatment of psoriasis. This warning also applies to biosimilar infliximab products.

In a clinical trial using infliximab in patients with moderate to severe COPD, an increase in malignancies, the majority being of the lung or head and neck region, were reported in patients receiving infliximab

compared to control patients. All patients had a history of heavy smoking. Providers should be cautious when using infliximab and its biosimilars in patients with moderate to severe COPD. In addition, a population-based retrospective cohort study of a Swedish health registry found a 2- to 3-fold increase the incidence of invasive cervical cancer in women with RA treated who were with infliximab. Periodic screening should occur in women treated with infliximab and its biosimilars.

In a randomized, placebo-controlled trial with 180 patients with granulomatosis with polyangiitis (Wegener's granulomatosis), etanercept-treated patients experienced more non-cutaneous solid malignancies than patients who received placebo. Clinical outcomes with etanercept plus cyclophosphamide, methotrexate, and corticosteroids did not improve compared to the 3-drug treatment alone. Etanercept is not indicated for the management of granulomatosis with polyangiitis.

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF antagonists. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., agranulocytosis, leukopenia, pancytopenia, and thrombocytopenia) have been infrequently reported with multiple TNF antagonists, including certolizumab pegol and golimumab. Use caution in patients being treated with TNF antagonists who have ongoing, or a history of, significant hematologic abnormalities.

Cases of worsening congestive heart failure (CHF), some with a fatal outcome, and new onset CHF have been reported with TNF antagonists. Clinical trials of TNF antagonists show a higher rate of serious CHF-related adverse reactions. Physicians should exercise caution when using TNF antagonists in patients who have heart failure and monitor them carefully.

In 2 clinical trials evaluating the use of etanercept for the treatment of heart failure, 1 study suggested higher mortality in the etanercept-treated patients compared to placebo. There have been postmarketing reports of worsening of CHF, with and without precipitating factors, in patients taking etanercept. New onset CHF (< 0.1%) has been reported, including in patients without known pre-existing cardiovascular (CV) disease. Use etanercept with caution in patients with a history of CHF.

Infliximab and its biosimilars at doses > 5 mg/kg are contraindicated in patients with moderate to severe heart failure. In a randomized study evaluating infliximab in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), infliximab treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure. In addition, cases of stroke, myocardial infarctions [MIs], hypotension, hypertension, and arrhythmias have been reported during and within 24 hours of initiation of an infliximab infusion, and cases of transient visual loss have been reported during or within 2 hours of infusion. Discontinue if new or worsening symptoms of heart failure appear. Any patient with heart failure should be closely monitored during therapy.

Treatment with agents that inhibit TNF has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis, peripheral demyelinating polyneuropathy, and new onset or exacerbation of seizure disorders have been observed. Exercise caution with the use of TNF antagonists in patients with pre-existing or recent-onset CNS demyelinating disorders.

Treatment with TNF antagonists may result in the formation of autoantibodies, and newer drug-tolerant assays suggest immunogenicity may be higher than originally thought. Rarely, the development of a

lupus-like syndrome may occur. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment initiation with TNF antagonists, treatment should be discontinued, and the patient should be carefully evaluated.

Serious hypersensitivity reactions, including anaphylaxis, angioedema, hypotension, anaphylactoid reaction, serum sickness, and urticaria, have been reported with TNF antagonists. If an anaphylactic or other serious allergic reaction occurs, administration should be discontinued immediately, and appropriate therapy instituted. The offending TNF antagonist should not be readministered. The needle shield within the certolizumab pegol prefilled syringe contains a derivative of natural rubber latex, which could cause an allergic reactions in susceptible individuals.

Infliximab has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of infliximab infusion. Serum sickness-like reactions have been observed in patients after initial infliximab therapy (e.g., as early as after the second dose), and when infliximab therapy was reinstituted following an extended period without infliximab treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema, and/or dysphagia. In RA, Crohn's disease, and psoriasis clinical trials, readministration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment. In general, the benefits and risks of readministration of infliximab after a period of no treatment, especially as a re-induction regimen given at weeks 0, 2, and 6, should be carefully considered. If infliximab maintenance therapy for psoriasis is interrupted, infliximab should be restarted as a single dose followed by maintenance therapy. This also applies to infliximab biosimilars.

Reports of severe hepatic reactions, including acute liver failure, have been reported in patients receiving TNF antagonists. In a small study of 48 hospitalized patients treated with etanercept or placebo for moderate to severe alcoholic hepatitis, the mortality rate in patients treated with etanercept was similar to patients treated with placebo at 1 month, but significantly higher after 6 months. Physicians should use caution when using etanercept in patients with moderate to severe alcoholic hepatitis.

It is recommended that JIA patients, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating therapy.

Patients on adalimumab (including its biosimilar), etanercept, and golimumab may receive concurrent vaccinations, except for live vaccines. Patients with a significant exposure to varicella virus should temporarily discontinue etanercept therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin. At least a 6-month waiting period following birth is recommended prior to live vaccine administration in infants with *in utero* exposure to IV golimumab.

Patients treated with certolizumab pegol may receive vaccinations, except for live or live attenuated vaccines. In clinical trials, similar proportions of patients developed protective levels of anti-vaccine antibodies between certolizumab pegol and placebo treatment groups; however, patients receiving certolizumab pegol and concomitant methotrexate had a lower humoral response compared with patients receiving certolizumab pegol alone. The clinical significance of this is unknown. No data are available on the response to vaccinations or the secondary transmission of infection by live vaccines in patients receiving certolizumab pegol.

Vaccinations should be updated according to current vaccination guidelines prior to initiating treatment with infliximab. Live vaccines are not recommended for concurrent use with infliximab and its biosimilars. A fatal outcome due to disseminated TB infection was reported in an infant who received a TB vaccine after *in utero* exposure to infliximab. At least a 6-month waiting period following birth is recommended prior to live vaccine administration in infants with *in utero* exposure to infliximab. The safety of live or live-attenuated vaccines in infants who were exposed to other TNF antagonists *in utero* is unknown; a risk-benefit assessment should occur prior to vaccinating these infants.

abrocitinib (Cibinqo)

Abrocitinib is contraindicated in patients taking antiplatelet therapies (with the exception of low-dose aspirin, ≤ 81 mg daily), during the first 3 months of therapy due to the potential for certain laboratory abnormalities (e.g., thrombocytopenia and lymphopenia).

As with other JAK inhibitors, abrocitinib carries a boxed warning for mortality, serious infections, malignancy, major adverse cardiovascular events (MACE) (defined as cardiovascular [CV] death, non-fatal myocardial infarction [MI], and non-fatal stroke), and thrombosis. MACE occurred in abrocitinib-treated patients when studied for atopic dermatitis; therapy should be discontinued in patients who have a MI or stroke. Consideration should be given before starting or continuing abrocitinib, especially in those who are current/past smokers and those with other CV risk factors. Patients at increased risk for thrombosis should not receive abrocitinib as deep vein thrombosis (DVT) and pulmonary embolism (PE), sometimes fatal, have occurred in abrocitinib-treated patients when used for atopic dermatitis as well as in patients receiving JAK inhibitors for inflammatory conditions.

Due to the higher risk for serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including TB, therapy should be discontinued if serious or opportunistic infection occurs, and patients should be tested for latent TB before and during therapy, with latent TB treated before initiation. All patients should be monitored for active TB during treatment. Use of abrocitinib should be avoided in patients with active, serious infection (e.g., active hepatitis B or hepatitis C) including localized infections; careful consideration should be given before starting in those with chronic/recurrent infections. When abrocitinib was used for atopic dermatitis, the most common serious infections in clinical studies were herpes simplex, herpes zoster, and pneumonia. Patients should be closely monitored for infection(s) during and following therapy with abrocitinib. The prescribing information details additional considerations for TB and viral reactivation.

Malignancies, including non-melanoma skin cancer (NMSC), have occurred in patients receiving abrocitinib for atopic dermatitis; skin examinations should be regularly conducted for those at increased risk of skin cancer, and patients should be advised to limit exposure to sunlight and UV light by wearing protective clothing and using broad-spectrum sunscreen. Malignancies, including lymphomas, have also been reported in patients taking JAK inhibitors for inflammatory conditions; current or past smokers are at a higher risk of malignancy. Consideration should be given before starting or with continuation of abrocitinib, especially in those with a known malignancy (other than treated NMSC), those who develop a malignancy while on therapy, and those who are current/past smokers.

Abrocitinib was associated with an increased incidence of thrombocytopenia and lymphopenia. A complete blood count (CBC) is recommended at baseline, 4 weeks after initiation, and 4 weeks after dose increases; for patients on chronic therapy who develop hematologic abnormalities, lab assessments may be extended. As dose-dependent increases in blood lipids occurred in abrocitinib-treated patients, lipid

parameters should be evaluated about 4 weeks after starting therapy and managed based on clinical guidelines for hyperlipidemia.

Age-appropriate vaccinations should be completed prior to starting abrocitinib, and live vaccine administration should be avoided immediately before, during, and immediately following abrocitinib therapy.

abatacept (Orencia)

Abatacept should not be administered to patients with known hypersensitivity to abatacept or any of its components.

Anaphylaxis or anaphylactoid reactions have been reported following administration of abatacept (0.074% of patients). Appropriate medical support for the treatment of hypersensitivity reactions should be available when abatacept is administered.

In clinical trials, patients receiving concomitant abatacept (via IV administration) and TNF antagonist therapy experienced more infections (63%) and serious infections (4.4%) compared to patients treated with only TNF antagonists (43% and 0.8%, respectively). No additional efficacy was observed with concomitant administration; therefore, concurrent abatacept and TNF antagonist therapy is not recommended. Serious infections, including sepsis and pneumonia, have been reported in patients receiving abatacept. In clinical studies, the safety experience for abatacept was similar for both SC- and IV-administered dosages.

Patients should be screened for latent TB infection prior to initiating therapy with abatacept. Abatacept has not been studied in patients with a positive TB screening test; therefore, safety of abatacept in patients with latent TB is not known. Additionally, screening for hepatitis B should be performed prior to initiating therapy with abatacept according to published guidelines.

Drugs affecting T cell activation, such as abatacept, can affect host defenses against malignancies or infections. Like infections, malignancies have been reported with abatacept, including skin cancer; periodic skin examinations are recommended.

Patients with chronic obstructive pulmonary disease (COPD) reported more adverse events in clinical trials than those treated with placebo. Use caution when administering abatacept to patients with RA and COPD and monitor for worsening of their respiratory status.

Live vaccines should not be given concurrently or within 3 months of discontinuation of abatacept. Patients with JIA should be brought up-to-date with all immunizations prior to abatacept therapy. Based on its mechanism of action, abatacept may blunt the effectiveness of some immunizations. There are clinical considerations for administering live vaccines to infants who were exposed to abatacept *in utero*.

anakinra (Kineret)

Anakinra is contraindicated in patients with known hypersensitivity to *Escherichia coli*-derived proteins or any components of the product. Patients with DIRA may have an increased risk of allergic reactions, particularly in the first several weeks of treatment; patients should be monitored closely during this time.

Concurrent use of anakinra and etanercept therapy resulted in a higher rate of serious infections in the combination arm (7%) compared to etanercept alone (0%) without an increase in ACR response rates compared to etanercept monotherapy. Combination therapy with anakinra and TNF antagonists is not recommended.

Anakinra has been associated with an increased incidence of serious infections versus placebo (2% versus 1%, respectively) and should be discontinued if a patient develops a serious infection. Treatment with anakinra should not be initiated in patients with active infections. Safety and efficacy of anakinra in immunosuppressed patients or in patients with chronic infections have not been evaluated. In patients with NOMID or DIRA, if anakinra discontinuation is contemplated, the risk of a disease flare upon discontinuation of therapy should be weighed against the potential risk of continued treatment.

apremilast (Otezla)

Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with apremilast. Apremilast is contraindicated in patients with known hypersensitivity to any components of the product.

Apremilast is associated with an increased risk of depression. Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts, or other mood changes, and, if such changes occur, to contact their healthcare provider. Risks and benefits of treatment with apremilast should be carefully weighed in patients with a history of depression and/or suicidal thoughts or behavior.

During clinical trials, apremilast was associated with weight decrease. Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of apremilast.

Postmarketing cases of severe diarrhea, nausea, and vomiting, including those leading to hospitalization, have occurred with apremilast. Most events occurred within the first few weeks of treatment. Monitor patients more closely who may be more susceptible to volume depletion or hypotension resulting from these adverse effects, including elderly patients; a dose reduction or treatment interruption may be clinically appropriate.

baricitinib (Olumiant)

Baricitinib has no contraindications.

Baricitinib carries a boxed warning for serious infections, mortality, malignancy, MACE, and thrombosis. The most common infections reported with its use include pneumonia, herpes zoster, and urinary tract infections. Opportunistic infections, such as invasive fungal infections and TB, were also reported; therefore, use of baricitinib should be avoided in patients with any active, serious, or opportunistic infections, including localized infections. Patients should be monitored closely for the development of any signs or symptoms of infection during and after treatment. If infection occurs, therapy should be interrupted until the infection is controlled. Use of live vaccines should be avoided. Prior to initiating therapy, patients should be evaluated for latent or active TB infection. Anti-TB therapy should be given prior to initiation of baricitinib in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed and those who are TB-negative but are at high risk.

Malignancies have occurred in clinical studies of baricitinib. A higher rate of malignancies, as well as lymphomas and lung cancers specifically, occurred in a large, postmarketing safety study that compared another JAK inhibitor, tofacitinib (described further below), to TNF antagonists. A higher rate of non-melanoma skin cancers has occurred in patients treated with baricitinib. Periodic skin examination is recommended in patients who may be at a higher risk. The risks and benefits of initiating and continuing baricitinib should be considered in patients with known or developed malignancies.

Initiation of therapy should also be cautioned in patients who are at an increased risk for thrombosis; reports of DVT, PE, and arterial thrombosis events of the extremities were observed in patients treated with baricitinib. In a large, postmarketing safety study, treatment with another JAK inhibitor, tofacitinib (described further below), resulted in an increased risk for thrombosis compared to TNF antagonists, specifically in patients ≥ 50 years of age with ≥ 1 other CV risk factor. Patients experiencing symptoms consistent with a thrombosis event should have baricitinib discontinued and a full clinical workup to evaluate and treat them appropriately.

Baricitinib also carries a boxed warning for mortality. In a large, postmarketing safety study, treatment with another JAK inhibitor, tofacitinib (described further below), resulted in an increased risk for all-cause mortality compared to TNF antagonists in RA patients ≥ 50 years old with ≥ 1 CV risk factor. The risks and benefits of initiating and continuing baricitinib should be considered.

In 2021, the FDA approved labeling updates for all JAK inhibitors, including a boxed warning for major adverse CV events (MACE; CV death, MI, and stroke) due to a higher rate of these events in patients treated with a tofacitinib, another JAK inhibitor, than when treated with a TNF antagonist in patients with RA (described further below). The benefits and risk of initiating or continuing baricitinib should be considered, especially in patients with known risk factors, such as those who are current or past smokers of those with other CV risk factors. Baricitinib should be discontinued in patients who have experienced an MI or stroke.

Hypersensitivity reactions (e.g., angioedema, urticaria, rash), including serious reactions, have been reported in patients using baricitinib; if such reactions occur, it should be discontinued.

GI perforation has also been reported in clinical studies with baricitinib; therefore, use is cautioned in patients with a history of diverticulitis or those at high risk for GI perforation. Promptly evaluate any new-onset of abdominal symptoms for GI perforation. Laboratory abnormalities were also observed with baricitinib use in clinical studies and include neutropenia, lymphopenia, anemia and elevations of liver enzymes and lipids; baseline and routine monitoring of these laboratory parameters is required.

Due to its side effect profile, baricitinib is not recommended in patients with an absolute lymphocyte count < 500 cells/mm^3, absolute neutrophil count (ANC) < 1,000 cells/mm^3, or hemoglobin < 8 g/dL.

brodalumab (Siliq)

Brodalumab is contraindicated in patients with Crohn's disease because it may worsen the disease. Discontinue brodalumab if a patient develops Crohn's disease during treatment.

Brodalumab has a boxed warning regarding suicidal ideation and behavior. In clinical trials, suicidal ideation and behaviors were noted in patients treated with brodalumab (0.37 per 100 subject years; 8 of 10 patients who attempted or completed suicide had a history of depression and/or suicidal ideation/behavior); however, a causal association between treatment with brodalumab and increased risk of suicidal ideation and behavior has not been established. Prescribers should weigh the risks and benefits when prescribing brodalumab to patients with a history of depression or suicidality and educate patients on when to receive medical help. Due to the observed suicidal ideation and behavior, if adequate response is not seen within 12 to 16 weeks, discontinuation of therapy should be considered.

Brodalumab may increase risks of infection when compared to placebo (0.5% versus 0.2%, respectively) and fungal infections (2.4% versus 0.9%, respectively). Patients should be evaluated for TB infection prior to starting therapy. Patients with TB should not have brodalumab administered. Patients with a past

history of latent or active TB in whom an adequate course of anti-TB therapy cannot be confirmed should reconsider anti-TB therapy.

Live vaccines should be avoided in patients taking brodalumab.

canakinumab (Ilaris)

Canakinumab is contraindicated in patients with known hypersensitivity to any components of the product.

Canakinumab blocks IL-1 which may interfere with immune response to infections and has been associated with an increased incidence of serious infections. Physicians should exercise caution when administering canakinumab to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to infections. Canakinumab should be discontinued if a patient develops a serious infection and do not administer it to patients during an active infection requiring medical intervention.

Live vaccines should not be given concurrently with canakinumab. Prior to initiation of therapy with canakinumab, patients should receive all recommended vaccinations. Live vaccines should not be given concurrently with canakinumab due to lack of data on efficacy or the risk of secondary transmission. Likewise, canakinumab may interfere with the normal immune response to new antigens.

Treatment with immunosuppressants may result in an increased risk of malignancy.

Macrophage activation syndrome (MAS) is a life-threatening disorder that has been reported in in patients with rheumatic conditions, including those treated with canakinumab in clinical trials, and should be treated aggressively.

guselkumab (Tremfya)

Guselkumab (Tremfya) is contraindicated in patients with a history of serious hypersensitivity to it or any of the product components. Hypersensitivity reactions, including anaphylaxis some requiring hospitalization, have occurred with guselkumab. Rash has also occurred.

Guselkumab carries a warning for an increased risk of infection; the risks and benefits of guselkumab should be considered prior to its use. In clinical trials of plaque psoriasis, the rate of infections was higher in the guselkumab group versus the placebo group (23% versus 21%) through 16 weeks of treatment. While the risk of serious infections in both groups was ≤ 0.2%, infections reported more commonly with guselkumab included upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex. Similar results were seen in psoriatic arthritis. If a patient develops a serious or clinically important infection or is not responding to treatment, the patient should be monitored closely and guselkumab should be discontinued until the infection resolves.

Similar to other agents in this class, patients should be evaluated for TB prior to initiating treatment with guselkumab. Anti-TB therapy should be considered prior to initiating guselkumab in patients with a past history of latent TB or patients with active TB who have not received an appropriate course or treatment.

Prescribers should consider completion of all age appropriate immunizations prior to initiating a patient on guselkumab. The use of live vaccines should be avoided in patients using guselkumab.

inebilizumab-cdon (Uplizna)

Use of inebilizumab-cdon is contraindicated in patients who previously experienced a severe infusion reaction to the product or any of its inactive ingredients, patients with active hepatitis B infection, and patients with active or untreated latent TB.

Inebilizumab-cdon can cause infusion reactions during initial and subsequent infusions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, and rash. Pre-medication is recommended 30 to 60 minutes prior to each dose to reduce the frequency and severity of the reactions. Management of infusion reactions is dependent on presentation and severity. For life-threatening reactions, inebilizumab-cdon should be immediately and permanently discontinued. For patients with less severe reactions, temporarily withholding the infusion, a slower infusion rate, and/or symptomatic management may be used.

Inebilizumab-cdon use has also been associated with increased risk of infections and carries the potential for increased risk of immunosuppressant effects when used with other immunosuppressants, risk of hepatitis B reactivation, and risk of developing progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system. The most common infections in clinical trials with inebilizumab-cdon were urinary tract infection (20%), nasopharyngitis (13%), upper respiratory tract infection (8%), and influenza (7%). If infection occurs, it is recommended to delay inebilizumab-cdon administration until the active infection is resolved.

Live-attenuated and live vaccines are not recommended during treatment with inebilizumab-cdon, and all immunizations should be completed ≥ 4 weeks prior to initiating therapy. Prior to the first dose, hepatitis B virus screening, TB screening, serum immunoglobulins, and vaccination status should be assessed.

Additional warnings include the reduction in immunoglobulins (e.g., IgG and immunoglobulin M [IgM]) and fetal risk. It is recommended to monitor the levels of immunoglobulins of patients before, during, and after treatment with inebilizumab-cdon. Discontinuation of therapy may be considered if a patient experiences serious opportunistic infections or recurrent infections with IgG or IgM or has prolonged hypogammaglobulinemia that requires treatment. The use of inebilizumab-cdon may cause fetal harm based on animal data due to B-cell lymphopenia and a decreased antibody response; therefore, it is recommended that female patients of reproductive potential use contraception during treatment and for at least 6 months after treatment.

ixekizumab (Taltz)

Ixekizumab is contraindicated in patients with serious hypersensitivity reaction to ixekizumab or to any of the excipients. Serious hypersensitivity reactions reported with ixekizumab include anaphylaxis, angioedema, and urticaria.

Treatment with ixekizumab may put patients at an increased risk for infection. In clinical trials of plaque psoriasis in adults, the rate of infections was higher in the ixekizumab group versus the placebo group (27% versus 23%). The types of infections that occurred more frequently in the ixekizumab group versus the placebo group included upper respiratory tract infections, oral candidiasis, conjunctivitis, and tinea infections. A similar risk was seen in pediatrics and for use in the treatment of other indications.

Prior to initiating treatment with ixekizumab, patients should be evaluated for TB and ixekizumab should not be given to patients with active TB infection. Anti-TB therapy should be considered prior to initiating

ixekizumab in patients with a past history of latent TB or patients with active TB who have not received an appropriate course or treatment.

Prior to initiating therapy with ixekizumab, completion of all age appropriate immunizations according to current immunization guidelines should be considered.

Patients receiving ixekizumab should be monitored for new onset inflammatory bowel disease (IBD) or exacerbations of existing disease, including Crohn's disease and ulcerative colitis, which occurred at a greater rate with ixekizumab in placebo-controlled trials. Patients should be monitored for onset or exacerbation; prescribers should discontinue ixekizumab and initiate medical management if this occurs.

As a therapeutic protein, ixekizumab has the potential for immunogenicity, but the assay to test for neutralizing antibodies has limitations detecting neutralizing antibodies and the incidence could be underestimated.

rilonacept (Arcalyst)

Rilonacept blocks IL-1 which may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking rilonacept. Discontinue treatment with rilonacept if a patient develops a serious infection and do not initiate treatment with rilonacept in patients with active or chronic infections.

Rare hypersensitivity reactions have been associated with rilonacept administration. If a hypersensitivity reaction occurs, discontinue administration of rilonacept.

Live vaccines should not be given concurrently with rilonacept. Prior to initiation of therapy with rilonacept, patients should receive all recommended vaccinations.

The impact of rilonacept treatment on malignancy risk is unknown.

Patients should also be monitored for changes in their lipid profiles and provided with medical treatment if warranted.

risankizumab-rzaa (Skyrizi)

Risankizumab-rzaa is contraindicated in patients with a history of serious hypersensitivity to the active ingredient or any of its excipients. Serious hypersensitivity reactions, including anaphylaxis, have been reported with risankizumab-rzaa; should a reaction occur, discontinue risankizumab-rzaa immediately.

Risankizumab-rzaa may increase the risk of infections. For patients with recurrent or chronic infection, a risk and benefit assessment should occur prior to initiating risankizumab-rzaa and patients should be counseled on these risks and signs or symptoms of an infection. If a patient develops an infection or the infection is not responding to standard therapy, discontinue treatment with risankizumab-rzaa until infection resolution.

Likewise, patients should be evaluated for TB infection prior to treatment with risankizumab-rzaa. Do not use risankizumab-rzaa in patients with active TB. Anti-TB therapy should be considered prior to initiating treatment in patients with a history of latent or active TB if a prior adequate treatment course cannot be confirmed. Patients should be monitored for signs and symptoms of active TB during and following risankizumab-rzaa treatment. In phase 3 studies, no patients with latent TB developed active TB through a mean follow up of 61 weeks.

All age appropriate immunizations, based on current guidelines, should be completed prior to treatment with risankizumab-rzaa. Avoid use of risankizumab-rzaa with live vaccines; no data are available on the response to either live or inactive vaccines when used during treatment with risankizumab-rzaa.

Drug-induced liver injury has been reported in a patient with CD after 2 IV doses of risankizumab-rzaa and resolved with corticosteroid treatment. Obtain liver enzymes and bilirubin levels prior to starting risankizumab-rzaa for the treatment of CD, during induction at least up to 12 weeks of therapy, and according to routine patient management. Other treatment options should be considered in those with liver cirrhosis.

satralizumab-mwge (Enspryng)

Satralizumab-mwge is contraindicated in patients with a known hypersensitivity to satralizumab or any of the inactive drug components. Additionally, satralizumab-mwge is contraindicated in persons with active hepatitis B infection or active or untreated latent TB. Other IL-6 receptor antagonists have been associated with hypersensitivity reactions (e.g., rash, urticaria, fatal anaphylaxis). Monitor satralizumab-mwge patients closely for signs of hypersensitivity.

IL-6 receptor antagonists, including satralizumab-mwge, have been associated with an increased risk of infections. This risk includes serious and potentially fatal infections. The most common infections seen in clinical trial were nasopharyngitis, upper respiratory infections, pharyngitis, and cellulitis. Any patient with an active infection should not receive satralizumab-mwge therapy until the infection has resolved.

Other immunosuppressant therapies have shown to increase the risk of hepatitis B virus reactivation. All patients considered for satralizumab-mwge therapy should be tested for HBV prior to initiating therapy. Any person with active hepatitis should not receive satralizumab-mwge. Consultation with a liver disease expert is recommended prior to initiating and throughout therapy in any persons who are chronic carriers of HBV or are HBsAg negative but HB core antibody positive.

Other IL-6 receptor antagonists have been associated with TB infection. Prior to initiating satralizumab-mwge therapy, patients should be assessed for TB risk factors and receive TB testing for latent infections. All patients should be monitored for signs and symptoms of TB throughout satralizumab-mwge therapy.

Live or live-attenuated vaccines should be given ≥ 4 weeks prior to starting satralizumab-mwge therapy as the safety of concurrent administration has not been evaluated. Non-live vaccines should be given ≥ 2 weeks prior to therapy initiation, if possible.

Patients receiving satralizumab-mwge have experienced mild and moderate liver enzyme elevations. Throughout the first 3 months of therapy, alanine aminotransferase (ALT) and aspartate transaminase (AST) laboratory values should be monitored every 4 weeks with subsequent monitoring every 3 months thereafter for 1 year. ALT and AST monitoring following 1 year should be performed as clinically indicated.

Satralizumab-mwge treated patients also have experienced decreases in neutrophil counts and should therefore have their neutrophil count monitored between 4 to 8 weeks after starting therapy. After this initial period, neutrophil monitoring should be performed at regular intervals.

sarilumab (Kevzara)

Sarilumab is contraindicated patients with known hypersensitivity to sarilumab or any component of the product.

Sarilumab carries a boxed warning regarding the risk of developing serious infection, including active TB, invasive fungal infections, bacterial, viral, or other opportunistic infections. Its use should be avoided in patients with an active infection, including localized infection. Risks and benefits should be considered prior to initiating therapy in patients with chronic or recurrent infection, a history of serious or opportunistic infections, underlying conditions that increase the risk of infection, and in patients with known or possible exposure to TB. Patients should be tested for latent TB, and, if positive, should be treated prior to sarilumab therapy. In addition, viral reactivation of herpes zoster is possible. Patients treated with sarilumab should be monitored for signs and symptoms of infection during treatment.

Concurrent use of sarilumab with biological DMARDs should be avoided due to potential increased immunosuppression and increased risk of infection. Concomitant use with TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies, and selective co-stimulation modulators has not been studied.

Treatment with sarilumab may lead to a higher incidence of neutropenia, thrombocytopenia, and elevated liver enzymes; laboratory values should be evaluated prior to sarilumab therapy, at 4 and 8 weeks after starting therapy, and every 3 months thereafter.

Lipid abnormalities have been associated with sarilumab and should be assessed 4 to 8 weeks after starting therapy, then every 6 months. Hyperlipidemia should be managed according to standard guidelines. Gastrointestinal perforations have been associated with use of sarilumab. Risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids. Patients presenting with new onset abdominal symptoms should be promptly evaluated.

Treatment with immunosuppressants, such as sarilumab, may increase the risk of malignancies.

secukinumab (Cosentyx)

Secukinumab may increase the risk of infections, including severe and sometimes fatal infections. Exercise caution when considering the use of secukinumab in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and secukinumab should be discontinued until the infection resolves.

Evaluate patients for TB infection prior to initiating treatment with secukinumab. Do not administer secukinumab to patients with active TB infection. Initiate treatment of latent TB prior to administering secukinumab. Consider anti-TB therapy prior to initiation of secukinumab in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving secukinumab should be monitored closely for signs and symptoms of active TB during and after treatment.

Exercise caution when prescribing secukinumab to patients with IBD, as exacerbations of Crohn's disease, in some cases serious, were observed in secukinumab-treated patients during clinical trials. Patients who are treated with secukinumab and have IBD should be monitored closely.

Anaphylaxis and cases of urticaria occurred in secukinumab-treated patients in the clinical trials. If an anaphylactic or other serious allergic reaction occurs, administration of secukinumab should be discontinued immediately and appropriate therapy initiated.

The removable cap of the secukinumab products contains natural rubber latex, which may cause an allergic reaction in latex-sensitive individuals. The safe use of Cosentyx Sensoready® pen or prefilled syringe in latex-sensitive individuals has not been studied.

Prior to initiating therapy with secukinumab, consider completion of all age appropriate immunizations according to current immunization guidelines. Patients treated with secukinumab should not receive live vaccines. Non-live vaccinations received during a course of secukinumab may not elicit an immune response sufficient to prevent disease.

tildrakizumab-asmn (Ilumya)

Tildrakizumab-asmn is contraindicated in patients with a known serious hypersensitivity reaction to it or any of the excipients. Cases of angioedema and urticaria have occurred with tildrakizumab-asmn. It should be discontinued immediately should serious hypersensitivity occur.

Tildrakizumab-asmn can increase the risk of infection. Treatment with tildrakizumab-asmn should not be initiated in patients with any significant active infection until the infection resolves or is adequately treated. The risks and benefits of tildrakizumab-asmn should be considered prior to initiating therapy in patients with a chronic infection or a history of recurrent infection. Discontinuation may be required in patients with a serious infection until infection resolution. Patients should be evaluated for TB prior to beginning therapy, and treatment of latent TB should occur prior to initiation of tildrakizumab-asmn; it should not be administered to patients with active TB.

All age appropriate immunizations according to current immunization guidelines should be administered prior to initiating therapy with tildrakizumab-asmn. Live vaccines should be avoided in patients treated with tildrakizumab-asmn.

tocilizumab (Actemra)

Tocilizumab should not be administered to patients with known hypersensitivity to tocilizumab.

Patients receiving tocilizumab are at an increased risk for developing serious infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens that may lead to hospitalization or death. Most patients in clinical trials who developed serious infections were on concurrent immunosuppressants, such as methotrexate or corticosteroids. If a serious infection develops, tocilizumab should be discontinued until the infection is controlled. Infections reported included active TB, invasive fungal infections, bacterial, viral, and other infections due to opportunistic pathogens. Patients should be tested for latent TB before and during treatment with tocilizumab. In patients with chronic or recurrent infections, the risks and benefits of treatment with tocilizumab should be carefully considered prior to initiating therapy with tocilizumab. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tocilizumab, including the possibility of TB in patients who tested negative for latent TB infection prior to initiating therapy. Tocilizumab should not be initiated in patients with active infections, including localized infections. The risk and benefits of tocilizumab therapy should be considered prior to initiation of therapy. Patients with higher infection risks include those with chronic or recurrent infection, exposure to TB, history of serious or an opportunistic infection, with a history of travel or residence in areas of endemic TB or endemic mycoses, or those with underlying conditions that may predispose them to infections. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment

with tocilizumab, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants.

Cases of viral reactivation of herpes zoster have been reported. Patients who tested positive for hepatitis were excluded from clinical trials of tocilizumab.

Gastrointestinal perforation has been reported in clinical trials with tocilizumab, mostly as a result of complications of diverticulitis. Patients with new onset abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Tocilizumab therapy has been associated with a higher incidence of neutropenia and thrombocytopenia. Tocilizumab should not be initiated in patients with a low absolute neutrophil count (ANC < 2,000/mm^3) or platelet counts of < 100,000/mm^3. Therapy is not recommended if the ANC during tocilizumab therapy is less than 500/mm^3 or platelet count falls to less than 50,000/mm^3. Monitor neutrophils and platelets 4 to 8 weeks after the start of therapy and every 3 months thereafter. Dose modifications for tocilizumab are recommended based on ANC and platelet counts.

Serious cases of hepatic injury have occurred in patients taking tocilizumab (either formulation), including cases that have resulted in liver transplant or death. The onset of injury ranged from months to years following treatment and some cases presented only with dysfunction and mildly elevated transaminases (although most cases presented with marked elevations > 5 times the upper limit of normal [ULN]). Elevations of liver transaminases were reported in clinical trials with tocilizumab but did not result in permanent or clinically evident hepatic injury. Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic drugs, such as methotrexate, were used in combination with tocilizumab. Obtain a liver test panel prior to initiating tocilizumab, every 4 to 8 weeks after initiating therapy for 6 months, and every 3 months thereafter in patients being treated for RA, SSc-ILD, or GCA. Therapy with tocilizumab should not be initiated in patients for RA, SSc-ILD, or GCA with baseline elevations of ALT or AST of > 1.5 times the ULN. If patients develop elevated AST or ALT (> 5 times ULN), tocilizumab should be discontinued. Dose modifications for tocilizumab due to elevations of ALT and/or AST are recommended (see prescribing information for full details). Any patient reporting symptoms that could indicated liver injury (e.g., fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice) should have liver function tests measured promptly. If they are found to be elevated (AST > 3 times ULN, serum total bilirubin > 2 times ULN), treatment should be interrupted, and the cause should be established; treatment should only be restarted in patients who have an explanation for liver impairment from another cause. A similar pattern of elevation was found in clinical trials of tocilizumab for pJIA and sJIA. In these patients, a liver test panel should be monitored at the time of the second administration and every 4 to 8 weeks for pJIA and every 2 to 4 weeks for sJIA.

Tocilizumab is associated with increases in lipid parameters including total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and/or high-density lipoprotein cholesterol (HDL-C). Lipid parameters should be assessed at approximately 4 to 8 weeks after initiation of tocilizumab therapy and then measured every 6 months. Patients should be managed according to clinical guidelines for hyperlipidemia. An open-label study described in tocilizumab's labeling compared CV outcomes in patients with tocilizumab to those in patients using etanercept and demonstrated noninferiority of tocilizumab (hazard ratio [HR], 1.05; 95% CI, 0.77 to 1.43).

The effect that tocilizumab has on the development of malignancies and demyelinating disorders is unknown, but malignancies, multiple sclerosis, and chronic inflammatory demyelinating polyneuropathy

were reported during clinical trials. Prescribers should exercise caution in considering the use of tocilizumab in patients with pre-existing or recent onset demyelinating disorders.

Hypersensitivity reactions, including anaphylaxis, have been reported during tocilizumab IV infusions (0.2%) and with SC injections (0.7%). Anaphylaxis with IV administration has resulted in death. Reactions have occurred with a range of doses, sometimes as early as the first dose, and even in patients who have received premedication.

Tocilizumab has not been studied in combination with other biological DMARDS including TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies, and selective co-stimulation modulators. Combination therapy should be avoided as there is a possibility of increased immunosuppression and increased risk of infection.

tofacitinib (Xeljanz, Xeljanz XR)

Boxed warnings include increased risk of serious and sometimes fatal bacterial, mycobacterial, fungal, and viral infections in patients treated with tofacitinib. Most commonly reported serious infections included pneumonia, cellulitis, herpes zoster, diverticulitis, appendicitis, and urinary tract infections. Active TB was also reported. TB screening and appropriate treatment prior to initiation of tofacitinib treatment is recommended. Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with tofacitinib. The impact of tofacitinib on chronic viral hepatitis reactivation is unknown as patients who screened positive for hepatitis B or C were excluded from clinical trials; however, postmarketing cases of hepatitis B reactivation have been reported. Tofacitinib should not be initiated in patients with an active infection, including localized infections. The risk and benefits of treatment should be considered when prescribing tofacitinib in patients with a history of chronic, recurrent, or serious infection, prior exposure to TB, or a comorbid condition that predisposes them to infection. In patients with UC, a higher incidence of serious infection occurred in those treated with 20 mg versus 10 mg total daily dose. Caution should be used in patients with a history of chronic lung disease, those who develop interstitial lung disease, and those with increasing degrees of lymphopenia as they may be more prone to infections.

A boxed warning also exists regarding the increased risk of malignancies, including lymphomas and solid tumors. Current or past smokers are at an increased risk. A higher rate of malignancies, excluding non-melanoma skin cancer, occurred in patients treated with tofacitinib 5 mg or 10 mg twice daily compared to TNF antagonists in a key RA safety study (incidence rate per 100 patient years 5 or 10 mg twice daily: 1.13; TNF antagonist: 0.77). A data subset of lymphomas and lung cancers occurred at a higher rate in patients treated with tofacitinib 5 to 10 mg twice daily compared to TNF antagonists in the key RA safety study (incidence rate per 100 patient years for lymphomas 10 mg/day: 0.07, 20 mg/day: 0.11, TNF antagonist: 0.02; incidence rate per 100 patient years for lung cancers [current or past smokers] 10 mg/day: 0.48, 20 mg/day: 0.59, TNF antagonist: 0.27). A risk versus benefit assessment should occur prior to initiating treatment or for continuing treatment with tofacitinib, particularly in those with risk factors or with known or developed malignancy. A dose of 10 mg twice daily is not recommended for patients with RA or PsA. Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications.

In February 2019, the FDA issued a Drug Safety Communication to alert the public that an ongoing safety study found an increased risk of thrombosis (PE) and death when the 10 mg twice daily dosing was used in patients with RA, an off-label use at this dose.[227] The FDA reminded providers that dosing should

following the prescribing information and to advise patients to seek immediate medical attention if they experience signs or symptoms of PE. Boxed warnings regarding mortality and thrombosis were subsequently added to the product labeling; patients ≥ 50 years of age with RA and ≥ 1 CV risk factor who were treated with 10 mg twice daily had a higher rate of all-cause mortality, including sudden CV death, and thrombosis (e.g., PE, DVT, arterial thrombosis) compared to those treated with a dose of 5 mg twice daily. The incidence rate of all-cause mortality per 100 patient years in a key RA safety study was 0.88 for tofacitinib 5 mg twice daily, 1.23 for tofacitinib 10 mg twice daily, and 0.69 for TNF antagonists. A risk versus benefit assessment should occur prior to initiating treatment and for continued treatment with tofacitinib. Patients experiencing symptoms of thrombosis should be promptly evaluated, and tofacitinib should be discontinued. The incidence rate of DVT per 100 patient years in a key RA safety study was 0.22 for tofacitinib 5 mg twice daily, 0.28 for tofacitinib 10 mg twice daily, and 0.16 for TNF antagonists. The incidence rate of PE per 100 patient years in the key RA safety study was 0.18 for tofacitinib 5 mg twice daily, 0.49 for tofacitinib 10 mg twice daily, and 0.05 for TNF antagonists. In a long-term extension study in UC, 5 cases of PE occurred in patients taking 10 mg twice daily, including 1 death in a patient who had advanced cancer. For UC, the lowest effective dose for the shortest duration to achieve and maintain a therapeutic response should be use. Tofacitinib 10 mg twice daily and tofacitinib XR 22 mg once daily is not recommended for the treatment of RA or PsA; only FDA-approved dosing is recommended.

In 2021, the FDA approved labeling updates for all JAK inhibitors, including a boxed warning for MACE (CV death, non-fatal MI, and non-fatal stroke) due to a higher rate of these events in patients, specifically those ≥ 50 years of age and with ≥ 1 CV risk factor, treated with a tofacitinib than when treated with a TNF antagonist in patients with RA. Tofacitinib should be discontinued in patients who have experienced an MI or stroke. The incidence rate of MACE per 100 patient years in a key RA safety study was 0.91 for tofacitinib 5 mg twice daily, 1.11 for tofacitinib 10 mg twice daily, and 0.79 for TNF antagonists. The incidence rate of fatal or non-fatal MI per 100 patient years in the key RA safety study was 0.36 for tofacitinib 5 mg twice daily, 0.39 for tofacitinib 10 mg twice daily, and 0.2 for TNF antagonists. Current or past smokers are also at an increased risk.

Gastrointestinal perforations have been reported in clinical trials with tofacitinib. Tofacitinib should be used with caution in patients who may be at increased risk for GI perforation, such as a history of diverticulitis. New onset of abdominal symptoms should be evaluated promptly for early identification of GI perforation.

Hypersensitivity reactions, including angioedema and urticaria, have been reported in patients receiving tofacitinib. It should be promptly discontinued should these reactions occur.

Treatment with tofacitinib has been associated with decreases in lymphocyte, neutrophil, and red blood cell counts. It is recommended that tofacitinib not be initiated in patients with a lymphocyte count < 500 cells/mm^3, an ANC < 1,000 cells/mm^3, or a hemoglobin level < 9 g/dL. In patients receiving tofacitinib, lymphocyte counts should be obtained at baseline and every 3 months thereafter. Neutrophil and hemoglobin should be monitored at baseline, 4 to 8 weeks after initiation of therapy, and every 3 months thereafter. Dosing recommendations for patients with reduced lymphocyte or neutrophil counts and those with a reduced hemoglobin are detailed in the prescribing information.

Tofacitinib was associated with an increased incidence of elevated liver enzymes. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is

suspected, the administration of tofacitinib should be interrupted until this diagnosis has been ruled out. Treatment with tofacitinib is not recommended in patients with severe hepatic impairment.

Dose dependent increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were observed in clinical trials. Increases occurred within 1 to 3 months of the start of tofacitinib therapy and remained stable thereafter with continued treatment. No evidence for an increase in CV risk has been observed. Lipid assessments should be performed approximately 4 to 8 weeks following initiation of therapy, and patients should be managed according to clinical guidelines for the management of hyperlipidemia.

Limited data are available on the response to vaccination or on the secondary transmission of infection by live vaccines to patients receiving tofacitinib. Live vaccines should not be given concurrently. Immunizations should be updated consistent with current immunization guidelines prior to initiating tofacitinib therapy. The interval between initiation of tofacitinib therapy and live vaccinations should be in accordance with current vaccination guidelines.

Since the extended-release formulation (Xeljanz XR) contains some non-deformable material, caution should be used when it is used in patients with pre-existing GI narrowing due to rare reports of obstructive symptoms in this population.

upadacitinib (Rinvoq)

Upadacitinib is contraindicated in patients with known hypersensitivity to upadacitinib or any of its components. Reactions, including anaphylaxis and angioedema, have been reported.

Boxed warnings for upadacitinib advise of the potential for serious infections that can lead to hospitalization or death, including TB and opportunistic infections (e.g., bacterial, fungal, viral) in patients treated with upadacitinib. Use of upadacitinib should be avoided in patients with an active, serious infection, even if the infection is localized. The risk and benefits of therapy should be considered in those with chronic or recurrent infection, TB exposure, a history of serious or opportunistic infection, a predisposition to infection, and in those living or traveling to endemic areas for TB or mycoses. Patients should be tested for TB prior to starting upadacitinib and monitored periodically during therapy; treat appropriately if TB is detected. Patients should be promptly evaluated if signs and symptoms of infection occur during therapy. Therapy should be interrupted if a serious infection occurs. Viral reactivation has been reported in agents treated with upadacitinib. The risk of herpes zoster appears higher in patients treated with upadacitinib in Japan. Viral hepatitis screening should occur in accordance with clinical guidelines; upadacitinib should not be used in patients with active hepatitis B or C.

Upadacitinib also carries a boxed warning regarding the risk of malignancies, excluding non-melanoma skin cancer (NMSC). A higher rate of malignancies occurred with another JAK inhibitor compared to TNF antagonist, as described above with tofacitinib. The risks and benefits of upadacitinib should be considered prior to starting therapy in patients with known malignancy unless it is a successfully treated NMSC. NMSC has been detected in patients treated with upadacitinib; therefore, periodic skin assessments should be performed if the patient is at an increased risk. Limit the exposure to sunlight and UV light.

Upadacitinib also carries a boxed warning for thrombosis, including DVT, PE, and arterial thrombosis, which have been reported with JAK inhibitors in treating inflammatory conditions, including fatal cases. As described above with data for tofacitinib, this has occurred with another JAK inhibitor at a higher rate that in patients treated with a TNF antagonist. In patients at increased risk for thrombosis, the risks and

benefits of upadacitinib should be weighed prior to treatment; upadacitinib should be avoided in patients at increased risk of thrombosis. Prompt evaluation and treatment should be performed if symptoms are present.

Upadacitinib also carries a boxed warning for mortality, as a higher rate of all-cause mortality occurred with another JAK inhibitor compared to TNF antagonist, as described above for tofacitinib. The risk is greater in patients ≥ 50 years of age with ≥ 1 CV risk factor. The risks and benefits for initiating or continuing therapy with upadacitinib should be considered.

In 2021, the FDA approved labeling updates for all JAK inhibitors, including a boxed warning for MACE (CV death, MI, and stroke) due to a higher rate of these events in patients treated with a tofacitinib than when treated with a TNF antagonist in patients with RA.

While causation has not been established, GI perforations have been reported in patients treated with upadacitinib; many of the cases were in patients with RA also on background NSAIDS. Use caution when prescribing upadacitinib in patient at increased risk for GI perforation (e.g., history of diverticulitis, concurrent NSAIDs). Promptly evaluate if abdominal symptoms occur.

Increased incidence of neutropenia, lymphopenia, anemia, and elevated liver enzymes have occurred with upadacitinib. These parameters should be evaluated at baseline and treated as appropriate. Avoid starting upadacitinib and interrupt treatment in patients with an ANC < 1,000 cells/mm^3, absolute lymphocyte count (ALC) < 500 cells/mm^3, or hemoglobin < 8 g/dL. If liver enzyme abnormalities occur, promptly assess for potential drug-induced liver injury. Interrupt treatment if serious infection develops until infection is controlled or if drug-induced liver injury is suspected.

Statin-responsive elevations in serum lipids (e.g., total cholesterol, LDL-C, HDL-C) have been reported with upadacitinib. The effect on CV status has not been established. Monitor patients 12 weeks after starting upadacitinib and according to accepted medical guidelines thereafter.

Use of live, attenuated vaccines during or immediately before the start of upadacitinib treatment is not recommended. Update immunization status prior to therapy according to current guidelines.

ustekinumab (Stelara)

Ustekinumab is contraindicated in patients with a history of clinically significant hypersensitivity to ustekinumab or to any of the excipients. Serious allergic reactions including angioedema and anaphylaxis have been reported with ustekinumab. Discontinue use of ustekinumab and institute appropriate therapy.

Ustekinumab may increase the risk of infections and reactivation of latent infections. Patients genetically deficient in IL-12/IL-23 are vulnerable to disseminated infections from mycobacteria, salmonella, and Bacillus Calmette-Guerin (BCG) vaccinations. It is not known whether patients with pharmacologic blockade of IL-12/IL-23 with ustekinumab will be susceptible to these types of infections. During clinical trials for the treatment of psoriasis, serious infections diagnosed included diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, osteomyelitis, viral infections, genitourinary infections, urinary tract infections, and sepsis. In the psoriatic arthritis trials, serious infections included cholecystitis. In patients with Crohn's disease, types of infections experienced included anal abscess, gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeria meningitis. In patients with ulcerative colitis, types of infections experienced included gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis. Ustekinumab should not be given to patients with any clinically important active infection. Caution should

be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. Diagnostic tests to screen for these infections should be considered, as dictated by clinical circumstances. Patients should be evaluated for TB prior to initiating therapy with ustekinumab. Do not administer ustekinumab to patients with active TB. Consider initiation of anti-TB therapy prior to ustekinumab therapy for patients with a past history of latent TB or active TB or those in who an adequate course of treatment cannot be confirmed.

As an immunosuppressant, ustekinumab may increase the risk of malignancy. There have been reports of multiple rapidly appearing cutaneous squamous cell carcinomas in patients who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving ustekinumab should be monitored for non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy, and those with a history of psoralen plus ultraviolet light (PUVA) treatment should be followed closely. The safety of ustekinumab in patients with a history of or a known malignancy has not been evaluated. Ustekinumab has not been studied beyond 2 years of use.

Two cases of reversible posterior leukoencephalopathy syndrome (RPLS), also known as posterior reversible encephalopathy syndrome (PRES), have been reported in clinical trials with ustekinumab. RPLS is a neurological disorder that is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion, and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents, and immunosuppressive therapy. Fatal outcomes from RPLS have been reported. If RPLS is suspected, ustekinumab should be promptly discontinued and the patient should be treated appropriately.

Prior to initiating therapy, patients should receive all age-appropriate immunizations.

BCG vaccines should not be given during treatment with ustekinumab or for 1 year prior to initiating treatment or for 1 year after discontinuation. Use caution when administering live vaccines to household contacts of patients receiving ustekinumab due to the potential risk of viral shedding from the household contacts and transmission to the patient. Non-live vaccinations received during ustekinumab therapy may not elicit an immune response sufficient to prevent disease.

Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab may decrease the protective effect of allergy immunotherapy and may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergy immunotherapy, particularly for anaphylaxis.

Ustekinumab carries a warning regarding noninfectious pneumonia; postmarketing cases of in interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported, with symptoms (e.g., cough, dyspnea, interstitial infiltrates) following 1 to 3 doses. Serious outcomes, including respiratory failure and prolonged hospitalization, have been reported, although these cases generally improved following ustekinumab discontinuation and administration of corticosteroids (some cases). If this diagnosis is confirmed, ustekinumab should be discontinued and the patients should be treated for these symptoms appropriately.

As a therapeutic protein, there is potential for immunogenicity with ustekinumab.

vedolizumab (Entyvio)

Vedolizumab is contraindicated in patients with a history of hypersensitivity to vedolizumab or to any of the excipients. Treatment with vedolizumab is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding vedolizumab in patients who develop a severe infection while on treatment.

Infusion-related reactions and hypersensitivity reactions (e.g., anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, increased blood pressure, heart rate) have been reported with the first and subsequent vedolizumab infusions. If anaphylaxis or other serious reactions occur, discontinue vedolizumab treatment and initiate appropriate management.

Another integrin receptor antagonist has been associated with PML. One case of PML was reported in a vedolizumab-treated patient in the postmarketing setting, although there may be multiple factors that could have contributed to PML. Monitor patients on vedolizumab for any new onset, or worsening, of neurological signs and symptoms.

Reports of liver injury (e.g., elevated transaminases, elevated bilirubin) have occurred with vedolizumab; discontinue vedolizumab in patients with signs or symptoms of liver injury.

Prior to initiation, all patients should be brought up to date on all vaccinations based on immunization guidelines; vedolizumab-treated patients may receive non-live vaccines, as well as live vaccines (when the benefits outweigh the risks).

As a therapeutic protein, there is potential for immunogenicity with vedolizumab.

Risk Evaluation and Mitigation Strategy (REMS)[228]

Brodalumab is only available through the Siliq Risk Modification and Mitigation Strategies (REMS) Program due to the observed suicidal ideation and behavior in patients treated with the drug. Prescribers must be certified in the program, patients must sign a Patient-Prescriber Agreement Form, and pharmacies must be certified with the program and only dispense to authorized patients.

While previously the FDA required REMS programs for tocilizumab (Actemra), tofacitinib (Xeljanz, Xeljanz XR), and ustekinumab (Stelara), the FDA determined that the REMS was no longer necessary.

DRUG INTERACTIONS[229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259]

Interactions relating to vaccine use is within the Warnings section above.

abrocitinib (Cibinqo)

Due to increased exposure of abrocitinib and active metabolites when concurrently used with strong cytochrome P450 (CYP450) 2C19 (CYP2C19) inhibitors, a decreased dose of abrocitinib is recommended with concurrent use of these medications. Similarly, moderate to strong inhibitors of both CYP2C19 and CYP2C9 may increase exposure of abrocitinib and active metabolites; avoid concurrent use with drugs that are moderate to strong inhibitors of both CYP2C19 and CYP2C9. Concurrent use with strong CYP2C19 or CYP2C9 inducers should be avoided, as it may decrease drug levels of abrocitinib and active metabolites, decreasing efficacy.

Monitor and titrate the dose of P-glycoprotein (P-gp) substrates with a narrow therapeutic index (e.g., digoxin) when given concurrently with abrocitinib, as it can increase drug levels of P-gp substrates leading to adverse reactions. Due to the potential for concurrent use of abrocitinib and antiplatelet drugs to increase the risk for bleeding with thrombocytopenia, antiplatelet drugs (except for low-dose aspirin) are contraindicated during the first 3 months of abrocitinib treatment.

abatacept (Orencia)

Concurrent administration of a TNF antagonist with abatacept is not recommended since combination therapy has been associated with an increased risk of serious infections with no additional efficacy over TNF antagonist monotherapy. There is insufficient experience to assess the safety and efficacy of abatacept administered concurrently with anakinra; therefore, such use is not recommended.

adalimumab (Humira), adalimumab-atto (Amjevita)

Adalimumab or its biosimilar should not be used with anakinra, abatacept, or other TNF antagonists, although it is unknown if any adverse effects would occur. Concomitant therapy may increase the potential for infections and have an impact on the development and course of malignancies. Although not specifically evaluated, patients receiving immunosuppressives along with adalimumab or its biosimilar may be at a greater risk of developing an infection. In studies of adalimumab, many of the serious infections occurred in patients on immunosuppressive therapy.

The clearance of adalimumab was decreased by 44% after multiple doses of methotrexate. No dose adjustment for either drug is needed when methotrexate and adalimumab are used together. This also applies to the biosimilar product.

anakinra (Kineret)

In a study in which patients with active RA were treated for up to 24 weeks with concurrent anakinra and etanercept therapy, a 7% rate of serious infections was observed, which was higher than that observed with etanercept alone (0%). Two percent of patients treated concurrently with anakinra and etanercept developed neutropenia. Combination therapy with any TNF antagonists and anakinra is not recommended.

apremilast (Otezla)

Co-administration of the strong CYP450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. The use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with apremilast is not recommended.

baricitinib (Olumiant)

Administration of baricitinib with strong organic anion transporter 3 (OAT3) inhibitors (e.g., probenecid) increases its exposure; a dose reduction is recommended.

Use of baricitinib in combination with other JAK inhibitors or with biologic DMARDs has not been studied.

brodalumab (Siliq)

Consider monitoring patients starting or discontinuing brodalumab when concomitantly receiving drugs that are CYP450 substrates, especially those with a narrow therapeutic index, and consider modifying the dose of the CYP450 substrate.

canakinumab (Ilaris)

No formal drug interaction studies have been conducted with canakinumab. However, concomitant use of canakinumab with TNF antagonists should be avoided because of the potential for an increased risk of infections.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation which may occur during canakinumab treatment. This may cause an interaction with CYP450 substrates and patients being treated with CYP450 enzymes should be monitored and may need to be adjusted as needed.

certolizumab pegol (Cimzia)

Concurrent administration of anakinra and another TNF antagonist has shown an increased risk of serious infections, an increased risk of neutropenia, and no added benefit compared to these medicinal products alone. Do not administer certolizumab pegol in combination with biological DMARDs or other TNF antagonist therapies.

Interference with certain coagulation assays has been detected in patients treated with certolizumab pegol. Certolizumab pegol may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities. Interference with thrombin time and prothrombin time assays has not been observed. There is no evidence that certolizumab pegol therapy has an effect on *in vivo* coagulation.

etanercept (Enbrel)

Concurrent or recent exposure to myelosuppressive anti-rheumatic agents (e.g., azathioprine, cyclophosphamide, leflunomide, or methotrexate) has been associated with pancytopenia, including aplastic anemia, in some patients treated with etanercept. Etanercept is, however, commonly given in combination with methotrexate. The use of etanercept with cyclophosphamide is not recommended.

In a study of patients with granulomatosis with polyangiitis, the addition of etanercept to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous solid malignancies. Use of etanercept in patients receiving concurrent cyclophosphamide therapy is not recommended.

Patients in a clinical study who were on established therapy with sulfasalazine, to which etanercept was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to groups treated with either therapy alone. The clinical significance of this observation is unknown.

Serious infections were seen in clinical studies with concurrent use of anakinra or abatacept and etanercept, with no added benefit.

golimumab (Simponi, Simponi Aria)

When used in combination with abatacept (Orencia) or anakinra (Kineret), an increased risk of serious infections with no added therapeutic benefit has been observed with other TNF antagonists in clinical RA studies. Therefore, use of golimumab with abatacept or anakinra is not recommended.

During chronic inflammation, the formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα). Consequently, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of golimumab in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted, as needed.

guselkumab (Tremfya)

During chronic inflammation, the formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα). Consequently, it is expected that for a molecule that antagonizes cytokine activity, such as guselkumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of guselkumab in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect or drug concentration is recommended and the individual dose of the drug product may be adjusted, as needed.

inebilizumab-cdon (Uplizna)

Coadministration of inebilizumab-cdon with other immunosuppressant drugs, such as systemic corticosteroids, may increase the risk of infections; therefore, consider the potential for additive immunosuppression if these agents are to be administered concurrently.

infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), and infliximab-dyyb (Inflectra)

Patients receiving immunosuppressives tend to have fewer infusion-related reactions to infliximab as compared to patients not receiving immunosuppressive therapy. In patients receiving immunosuppressant therapy with azathioprine, mercaptopurine, or methotrexate, antibody development to infliximab is lower compared to patients not receiving concurrent immunosuppression. Many serious infections during infliximab therapy have occurred in patients receiving concurrent immunosuppressives. This also applies to infliximab biosimilars.

Rheumatoid arthritis patients who received methotrexate in combination with infliximab or its biosimilars have higher serum concentrations of infliximab products as compared to those who receive infliximab alone.

Combination therapy with any TNF antagonists and anakinra or abatacept is not recommended due to the potential for increased risk of infections without any increase in efficacy as seen in clinical trials with etanercept and anakinra. The use of tocilizumab in combination with biological DMARDs such as TNF antagonists, including infliximab or its biosimilars, should be avoided because of the possibility of increased immunosuppression and increased risk of infection.

No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving TNF antagonist therapy. It is recommended that live vaccines not be given concurrently.

It is recommended that all pediatric Crohn's disease patients be brought up-to-date with all vaccinations prior to initiating infliximab therapy.

It is recommended that therapeutic infectious agents (e.g., BCG in bladder cancer) not be given concurrently with infliximab or its biosimilars.

ixekizumab (Taltz)

Ixekizumab has no known clinically significant drug interactions with substrates of CYP1A2, 2C9, 2C19, or 3A4; however, its effect on the activity of CYP2D6 cannot be ruled out based on currently available data.

rilonacept (Arcalyst)

No formal drug interaction studies have been conducted with rilonacept. However, concomitant use of rilonacept with TNF antagonists should be avoided because of the potential for an increased risk of infections.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation which may occur during rilonacept treatment. This may cause an interaction with CYP450 substrates and patients being treated with CYP450 enzymes should be monitored and may need to be adjusted as needed.

risankizumab-rzaa (Skyrizi)

Risankizumab-rzza labeling does not report drug-drug interactions.

sarilumab (Kevzara)

Elevated IL-6 concentrations, occurring in patients with RA, may down-regulate CYP450 enzyme activity, thereby increasing concentrations of drugs that are CYP substrates, as compared to subjects without RA. Inhibition of IL-6 signaling by IL-6Rα antagonists, such as sarilumab, may alter drug concentrations by reversing the inhibitory effect of IL-6 and restore CYP activity. This effect may be clinically relevant for drugs that are CYP substrates with a narrow therapeutic index, such as warfarin or theophylline; drug concentrations should be monitored and doses adjusted as appropriate.

Caution should be taken with concurrent use of sarilumab with CYP3A4 substrates that may lead to a loss of efficacy (e.g., oral contraceptives, lovastatin, atorvastatin). This effect may continue for several weeks after discontinuing sarilumab therapy.

satralizumab-mwge (Enspryng)

Satralizumab-mwge has no known drug interactions.

secukinumab (Cosentyx)

No formal drug interaction studies have been conducted with secukinumab; however, concomitant use of secukinumab with TNF antagonists should be avoided because of the potential for an increased risk of infections.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-17A) during chronic inflammation which may occur during secukinumab treatment. This may cause an interaction with CYP450 substrates and patients being treated with CYP450 enzymes should be monitored and may

need to have therapy adjusted; however, results from a drug-drug interaction study showed no clinically relevant interaction for drugs metabolized by CYP3A4.

tildrakizumab-asmn (Ilumya)

There are no known drug interactions with tildrakizumab-asmn.

tocilizumab (Actemra)

Tocilizumab has not been studied in combination with biological DMARDs, such as TNF antagonists.

In infection and inflammation, the CYP450 enzymes are down-regulated by cytokines, including IL-6. By inhibiting IL-6 signaling in RA patients by tocilizumab, CYP450 enzyme activity may be restored to higher levels than those in the absence of tocilizumab. This may increase the metabolism of CYP450 substrates. *In vitro* studies showed that tocilizumab may change the expression of many of the CYP450 enzymes responsible for drug metabolism, including CYP 1A2, 2C9, 2D6, and 3A4. The effect of tocilizumab on CYP450 enzymes may be clinically relevant for CYP450 substrates with a narrow therapeutic index. Upon initiation or discontinuation of tocilizumab, patients being treated with medications metabolized via CYP450 systems may need to be monitored (e.g., warfarin) or drug concentration evaluated (e.g., theophylline, cyclosporine) and adjustments made, if necessary. The effect of tocilizumab may be apparent for several weeks following the last dose.

tofacitinib (Xeljanz, Xeljanz XR)

Tofacitinib exposure is increased when co-administered with potent inhibitors of CYP450 enzymes, CYP3A4 (e.g., ketoconazole), and with co-administration of drugs that are both moderate inhibitors of CYP3A4 and potent inhibitors of CYP2C19 (e.g., fluconazole). The dose of tofacitinib should be reduced to 5 mg once daily in patients taking this medication for PsA or RA and reduced in half (5 mg twice daily or 5 mg once daily) in UC patients (the extended-release formulation should not be used). In contrast, potent inducers of CYP3A4 (e.g., rifampin) decrease tofacitinib exposure and concomitant use is not recommended.

There is a risk of added immunosuppression when tofacitinib is co-administered with potent immunosuppressive drugs (e.g., azathioprine, tacrolimus, cyclosporine). Combined use with potent immunosuppressives has not been studied in RA.

upadacitinib (Rinvoq)

Co-administration with a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin) may increase upadacitinib exposure and, subsequently, adverse reactions; therefore, adverse reactions should be monitored in patients taking a strong CYP3A4 inhibitor with upadacitinib 15 mg once daily. A maximum maintenance dose of 15 mg once daily and induction dose of 30 mg once daily should be used in patients with UC taking concomitant strong CYP3A4 inhibitors. Use of 30 mg once daily doses with strong CYP3A4 inhibitors in patients with atopic dermatitis is not recommended. Conversely, co-administration with strong CYP3A4 inducers (e.g., rifampin) is not recommended due to the potential for reduced therapeutic effect of upadacitinib.

ustekinumab (Stelara)

Select immunomodulators (6-mercaptopurine, azathioprine, methotrexate) have been used concomitantly with ustekinumab in Crohn's disease studies and did not appear to influence the overall

safety or efficacy of ustekinumab. The safety of ustekinumab given with other immunosuppressive drugs or phototherapy has not been evaluated.

CYP450 substrates should be monitored, as ustekinumab can alter the formation of CYP450 enzymes. This is especially important for agents with a narrow therapeutic effect, such as warfarin and cyclosporine.

BCG vaccines should not be given during treatment with ustekinumab or for 1 year prior to initiating treatment or 1 year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving ustekinumab because of the potential risk for shedding from the household contact and transmission to patient. Non-live vaccinations received during ustekinumab therapy may not elicit an immune response sufficient to prevent disease. Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy.

Ustekinumab may decrease the protective effect of allergy immunotherapy and may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Use caution in patients receiving or who have received allergy immunotherapy and monitor for anaphylaxis.

Ustekinumab in combination with immunosuppressive agents or phototherapy has not been evaluated.

vedolizumab (Entyvio)

Concomitant use of vedolizumab with natalizumab (should be avoided because of the potential for increased risk of PML and other infections.

Concomitant use of vedolizumab with TNF antagonists should be avoided because of the potential for increased risk of infections.

ADVERSE EFFECTS[260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290]

Adverse Effects in Adults

Drug	Injection Site/ Infusion Reaction	Infection		Headache	Nausea
		Upper Respiratory	Other		
Anti-TNF Biologics					
adalimumab (Humira) adalimumab-atto (Amjevita)	20 (14)	17 (13)	Serious infections 4.7/100 p/yr (2.7/100 p/yr)	12 (8)	9 (8)
certolizumab pegol (Cimzia)	reported	18 to 21.9 (13 to 21)	Total infections in Crohn's patients 38 (30) Total Infections in RA patients 0.91/p/yr (0.72/ p/yr)	5 (with MTX; 4 with MTX alone; RA trials	nr
etanercept (Enbrel)	15 to 43 (6 to 11)	17 to 65 (17 to 30)	Total Infections: 27 to 81 (28 to 39) Serious Infections: 1.4 (0.8)	nr	nr
golimumab (Simponi)	SC: 6 (2)	SC: 16 (13)	SC – Serious Infections 5.7/100 p/yr (4.2/100 p/yr)	nr	nr
golimumab (Simponi Aria)	IV: 2 (1)	IV: 13 (12)	IV – Serious Infections 4.07/100 p/yr	nr	nr
infliximab (Remicade) infliximab-abda* (Renflexis) infliximab-axxq* (Avsola) infliximab-dyyb* (Inflectra)	20 (10)	32 (25)	27 to 36 (18 to 25)	18 (14)	21 (20)

nr = not reported, na = not applicable, p/yr = patient-year, MTX = methotrexate

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive. Incidences for placebo are indicated in parentheses.

*Adverse effects reported in the prescribing information are based on data with infliximab (Remicade).

Adverse Effects in Adults (continued)

Drug	Injection Site/ Infusion Reaction	Infection		Headache	Nausea
		Upper Respiratory	Other		
Other Biologic Agents					
abatacept (Orencia)	9 (6) IV: 2.5% (18/721) SC: 2.6% (19/736)	5 to 13	Total Infections 54 (48) Serious Infections 3 (1.9)	18 (13)	reported
anakinra (Kineret)	71 (29)	14 (17)	39 (37)	12 (9)	8 (7)
brodalumab (Siliq)	1.5 (1.3)	reported	25.4 (23.4)	4.3 (3.5)	1.9 (1.1)
canakinumab (Ilaris)	6.8	reported	37.8	14	14
guselkumab (Tremfya)	4.5 (2.8)	14.3 (12.8)	23 (21)	4.6 (3.3)	nr
inebilizumab-cdon (Uplizna)	12	8	≥ 20	8 (8)	reported
ixekizumab (Taltz)	17 (3)	14 (13)	27 (23)	nr	2 (1)
rilonacept (Arcalyst)	11 (3)	6 (1)	34 (27)	nr	4 (13)
risankizumab-rzaa (Skyrizi)	SC: 1.5 to 5.6 (1 to 2.8)	13 (9.7)	36.6 to 90.8/100 p/yr (36.4/100 p/yr)	3.5 (2)	nr
	IV: nr	10.6 (9.3)	nr	6.6 (5.6)	nr
sarilumab (Kevzara)	6 to 7 (1)	3 to 4 (2)	105 to 110/100 p/yr (81/100 p/yr)	nr	nr
satralizumab-mwge (Enspryng)	9 (8)	19 (12)	Total Infections: 51 to 168/100 p-yr (108 to 143/100 p/yr) Serious Infections: 4 to 5/100 p-yr (5 to 10/100 p-yr)	27 (12)	15 (9)
secukinumab (Cosentyx)	nr	2.5 to 3.2	Total Infections: 47.5 Serious Infections: 1.2	nr	nr
tildrakizumab-asmn (Ilumya)	3 (2)	14 (12)	Total Infections: 23 Serious Infections: ≤ 0.3	nr	nr
tocilizumab (Actemra)	SC: 7.1 to 10.1 (2.4 to 4.1)	nr	nr	nr	nr
tocilizumab (Actemra)	IV: 7 to 8 (5)	5 to 8 (6)	Serious Infections: 3.6 to 9.7/100 p/yr (1.5 to 12.5/100 p/yr)	5 to 7 (2-3)	nr
ustekinumab (Stelara)	1 to 2 (< 1)	4 to 24 (1 to 20)	Serious Infections: 0.01/p/yr (0.02/ p/yr)	5 to 10 (3 to 4)	3 (1 to 2)
vedolizumab (Entyvio)	4 (3)	7 (6)	0.85/p/yr (0.7/p/yr)	12 (11)	9 (8)

nr = not reported, na = not applicable, p-yr = patient-year, MTX = methotrexate

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive. Incidences for placebo are indicated in parentheses.

Adverse Effects in Adults (continued)

Drug	Injection Site/ Infusion Reaction	Infection		Headache	Nausea
		Upper Respiratory	Other		
Non-biologic Agents					
abrocitinib (Cibinqo)	na	nr	Serious Infections 1.3 to 3.9/100 p/yr (2.6/100 p/yr)	6 to 7.8 (3.5)	6 to 14.5 (2.1)
apremilast (Otezla)	na	0.6 to 11.5 (0.6 to 6)	nr	4.8 to 14.4 (1.8 to 10.7)	7.4 to 22 (1.4 to 10.7)
baricitinib (Olumiant)	na	16.3 (11.7)	Serious Infections 3.6 to 4.2/100 p/yr (4.2/100 p/yr)	nr	2.7 (1.6)
tofacitinib (Xeljanz, Xeljanz XR)	na	4 to 6 (3 to 4)	Serious Infections 1.7 to 2.7/100 p/yr (0.5/100 p/yr); Overall infections 20 to 22 (18)	3 to 9 (2 to 6)	1 to 4 (3)
upadacitinib (Rinvoq)	na	9 to 25 (7 to 17)	Serious Infections 2.3 to 8.4/100 p/yr (1.2 to 8.4/100 p/yr); Overall infections 127.8 to 180.3/100 p/yr (95.7 to 136.5/100 p/yr)	3.3 to 6 (1.4 to 4)	3 to 3.5 (1 to 2.2)

nr = not reported, na = not applicable, p-yr = patient-year, MTX = methotrexate
Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive. Incidences for placebo are indicated in parentheses.

All therapeutic proteins carry the potential risk of immunogenicity.

In placebo-controlled studies, 8% of patients receiving anakinra had decreases in neutrophil counts of at least 1 World Health Organization (WHO) toxicity grade compared with 2% of patients in the placebo control group. Six (0.3%) of the anakinra-treated patients experienced neutropenia. Neutrophil counts should be obtained prior to initiating anakinra, while on therapy, monthly for 3 months, and thereafter quarterly for a period up to 1 year.

To investigate whether TNF antagonists, together as a class, or separately as either monoclonal anti-TNFα antibodies (adalimumab, infliximab) or a fusion protein (etanercept), are related to higher rates of herpes zoster in patients with RA, patients were enrolled in a prospective cohort.[291] Patients were enrolled at the initiation of treatment with etanercept, adalimumab, infliximab, or anakinra, or when they changed conventional DMARD treatment. Treatment, clinical status, and adverse events were assessed by rheumatologists at fixed points during follow-up. Among the 5,040 patients receiving TNF antagonists or conventional DMARDs, 86 episodes of herpes zoster occurred in 82 patients. Thirty-nine of these occurrences could be attributed to treatment with adalimumab or infliximab, 23 to etanercept, and 24 to conventional DMARDs. Adjusted for age, rheumatoid arthritis severity, and glucocorticoids use, a significantly increased risk was observed for treatment with the monoclonal antibodies. Treatment with monoclonal anti-TNFα inhibitors (adalimumab, infliximab) may be associated with increased risk of herpes zoster, but further study is required.

In clinical trials for risankizumab-rzaa for the treatment of Crohn's disease, increases in lipid parameters (total cholesterol [TC] and low-density lipoprotein cholesterol [LDL-C]) from baseline and increases relative to placebo were seen at week 4 and remained stable to week 12. Following induction therapy, the mean TC increased by 9.4 mg/dL from baseline to a mean absolute value of 175.1 mg/dL at week 12. The mean LDL-C increased by 6.6 mg/dL from baseline to a mean absolute value of 92.6 mg/dL at week 12. Following maintenance treatment, the mean LDL-C increased by 2.3 mg/dL from baseline to week 52, to an absolute value of 102.2 mg/dL.

Adverse Effects in Pediatric Patients

Drug	Injection Site/ Infusion Reaction	Infection
Anti-TNF Biologics		
adalimumab (Humira)	16	45
adalimumab-atto (Amjevita)		
etanercept (Enbrel)	reported	reported
golimumab (Simponi Aria)	reported as similar to those observed in adults	
infliximab (Remicade)	18	65 to 68
infliximab-abda (Renflexis)*		
infliximab-axxq (Avsola)*		
infliximab-dyyb (Inflectra)*		
Other Biologic Agents		
abatacept (Orencia)	2 to 4	36
anakinra (Kineret)	16	Total infections: 2.3 infections/patient-year in first 6 months of therapy; 1.7 infections/patient-year after the first 6 months of therapy
ixekizumab (Taltz)	reported	reported
rilonacept (Arcalyst)	reported	reported
secukinumab (Cosentyx)	reported as similar to those observed in adults	
tocilizumab (Actemra)	16 – sJIA (IV); 41.2 – sJIA (SC) 20.2 – pJIA (IV) ; 28.8 – pJIA (SC)	Total Infections†: 163.7/100 patient years – sJIA (IV); 345/100 patient-years – pJIA (IV); (287/100 patient-years)
ustekinumab (Stelara)	reported as similar to those observed in adults	
Non-biologic Agents		
tofacitinib (Xeljanz)	reported as similar to those observed in adults	

nr = not reported; pJIA = polyarticular juvenile idiopathic arthritis; sJIA = systemic juvenile idiopathic arthritis

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive.

*Adverse effects reported in the prescribing information are based on data with infliximab (Remicade).

† Adverse effects experienced with the SC formulation of tocilizumab are described as comparable to those experienced with the IV formulation; however, the rate of injection site reactions was numerically higher in those treated with the SC formulation.

SPECIAL POPULATIONS[292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322]

Pediatrics

In November 2009, the boxed warning for the TNF antagonists was updated to include the risk of malignancies, some fatal, associated with the use of TNF antagonists in children and young adults. Approximately half of the cases were lymphoma. Some malignancies were rare and usually associated with immunosuppression and not typically observed in children and adolescents.

Adalimumab (Humira) and adalimumab-atto (Amjevita) are indicated for reducing signs and symptoms of JIA in children 2 years of age or older and for the treatment of pediatric CD (patients ≥ 6 years old). Adalimumab is also approved for the treatment of pediatric ulcerative colitis (patients ≥ 5 years old), treatment of non-infectious intermediate, posterior, and panuveitis in patients ≥ 2 years of age, and the treatment of hidradenitis suppurativa in patients ≥ 12 years of age. Approval of adalimumab in patients ≥ 12 years of age for uveitis is extrapolated from evidence in adults and pharmacokinetic data.

Etanercept (Enbrel) is indicated for the treatment of JIA in children at least 2 years of age and treatment of plaque psoriasis in children at least 4 years of age who are candidates for systemic therapy or phototherapy.

Intravenous golimumab (Simponi Aria) is approved for active pJIA and PsA in patients 2 years of age and older.

Infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), and infliximab-dyyb (Inflectra) are indicated in children (> 6 years) for the treatment of Crohn's disease and for the treatment of ulcerative colitis.

Abatacept (Orencia) is indicated for reducing signs and symptoms of JIA in children over 2 years and 6 years of age for its SC and IV products, respectively. Abatacept IV is approved for the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in pediatric patients at least 2 years old undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor.

Anakinra (Kineret) is approved for use in pediatric patients with neonatal-onset multisystem inflammatory disease (NOMID), a rare periodic fever syndrome which causes uncontrolled inflammation in multiple parts of the body beginning in the newborn period. It is also approved for the treatment of DIRA.

Canakinumab is approved for the treatment of sJIA in patients aged 2 years and older. It also is approved for cryopyrin-associated periodic syndromes (CAPS), including familiar cold autoinflammatory syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in pediatrics 4 years of age and older. It is also approved for the following other periodic fever syndromes in adults and pediatric patients 2 years of age and older: Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF).

Ixekizumab (Taltz) is indicated for the treatment of pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Rilonacept (Arcalyst) is approved for the treatment of CAPS and RP in pediatric patients 12 years of age and older. It is also approved for maintenance of remission of DIRA in pediatric patients weighing ≥ 10 kg.

Secukinumab (Cosentyx) is approved for use in children at least 6 years of age with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy, children at least 2 years old weighing at least 15 kg with PsA, and the treatment of active enthesitis-related arthritis (ERA) in patients at least 4 years old.

Tocilizumab (Actemra) is indicated for polyarticular and systemic JIA in children ages 2 years and older and for severe or life-threatening CAR-T cell-induced CRS in patients 2 years of age and older.

Ustekinumab (Stelara) is approved for the treatment of moderate to severe plaque psoriasis and active psoriatic arthritis in children ages 6 years to 17 years who are candidates for systemic therapy or phototherapy.

The safety and effectiveness of tofacitinib (Xeljanz) for polyarticular course JIA have been established in pediatric patients at least 2 years of age.

Safety and effectiveness of abrocitinib (Cibinqo) and upadacitinib (Rinvoq) in pediatric patients ≥ 12 years of age with atopic dermatitis have been established. Other indications for upadacitinib are not approved for use in pediatric patients.

Safety and effectiveness of apremilast (Otezla), baricitinib (Olumiant), brodalumab (Siliq), certolizumab pegol (Cimzia), golimumab (Simponi), guselkumab (Tremfya), inebilizumab-cdon (Uplizna), risankizumab-rzaa (Skyrizi), sarilumab (Kevzara), satralizumab-mwge (Enspryng), tildrakizumab-asmn (Ilumya), tofacitinib (Xeljanz XR), and vedolizumab (Entyvio) in pediatric patients have not been established.

Inhibition of TNFα during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants. Likewise, safety of live vaccines in infants exposed *in utero* to abatacept (Orencia) is unknown; therefore, consider risk and benefits prior to vaccinating such infants.

Pregnancy

Rilonacept is Pregnancy Category C. Cases of agranulocytosis have been reported in infants exposed to infliximab *in utero*. There are insufficient or no available human data on adalimumab-atto (Amjevita), abrocitinib (Cibinqo), baricitinib (Olumiant), brodalumab (Siliq), guselkumab (Tremfya), infliximab-axxq (Avsola), infliximab-abda (Renflexis), ixekizumab (Taltz), risankizumab-rzaa (Skyrizi), sarilumab (Kevzara), tildrakizumab-asmn (Ilumya), and upadacitinib (Rinvoq) for use in pregnant women to inform users of a drug-associated risk. Based on nonhuman data, upadacitinib may cause embryo-fetal harm when administered during pregnancy; a pregnancy test should be performed prior to starting upadacitinib in females of reproductive potential and effective contraception should be used during treatment and for 4 weeks after the last dose. Previously, adalimumab (Humira), anakinra, certolizumab pegol, etanercept, golimumab, infliximab (Remicade), infliximab-dyyb (Inflectra), secukinumab, and ustekinumab were classified as Pregnancy Category B; however, their labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) and now contains a description of the risk. Data are not sufficient on the use of most of these agents during pregnancy to inform of the risks of major birth defects or other adverse pregnancy outcomes. Data are currently unavailable to determine the drug-associated risk of inebilizumab-cdon (Uplizna) use in pregnancy; however, it may result in fetal risk when administered to a pregnant woman and they should be advised to use contraception during treatment and for at least 6 months after the last infusion. Data for satralizumab-mwge (Enspryng) in pregnancy are inadequate to advise of maternal or fetal risk. However, monoclonal antibodies can be transferred

through the placenta, especially in the third trimester of pregnancy. As a result, consideration should be given to the risks versus benefits before administration of live or live-attenuated vaccines to infants with exposure to satralizumab-mwge *in utero*.

Clinical data available with adalimumab from the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Humira Pregnancy Registry in pregnant women with RA or CD showed a rate of 10% for major birth defects with first trimester use of adalimumab versus 7.5% for major birth defects in the disease-matched comparison cohort. Despite this difference, there was a lack of a pattern in major birth defects and difference exposure between the groups. In addition, data from available observational studies in pregnant women have shown no increased risk of major malformations among live births; however, findings on other fetal or maternal outcomes have not been consistent across different studies. Monoclonal antibodies are transported across the placenta during the third trimester of pregnancy; this may affect immune response in exposed infants. Notably, certolizumab pegol plasma concentrations evaluated from 2 studies on use during the third trimester of pregnancy demonstrated that placental transfer of certolizumab pegol was negligible or low in most infants at birth (and low in others). Abatacept, apremilast, canakinumab, tocilizumab, tofacitinib, and vedolizumab were classified previously as Pregnancy Category C; however, their labeling also was updated and now contains a description of the risk, including a statement that data are insufficient to inform of a drug-related risk.

Hepatic/Renal Impairment

Anakinra is substantially excreted by the kidneys. Consider every other day administration in patients with severe renal insufficiency or end stage renal disease (creatinine clearance [CrCl] < 30 mL/min).

The dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment. No dose adjustment is required in patients with mild to moderate renal impairment.

Abrocitinib and baricitinib are not recommended for use in patients with severe hepatic impairment or those with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^3). A dose adjustment is recommended in patients with moderate renal impairment (eGFR, 30 to 60 mL/min/1.73 m^3).

No dose adjustment of sarilumab (Kevzara) is required for patients with mild to moderate renal impairment, but its use has not been assessed in patients with severe renal impairment, hepatic impairment, or in patients with positive hepatitis B or C serology.

Tofacitinib dose should not exceed 5 mg once daily as the immediate-release formulation in RA and PsA patients with moderate hepatic impairment and half of the normal recommended dose (5 mg twice daily or 5 mg once daily) in UC patients with moderate hepatic impairment. Tofacitinib is not recommended in severe hepatic impairment. Tofacitinib dose should not exceed 5 mg once daily in patients with RA or PsA and half of the normally recommended dose (5 mg twice daily or 5 mg once daily) as the immediate-release formulation in patients with moderate or severe renal impairment (including those undergoing hemodialysis; additional details on use in patients with hemodialysis are provided in the prescribing information). The extended-release formulation should not be used in these populations.

No dose adjustment of upadacitinib (Rinvoq) is required in patients with renal impairment when used for AS, RA, PsA, or nr-axSpA. A maximum dose of 15 mg once daily should be used in patients with severe renal impairment (eGFR, 15 to 30 mL/min/1.73 m^2) being treated for atopic dermatitis. In patients with severe renal impairment or mild to moderate hepatic impairment (Child-Pugh A or B) who are treated for UC, the recommended induction dose is 30 mg once daily and the recommended maintenance dose is 15

mg once daily. Upadacitinib has not been studied in end stage renal disease (ESRD); use in patients with ESRD and either UC or atopic dermatitis is not recommended. No dosage adjustments are recommended in patients with mild to moderate hepatic impairment (Child-Pugh A or B) when used to treat RA, AS, PsA, atopic dermatitis, or nr-axSpA.; it is not recommended in those with severe hepatic impairment (Child-Pugh C).

Other

The drug exposure of abrocitinib is increased in patients who are poor metabolizers of CYP2C19 compared to normal metabolizers due to reduced metabolic clearance. Dosage reduction of abrocitinib is recommended in patients who are known or suspected poor CYP2C19 metabolizers.

There have been reports of hypoglycemia following initiation of etanercept (Enbrel) therapy in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

A higher rate of serious infections and malignancies occurred in patients ≥ 65 years of age taking 30 mg of upadacitinib for the treatment of atopic dermatitis compared to younger populations or those treated with a dose of 15 mg.

DOSAGES[323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353]

<table>
<tr><th>Drug</th><th>Dose</th><th>Availability</th></tr>
<tr><td colspan="3">Anti-TNF Biologics</td></tr>
<tr><td>adalimumab (Humira)</td><td>RA, PsA, and AS: 40 mg SC every other week; methotrexate, glucocorticoids, salicylates, NSAIDs, analgesics, or other DMARDs may be continued
In RA, some patients not taking methotrexate may benefit from increasing the dosing frequency to 40 mg every week or 80 mg every other week
PSO and uveitis (adults): 80 mg SC initially (day 1) followed by 40 mg one week later (day 8) then 40 mg every other week starting on day 22
CD (adults and pediatrics ≥ 40 kg): 160 mg SC (given in 1 day or split over 2 consecutive days) once followed by 80 mg 2 weeks later (day 15), then 40 mg every other week beginning at week 4 (day 29)
CD (pediatrics 17 to < 40 kg): 80 mg SC once followed by 40 mg 2 weeks later (day 15), then 20 mg every other week beginning at week 4 (day 29)
UC (adults): Initial dose: 160 mg SC (given in 1 day or split over 2 consecutive days) followed by a second dose of 80 mg 2 weeks later (day 15)
Maintenance dose: 2 weeks later (day 29), begin 40 mg every other week; only continue in patients with UC who have evidence of clinical remission by 8 weeks (day 57) of therapy
UC (ages 5 to 17 years): 20 kg to < 40 kg: 80 mg SC on day 1, 40 mg on days 8 and 15, then 40 mg every other week or 20 mg every week starting on day 29
≥ 40 kg: 160 mg SC on day 1 (single dose or split over 2 consecutive days), 80 mg on days 8 and 15, then 80 mg every other week or 40 mg every week starting on day 29
JIA or pediatric uveitis (ages 2 to 17 years):
<table><tr><th>Body weight</th><th>Dose</th></tr><tr><td>10 kg to < 15 kg</td><td>10 mg every other week</td></tr><tr><td>15 kg to < 30 kg</td><td>20 mg every other week</td></tr><tr><td>≥ 30 kg</td><td>40 mg every other week</td></tr></table>
HS (adults and adolescents ≥ 60 kg): Initial dose: 160 mg SC (given in 1 day or split over 2 consecutive days) followed by a second dose of 80 mg 2 weeks later (day 15)
Maintenance dose: 2 weeks later (day 29), begin 40 mg weekly or 80 mg every other week
HS (adolescents 30 to < 60 kg): Initial dose: 80 mg followed by a second dose of 40 mg 1 week later (day 8)
Maintenance dose: 2 weeks later (day 21), begin 40 mg every other week</td><td>Prefilled syringes in a carton of 2 syringes:*
10 mg/0.1 mL, 20 mg/0.2 mL, 40 mg/0.4 mL, 40 mg/0.8 mL
Single-use, pre-filled pens in a carton of 2 pens:*
40 mg/0.4 mL, 40 mg/0.8 mL, 80 mg/0.8 mL
Psoriasis/Uveitis/Adolescent HS Starter Packages (prefilled pens):*
4 x 40 mg/0.8 mL, 80 mg/0.8 mL plus 2 x 40 mg/0.4 mL
Pediatric Crohn’s Disease Starter Packages (prefilled syringes):*
3 x 80 mg/0.8 mL; 1 x 80 mg/0.8 mL plus 1 x 40 mg/0.4 mL
Crohn’s Disease/ Ulcerative Colitis/ Hidradenitis Suppurativa Starter Packages (prefilled pens):*
6 x 40 mg/0.8 mL, 3 x 80 mg/0.8 mL
Pediatric Ulcerative Colitis Starter Packages (prefilled pens):* 4 x 80 mg/0.8 mL
Products in the following strengths are considered citrate-free:
10 mg/0.1 mL, 20 mg/0.2 mL, 40 mg/0.4 mL, and 80 mg/0.8 mL
Products in the following strengths may contain latex in the needle cover:
40 mg/0.8 mL
All products are preservative free</td></tr>
</table>

IV = intravenous; SC = subcutaneous

*May be administered by patient or caregiver after proper training by a healthcare professional.

Dosages (continued)

<table>
<tr><th>Drug</th><th>Dose</th><th>Availability</th></tr>
<tr><td colspan="3">Anti-TNF Biologics (continued)</td></tr>
<tr><td>adalimumab-atto
(Amjevita)</td><td>RA, PsA, and AS: 40 mg SC every other week; methotrexate, glucocorticoids, salicylates, NSAIDs, analgesics, or other DMARDs may be continued
In RA, some patients not taking methotrexate may benefit from increasing the dosing frequency to 40 mg every week or 80 mg every other week
PSO: 80 mg SC initially (day 1) followed by 40 mg one week later (day 8) then 40 mg every other week starting on day 22. Use beyond 1 year has not been evaluated in controlled trials.
CD (adults and pediatrics ≥ 40 kg): 160 mg SC (given in 1 day or split over 2 consecutive days) once, followed by 80 mg 2 weeks later (day 15), then 40 mg every other week beginning at week 4 (day 29)
CD (pediatrics 17 to < 40 kg): 80 mg SC once followed by 40 mg 2 weeks later (day 15), then 20 mg every other week beginning at week 4 (day 29)
UC (adults): Initial dose: 160 mg SC (given in 1 day or split over 2 consecutive days) followed by a second dose of 80 mg 2 weeks later (day 15)
Maintenance dose: 2 weeks later (day 29), begin 40 mg every other week; only continue in patients with UC who have evidence of clinical remission by 8 weeks (day 57) of therapy
JIA (ages 2 to 17 years):
<table><tr><th>Body weight</th><th>Dose</th></tr><tr><td>15 kg to < 30 kg</td><td>20 mg every other week</td></tr><tr><td>≥ 30 kg</td><td>40 mg every other week</td></tr></table>No dosage form allows for use of adalimumab-atto in patients < 15 kg</td><td>Single-use, prefilled syringe: 20 mg/0.4 mL (1 unit per carton), 40 mg/0.8 mL (1 and 2 units per carton)
Single-use, prefilled SureClick™ autoinjector: 40 mg/0.8 mL (1 and 2 units per carton)
All products are preservative free</td></tr>
<tr><td>certolizumab pegol
(Cimzia)</td><td>CD: 400 mg SC initially (given as 2 SC injections of 200 mg) and at weeks 2 and 4; in patients who obtain a clinical response, the recommended maintenance dose is 400 mg SC every 4 weeks
RA: 400 mg SC initially (given as 2 SC injections of 200 mg) and at weeks 2 and 4, followed by 200 mg every 2 weeks
For maintenance dosing, 400 mg every four weeks may be considered
PsA, AS, and nr-axSpA: 400 mg (given as 2 SC injections of 200 mg) initially and at weeks 2 and 4, followed by 200 SC mg every 2 weeks or 400 mg SC every 4 weeks
Plaque psoriasis: 400 mg (2 x 200 mg) SC every other week; for some patients (body weight ≤ 90 kg), a dose of 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week may be considered</td><td>Vial kit: two 200 mg vials of lyophilized powder for reconstitution with 1 mL diluent and needles/syringes
Starter kit:*
six 200 mg/mL prefilled syringes
Syringe kit:*
two 200 mg/mL prefilled syringes
Prefilled syringe contains latex-derivative; use caution in latex-sensitive patients</td></tr>
</table>

IV = intravenous; SC = subcutaneous

* May be administered by patient or caregiver after proper training by a healthcare professional.

Dosages (continued)

Drug	Dose	Availability
Anti-TNF Biologics *(continued)*		
etanercept (Enbrel)	**RA, PsA, AS:** 50 mg SC once weekly; methotrexate, glucocorticoids, salicylates, NSAIDs or analgesics may be continued **Plaque psoriasis in adults:** 50 mg SC twice weekly for 3 months followed by 50 mg weekly **JIA and plaque psoriasis in pediatrics**: Patients weighing ≥ 63 kg: 50 mg SC given once weekly; patients weighing < 63 kg: 8 mg/kg weekly with a maximum of 50 mg per week; higher doses of etanercept have not been studied in the pediatric population Glucocorticoids, NSAIDS, or analgesics may be continued in JIA	Prefilled syringe:* 25 mg/0.5 mL, 50 mg/1 mL Prefilled SureClick auto-injector:* 50 mg/1 mL Prefilled Mini™ single-dose cartridge for use with AutoTouch™ and AutoTouch Connect™ reusable auto-injectors:* 50 mg/1 mL Multidose vial kit:* 25 mg with 1 mL diluent Single-dose vial:* 25 mg/0.5 mL
golimumab (SC) (Simponi)	**RA, PsA, AS:** 50 mg SC once monthly For RA, give in combination with methotrexate For PsA or AS, may be given with or without methotrexate or other non-biologic DMARDs Corticosteroids, non-biologic DMARDs, and/or NSAIDs may be continued **UC:** 200 mg SC at week 0, followed by 100 mg SC at week 2 and then 100 mg SC every 4 weeks	Prefilled syringe for SC injection:* 50 mg/0.5 mL, 100 mg/1 mL SmartJect® auto-injector† for SC injection (pen):* 50 mg/0.5 mL, 100 mg/1 mL
golimumab (IV) (Simponi Aria)	**RA, PsA (adults), AS**: 2 mg/kg as an IV infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter For RA, give in combination with methotrexate For PsA or AS, may be given with or without methotrexate or other non-biologic DMARDs Corticosteroids, non-biologic DMARDs, and/or NSAIDs may be continued **PsA (pediatrics), pJIA**: 80 mg/m^2 as an IV infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter; dosing is based on body surface area (BSA)	Solution for IV infusion: 50 mg/4 mL (dilute before administration)
infliximab (Remicade)	**RA:** 3 mg/kg IV infusion, repeated at 2 and 6 weeks, then every 8 weeks; for patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks; use methotrexate in combination **AS:** 5 mg/kg IV infusion at 0, 2, and 6 weeks, then every 6 weeks **Plaque psoriasis, PsA**: 5 mg/kg IV infusion at 0, 2, and 6 weeks, then every 8 weeks thereafter May be given with or without methotrexate for PsA **CD (adults):** 5 mg/kg IV infusion given at 0, 2, and 6 weeks, then every 8 weeks; for patients who respond and then lose their response, consider increasing to 10 mg/kg **CD (pediatrics):** 5 mg/kg IV infusion at 0, 2, and 6 weeks, then every 8 weeks **UC (adults and pediatrics):** 5 mg/kg IV infusion at 0, 2, and 6 weeks, then every 8 weeks	Single-dose vial: 100 mg/20 mL; given as 2-hour infusion
infliximab-abda (Renflexis)		Single-dose vial: 100 mg/20 mL; given as 2-hour infusion
infliximab-axxq (Avsola)		Single-dose vial: 100 mg/20 mL; given as 2-hour infusion
infliximab-dyyb (Inflectra)		Single-dose vial: 100 mg/20 mL; given as 2-hour infusion

IV = intravenous; SC = subcutaneous

*May be administered by patient or caregiver after proper training by a healthcare professional.

† The SmartJect autoinjector has specific instructions. Patients are instructed not to use the SmartJect autoinjector without training from a health care professional.

Dosages (continued)

<table>
<tr><th>Drug</th><th>Dose</th><th>Availability</th></tr>
<tr><td colspan="3">Other Biologic Agents</td></tr>
<tr><td>abatacept
(Orencia)</td><td>RA, PsA: IV infusion
IV dose based on body weight given over 30 minutes at 0, 2, and 4 weeks, then every 4 weeks thereafter
<table>
<tr><th>Body weight</th><th>IV Dose</th></tr>
<tr><td>< 60 kg</td><td>500 mg</td></tr>
<tr><td>60-100 kg</td><td>750 mg</td></tr>
<tr><td>> 100 kg</td><td>1,000 mg</td></tr>
</table>
RA: SC injection
Following a single IV loading dose, the first dose of 125 mg SC should be given within 1 day; 125 mg SC is given weekly thereafter
SC therapy may be initiated without the IV loading dose; If transitioning from IV therapy to SC, the first SC dose may be given instead of the next IV dose
PsA: SC injection
125 mg SC weekly; SC therapy may be initiated without the IV loading dose; if transitioning from IV therapy to SC, the first SC dose may be given instead of the next IV dose
JIA: IV infusion
Pediatric patients < 75 kg receive 10 mg/kg IV based on the patient's body weight; pediatric patients weighing > 75 kg should be administered abatacept at the adult dose, not to exceed 1,000 mg; IV dosing has not been studied in patients < 6 years of age
JIA: SC injection
SC therapy may be initiated without the IV loading dose; once weekly dosing (ClickJect formulation has not been evaluated in patients under the age of 18 years)
<table>
<tr><th>Body weight</th><th>SC Dose</th></tr>
<tr><td>10 to < 25 kg</td><td>50 mg</td></tr>
<tr><td>25 to < 50 kg</td><td>87.5 mg</td></tr>
<tr><td>≥ 50 kg</td><td>125 mg</td></tr>
</table></td><td>Single-dose vial:
250 mg/15 mL

Prefilled syringe:*
50 mg/0.4 mL,
87.5 mg/0.7 mL,
125 mg/mL for SC injection

Prefilled ClickJect™ autoinjector:*
125 mg/mL for SC injection</td></tr>
<tr><td>anakinra
(Kineret)</td><td>RA: 100 mg SC daily
Consider 100 mg every other day for RA patients who have severe renal insufficiency or end stage renal disease (creatinine clearance < 30 mL/min)
CAPS (NOMID): initiate at 1 to 2 mg/kg daily; adjust in increments of 0.5 to 1 mg/kg to a maximum of 8 mg/kg to control active inflammation; dose may be divided into twice daily administrations
DIRA: initiate at 1 to 2 mg/kg daily; adjust in increments of 0.5 to 1 mg/kg to a maximum of 8 mg/kg per day to control active inflammation</td><td>Prefilled syringe:*
100 mg/0.67 mL

Graduated syringe allows for doses between 20 and 100 mg</td></tr>
<tr><td>brodalumab
(Siliq)</td><td>Plaque psoriasis: 210 mg SC at week 0, 1, and 2 and then every 2 weeks thereafter; if an adequate response is not achieved after 12 to 16 weeks of treatment, consider discontinuing therapy (treatment beyond 16 weeks in those with an inadequate response is not likely to result in greater success)</td><td>Prefilled syringe:*
210 mg/ 1.5 mL</td></tr>
</table>

IV = intravenous; SC = subcutaneous

* May be administered by the patient or caregiver after proper training by a healthcare professional.

Dosages (continued)

Drug	Dose	Availability
Other Biologic Agents *(continued)*		
canakinumab (Ilaris)	**CAPS:** 150 mg SC for patients with body weight greater than 40 kg ▪ 2 mg/kg SC for patients with body weight ≥ 15 kg and ≤ 40 kg ▪ 3 mg/kg SC for patients 15 to 40 kg with an inadequate response ▪ All CAPS doses should be administered every 8 weeks **TRAPS/HIDS/MKD/FMF:** 150 mg SC for patients with body weight greater than 40 kg; dose may be increased to 300 mg/dose in response is inadequate ▪ 2 mg/kg SC for patients with body weight ≤ 40 kg; dose may be increased to 4 mg/kg/dose in response is inadequate All TRAPS/HIDS/MKD/FMF doses should be administered every 4 weeks **Still's disease (sJIA and AOSD):** 4 mg/kg (maximum, 300 mg) SC for patients with body weight ≥ 7.5 kg; all doses should be administered every 4 weeks	Solution for injection: 150 mg single-use vial, preservative-free
guselkumab (Tremfya)	**Plaque psoriasis and PsA:** 100 mg SC at week 0, 4, and every 8 weeks thereafter For PsA, may be administered alone or in combination with a conventional DMARD	Prefilled syringe:* 100 mg/mL Prefilled One-Press® patient-controlled injector:* 100 mg/mL
inebilizumab-cdon (Uplizna)	**NMOSD:** 300 mg IV infusion, followed by a second 300 mg IV infusion 2 weeks later, and then a third 300 mg IV infusion 6 months from the first infusion and every 6 months thereafter; each infusion should be administered over approximately 90 minutes Pre-medication with a corticosteroid, an antihistamine, and an antipyretic is recommended 30 to 60 minutes prior to each dose to reduce the likelihood and severity of infusion reactions; patients should be monitored for infusion reactions during and for a minimum of 1 hour following the infusion	Solution for injection: 100 mg/10 mL single-dose vial
ixekizumab (Taltz)	**AS and PsA:** 160 mg (two 80 mg injections) SC at week 0, and 80 mg SC every 4 weeks thereafter For PsA, may be administered alone or in combination with a conventional DMARD; for patients with coexistent moderate to severe plaque psoriasis, use the dosing regimen for plaque psoriasis **Nr-axSpA:** 80 mg SC every 4 weeks **Plaque psoriasis (adults):** 160 mg (two 80 mg SC injections) at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks thereafter **Plaque psoriasis (pediatrics):** ▪ > 50 kg: 160 mg (two 80 mg injections) SC at week 0, and 80 mg SC every 4 weeks thereafter ▪ 25 to 50 kg: 80 mg SC at week 0, and 40 mg SC every 4 weeks thereafter ▪ < 25 kg: 40 mg SC at week 0, and 20 mg SC every 4 weeks thereafter ▪ Doses < 80 mg (20 mg, 40 mg) must be prepared and administered by a qualified healthcare professional using the 80 mg prefilled syringe	Prefilled syringe:* 80 mg/mL Prefilled auto-injector:* 80 mg/mL (in packs of 1, 2, or 3 autoinjectors)

IV = intravenous; SC = subcutaneous

* May be administered by the patient or caregiver after proper training by a healthcare professional.

Dosages (continued)

Drug	Dose	Availability
Other Biologic Agents *(continued)*		
rilonacept (Arcalyst)	**CAPS (including FCAS and MWS) and RP:** ▪ Adults: Loading dose: 320 mg SC (two 160 mg injections at different sites); maintenance dose: 160 mg SC weekly ▪ Pediatrics (12 to 17 years): Loading dose: 4.4 mg/kg SC (maximum 320 mg); maintenance dose: 2.2 mg/kg (maximum 160 mg) SC weekly **DIRA:** Adults and pediatrics ≥ 10 kg: loading dose of 4.4 mg/kg (maximum 320 mg) as 1 or 2 SC injections (maximum 2 mL/injection) once weekly	Single-use vial:* 220 mg
risankizumab-rzaa (Skyrizi)	**CD:** for induction therapy, 600 mg via IV infusion over ≥ 1 hour at weeks 0, 4, and 8; for maintenance*, 360 mg SC at week 12 and every 8 weeks thereafter. **PsA, Plaque psoriasis:** 150 mg (1 x 150 mg or 2 x 75 mg syringes) SC at weeks 0 and 4 and every 12 weeks thereafter In PsA, it may be used alone or in combination with nonbiologic DMARDs	Prefilled syringe:* 75 mg/0.83 mL in kits of 1 or 2 syringes (150 mg), 150 mg/mL Prefilled pen:* 150 mg/mL Single-dose prefilled cartridge: 360 mg/2.4 mL for use with the On-Body-Injector* Vial: 600 mg/10 mL SDV
sarilumab (Kevzara)	**RA:** 200 mg SC every 2 weeks; may be used as monotherapy or in combination with methotrexate Should not be used in those with an ANC < 2,000/mm^3, platelets < 150,000/mm^3, or liver transaminases above 1.5 times the ULN The dose should be held if the ANC 500 to 1,000/mm^3, or platelets 50,000 to 100,000 cells/mm^3, or ALT > 3 to ≤ 5 times ULN; once the abnormal laboratory values resolve, therapy may be resumed at a reduced dosage of 150 mg every 2 weeks, then may be increased to 200 mg every 2 weeks as clinically appropriate; dose should also be held if a serious infection develops until the infection resolves Discontinue therapy if ANC < 500/mm^3, ALT > 5 times ULN, or platelet count < 50,000 cells/mm^3 that is confirmed by a repeat test	Prefilled pen:* 150 mg/1.14 mL, 200 mg/1.14 mL Prefilled syringe:* 150 mg/1.14 mL, 200 mg/1.14 mL
satralizumab-mwge (Enspryng)	**NMOSD:** 120 mg SC (to abdomen or thigh) at weeks 0, 2, and 4, followed by a maintenance dose of 120 mg every 4 weeks	Syringe: 120 mg/mL*

IV = intravenous; SC = subcutaneous

* May be administered by the patient or caregiver after proper training by a healthcare professional.

Dosages (continued)

Drug	Dose	Availability
Other Biologic Agents *(continued)*		
secukinumab (Cosentyx)	**Plaque psoriasis (adults):** 300 mg SC at 0, 1, 2, 3, and 4 weeks followed by 300 mg every 4 weeks For some patients, a dose of 150 mg may be acceptable in lieu of 300 mg **Plaque psoriasis (pediatrics ≥ 6 years old):** dose of 75 mg for patients weighing < 50 kg or 150 mg if they weigh ≥ 50 kg SC at 0, 1, 2, 3, and 4 weeks, followed by every 4 weeks thereafter **PsA (adults):** 150 mg SC at 0, 1, 2, 3, and 4 weeks, followed by 150 mg SC every 4 weeks (with loading dose) or 150 mg SC every 4 weeks (without loading dose) For some patients, a dose of 300 mg may be used if response to 150 mg is insufficient Patients with both psoriasis and psoriatic arthritis should receive the psoriasis dosing **Enthesitis-Related Arthritis (adults and pediatrics ≥ 4 years old), PsA (pediatrics ≥ 2 years old):** 75 mg (≥ 15 kg to < 50 kg) or 150 mg (≥ 50 kg) at 0, 1, 2, 3, and 4 weeks and every 4 weeks thereafter **AS, nr-axSpA:** 150 mg SC at 0, 1, 2, 3, and 4 weeks followed by 150 mg SC every 4 weeks (with loading dose) or 150 mg SC every 4 weeks (without loading dose) 300 mg every 4 weeks may be considered if symptoms persist with the 150 mg dosage regimen in AS only	Single-use Sensoready® pen:* 150 mg/mL in packs 1 or 2 pens (300 mg) Single-use prefilled syringe:* 75 mg/0.5 mL solution, 150 mg/mL solution in packs of 1 or 2 syringes (300 mg)
tildrakizumab-asmn (Ilumya)	**Plaque psoriasis:** 100 mg SC at weeks 0 and 4, and every 12 weeks thereafter by a healthcare provider	Single-dose prefilled syringe: 100 mg/mL

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* May be administered by the patient or caregiver after proper training by a healthcare professional.

Dosages (continued)

Drug	Dose	Availability
Other Biologic Agents *(continued)*		
tocilizumab (Actemra)	**RA (adults):** IV infusion starting dose 4 mg/kg 1-hour IV infusion every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response; do not exceed 800 mg per infusion **RA (adults):** SC injection In patients < 100 kg starting dose is 162 mg SC every other week, followed by an increase to every week based on clinical response In patients ≥ 100 kg, 162 mg SC every week When transitioning from IV to SC, administer the first SC dose instead of the next scheduled IV dose May be used as monotherapy or concomitantly with methotrexate or other DMARDs **Polyarticular JIA (ages 2 to 17 years):** *IV administration* for patients weighing < 30 kg: 10 mg/kg IV over 1 hour every 4 weeks; for patients weighing ≥ 30 kg: 8 mg/kg IV over 1 hour every 4 weeks *SC administration* for patients < 30 kg: 162 mg SC every 3 weeks; for patients weighing ≥ 30 kg: 162 mg SC every 2 weeks May give alone or in combination with methotrexate; when transitioning from IV to SC administration, administer the first SC dose instead of the next scheduled IV dose **Systemic JIA (ages 2 to 17 years):** *IV administration* for patients weighing < 30 kg: 12 mg/kg IV over 1 hour every 2 weeks; for patients weighing ≥ 30 kg: 8 mg/kg IV over 1 hour every 2 weeks *SC administration* for patients < 30 kg: 162 mg SC every 2 weeks; for patients weighing ≥ 30 kg: 162 mg SC every week May give alone or in combination with methotrexate; when transitioning from IV to SC administration, administer the first SC dose instead of the next scheduled IV dose **GCA:** *IV administration:* 6 mg/kg IV over 60 minutes every 4 weeks in combination with a tapering course of glucocorticoids; may be used alone following glucocorticoid discontinuation; do not exceed 600 mg per infusion *SC administration:* 162 mg SC once weekly, in combination with a tapering course of glucocorticoids; a dose of 162 mg SC given once every other week, in combination with a tapering course of glucocorticoids may be considered; may be used as monotherapy following glucocorticoid discontinuation; when transitioning from IV administration, give the first SC dose at the next scheduled IV dose **CRS:** 12 mg/kg IV over 1 hour in patients weighing < 30 kg and 8 mg/kg IV over 1 hour in patients weighing ≥ 30 kg; if no clinical improvement occurs after the first dose, up to 3 additional doses may be administered; the interval between doses should be ≥ 8 hours; may administer alone or in combination with corticosteroids **SSc-ILD:** 162 mg SC once weekly See prescribing information for details on dose modifications for liver enzyme elevation, low absolute neutrophil count (ANC), low platelet count, or infection; weight-based dosing for JIA should not be changed based on a single visit measurement, as weight may fluctuate	Single-dose vials: 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL Prefilled syringe:‡ 162 mg/0.9 mL ACTPen™ prefilled autoinjector:‡ 162 mg/0.9 mL

IV = intravenous; SC = subcutaneous

* May be administered by the patient or caregiver after proper training by a healthcare professional.

‡ May be administered by the patient or caregiver after proper training by a healthcare professional (SC formulation only).

Dosages (continued)

Drug	Dose	Availability
Other Biologic Agents *(continued)*		
ustekinumab (Stelara)	**CD and UC:** Initial dosing; dose is based on body weight; given as a single dose ▪ ≤ 55 kg: 260 mg IV (2 vials) ▪ > 55 to 85 kg: 390 mg IV (3 vials) ▪ > 85 kg: 520 mg IV (4 vials) Maintenance dose (CD and UC): 90 mg SC beginning 8 weeks after the initial IV dose and then 90 mg SC every 8 weeks thereafter **Plaque psoriasis (adults):** Dose is based on body weight; given under supervision by a physician and administered by a health care professional or by self-administration after training, if deemed appropriate For patients weighing ≤ 100 kg, the initial recommended dose is 45 mg SC followed by another dose 4 weeks later, followed by 45 mg SC every 12 weeks For patients weighing ≥ 100 kg, the recommended dose is 90 mg SC initially, followed by another dose 4 weeks later, followed by 90 mg SC every 12 weeks **Plaque psoriasis (pediatrics):** Administered on weeks 0, 4, and every 12 weeks thereafter; dose is based on body weight; given under supervision by a physician and administered by a health care professional or by self-administration after training, if deemed appropriate For patients weighing < 60 kg, the recommended dose is 0.75 mg/kg (specific kg dosing detailed in the labeling) SC; for patients weighing 60 kg to 100 kg, the recommended dose is 45 mg SC; for patients weighing ≥ 100 kg, the recommended dose is 90 mg SC **PsA (adults):** 45 mg SC followed by another dose 4 weeks later, followed by 45 mg every 12 weeks, for patients with co-existent moderate to severe plaque psoriasis weighing > 100 kg, the recommended dose is 90 mg SC initially, followed by another dose 4 weeks later, followed by 90 mg SC every 12 weeks **PsA (pediatrics):** Administered at weeks 0 and 4, then every 12 weeks thereafter; dose is 0.75 mg/kg in patients weighing < 60kg, 45 mg for those ≥ 60 kg, and 90 mg in those weighing > 100 kg with co-existing moderate to severe plaque psoriasis	Single-dose vials:* 45 mg/0.5 mL, 130 mg/26 mL Prefilled syringe:* 45 mg/0.5 mL, 90 mg/1 mL
vedolizumab (Entyvio)	**CD and UC:** 300 mg administered by a healthcare professional by IV infusion at weeks 0, 2, and 6 and then every 8 weeks thereafter	Single-use vial: 300 mg

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* May be administered by the patient or caregiver after proper training by a healthcare professional.

Dosages (continued)

Drug	Dose	Availability
Non-biologic Agents		
abrocitinib (Cibinqo)	**AD**: 100 mg orally once daily; may increase to 200 mg once daily if an adequate response is not achieved after 12 weeks; discontinue if an inadequate response is not seen with 200 mg once daily Recommended dosage is 50 mg once daily in patients with moderate renal impairment (eGFR 30 to 59 mL/min) or known or suspected CYP2C19 poor metabolizers; if an adequate response is not achieved after 12 weeks, may increase dose to 100 mg once daily; discontinue if an inadequate response is not seen with 100 mcg once daily May be used with or without a topical corticosteroid	Tablets: 50 mg, 100 mg, 200 mg
apremilast (Otezla)	**Plaque psoriasis, PsA, and Behçet's disease:** Initial titration: day 1: 10 mg in morning, day 2: 10 mg in morning and 10 mg in evening, day 3: 10 mg in morning and 20 mg in evening, day 4: 20 mg in morning and 20 mg in evening, day 5: 20 mg in morning and 30 mg in evening Maintenance Dose: 30 mg twice daily (beginning on day 6)	Tablet: 30 mg Starter Pack (28 day): 10 mg, 20 mg, and 30 mg tablets
baricitinib (Olumiant)	**Alopecia Areata:** 2 mg orally once daily, with or without food; increase to 4 mg once daily if needed; For patients with nearly complete scalp hair loss, consider 4 mg once daily; once an adequate response is achieved with 4 mg, decrease dose to 2 mg once daily **RA:** 2 mg taken orally once daily, with or without food; dose modification of 1 mg once daily when used with strong OAT3 inhibitors or in patients with moderate renal impairment May be used as monotherapy or given in combination with methotrexate or other non-biologic DMARD therapy	Tablet: 1 mg, 2 mg, 4 mg

Dosages (continued)

Drug	Dose	Availability
Non-biologic Agents *(continued)*		
tofacitinib (Xeljanz, Xeljanz XR)	**AS, RA, PsA:** 5 mg immediate-release (IR) orally twice daily or 11 mg extended-release (ER) once daily with or without food May be used as monotherapy or in combination with methotrexate or other nonbiologic (DMARDs); PsA in combination with nonbiologic DMARDs **pJIA:** dosing is weight-based: 10 kg to < 20 kg: 3.2 mg twice daily 20 kg to < 40 kg: 4 mg twice daily ≥ 40 kg: 5 mg twice daily **UC:** 10 mg immediate-release twice daily (IR) or 22 mg once daily extended-release (ER) for at least 8 weeks (induction), followed by 5 twice daily (IR) or 11 mg once daily (ER) (maintenance dosing) based on therapeutic response, using lowest dose to maintain response; if adequate therapeutic benefit after 16 weeks of treatment using 10 mg twice daily (IR) or 22 mg once daily (ER) is not achieved, discontinue tofacitinib; during maintenance, 10 mg twice daily should be limited to those with loss of response, used for the shortest duration, and only used after careful consideration of risks and benefits for the patient No dose adjustments or tapering/titration is required when switching from the IR to the ER formulation; the ER dose may be started once daily after discontinuation of the IR formulation when the next dose is due; the ER formulation is not interchangeable or substitutable with the oral solution Dose modifications: dose interruption is recommended for management of lymphopenia, neutropenia, and anemia with specific details in the prescribing information; dosage should be reduced to 5 mg once daily in AS, PsA, and RA patients and a 50% reduction in UC patients (5 mg once or twice daily [IR] or 11 mg once daily [ER]) with moderate or severe renal insufficiency, moderate hepatic impairment, or those receiving potent or multiple moderate inhibitors of CYP3A4 and a strong CYP2C19; the ER formulation should not be used when dose modifications are required, with the exception of its use for UC; for pJIA, doses should be administered once daily rather than twice daily in patients with moderate or severe renal insufficiency, moderate hepatic impairment, or those receiving potent or multiple moderate inhibitors of CYP3A4 and a strong CYP2C19; see prescribing information for full details on dose modifications	Tablet: 5 mg, 10 mg Extended-release tablet: 11 mg, 22 mg Oral solution: 1 mg/mL
upadacitinib (Rinvoq)	**AS, PsA, RA, nr-axSpA:** 15 mg once daily; may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs **AD:** ≥ 12 years to < 65 years old and ≥ 40 kg: 15 mg once daily; dose may be increased to 30 mg (use lowest effective dose) ≥ 65 years or CrCl < 30 mL/min: 15 mg once daily **UC:** 45 mg once daily for 8 weeks for induction; for maintenance, the dose is 15 mg once daily, although a dose of 30 mg may be considered for patients with refractory, severe, or extensive disease; the lowest effective dose should be used for maintenance therapy; discontinue if an adequate response is not achieved with a 30 mg maintenance dose Take orally without regard to food; swallow tablet whole; do not split, crush, or chew	Extended-release tablet: 15 mg, 30 mg, 45 mg

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Merck/Samsung Bioepis, Amgen, and Celltrion/Pfizer, the manufacturers of infliximab-abda (Renflexis), infliximab-axxq (Avsola), and infliximab-dyyb (Inflectra), respectively, conducted multiple *in vitro* analytical and non-clinical (e.g., pharmacokinetic) studies comparing their respective biosimilar products to either infliximab (Remicade) or the infliximab product marketed in Europe. These studies demonstrated that their product was highly similar to infliximab (Remicade). In addition, completed clinical studies with these agents are described below. The FDA used a composite of data to determine that infliximab-abda, infliximab-axxq (Avsola), and infliximab-dyyb are *biosimilar* to infliximab (Remicade); thus, they were approved for all eligible indications. Amgen's adalimumab-atto (Amjevita) demonstrated biosimilarity to adalimumab (Humira) based on nonclinical data (structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data), clinical immunogenicity data, and other clinical safety and effectiveness data.

Alopecia Areata

baricitinib (Olumiant)

Two randomized, double-blind, placebo-controlled trials, BRAVE-AA1 (NCT03570749) and BRAVE-AA2 (NCT03899259) evaluated baricitinib in a total of 1,200 adult male (ages 18 to 60 years) and female (ages 18 to 70 years) patients with alopecia areata.[354,355] Enrolled patients had ≥ 50% scalp hair loss as measured by the Severity of Alopecia Tool (SALT) for more than 6 months. At baseline, 53% of patients had ≥ 95% scalp hair loss, in 34% their current episode lasted ≥ 4 years, 69% had significant gaps in eyebrows or no notable eyebrow hair, and 58% had significant gaps in eyelashes or no notable eyelashes. Patients were randomized 3:2:2 to once-daily baricitinib 2 mg or 4 mg or placebo. The primary outcome was a SALT score of ≤ 20 at week 36. The primary endpoint was achieved in 22.8% and 38.8% of patients treated with baricitinib 2 mg and 4 mg, respectively, compared to 6.2% of those who received placebo in BRAVE-AA1 and 19.4%, 35.9%, and 3.3%, respectively, in BRAVE-AA2 ($p<0.001$ for each dose versus placebo in both trials).

Ankylosing spondylitis (AS)/axial spondyloarthritis (radiographic)

adalimumab (Humira)

A multicenter, randomized (2:1 ratio), double-blind, placebo-controlled study assessed the safety and efficacy of adalimumab 40 mg every other week in 315 patients with active AS.[356] Adalimumab or placebo was given for 24 weeks. At 12 weeks, the Assessment in Ankylosing Spondylitis International Working Group criteria with 20% improvement (ASAS20) was achieved in 58.2 and 20.6% for the adalimumab and placebo groups, respectively (p<0.001). The domains within the ASAS20 response criteria include measures of physical function, pain, inflammation (assessed by duration of morning stiffness), and patient's global assessment. Improvement is defined as 20% improvement and ≥ 10 units of absolute change (on a 0 to 100 scale) in each of 3 domains, with no worsening of a similar amount in the fourth domain.[357] At week 12, more patients in the adalimumab group (45.2%) had at least 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) compared to the placebo group (15.9%; p<0.001). Adalimumab-treated patients reported more adverse events (75% versus 59.8%; p<0.05). The incidence of infections was similar in both groups. A total of 255 patients (82%) entered the 2-year open-label extension study and continued on adalimumab 40 mg every other week.[358] ASAS responses were maintained; 64.5% were ASAS20 responders, and 50.6% were ASAS40 responders.

A closer evaluation of adalimumab on pain, fatigue, and morning stiffness was performed during the ATLAS (Adalimumab Trial Evaluating Long-Term Safety and Efficacy for Ankylosing Spondylitis) study.[359] Pain and fatigue were assessed by the scores of the Medical Outcomes Study Short Form-36 (SF-36) Health Survey and also by total back pain and nocturnal pain using visual analog scales. Fatigue and morning stiffness were also assessed by portions of the BASDAI. At week 12, adalimumab-treated patients experienced significant improvement compared with placebo-treated patients in the SF-36 bodily pain score (p<0.001), total back pain score (p<0.001), nocturnal pain score (p<0.001), fatigue (p<0.01), and morning stiffness (p<0.001). Treatment effects were maintained through 24-weeks of treatment. Adalimumab significantly improved patient-reported physical function and health-related quality of life in the 3-year open-label extension of the ATLAS study.[360]

In a randomized, multicenter, double-blind, placebo-controlled study, the efficacy of adalimumab and placebo were compared for reducing spinal and sacroiliac joint inflammation, as measured by magnetic resonance imaging (MRI), in 82 patients with ankylosing spondylitis.[361] Patients received adalimumab 40 mg or placebo every other week during an initial 24-week double-blind period. MRIs of both the spine and sacroiliac (SI) joints were obtained at baseline, week 12, and week 52. Spinal and SI joint inflammation were measured using the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index. The spine SPARCC score in placebo-treated patients increased by a mean of 9.4% from baseline, compared with a mean decrease of 53.6% in adalimumab-treated patients (p<0.001). The SI joint SPARCC score decreased by a mean of 12.7% from baseline in placebo-treated patients and by 52.9% in adalimumab-treated patients (p=0.017). The response in adalimumab-treated patients was maintained at week 52. Placebo-treated patients were switched to open-label adalimumab treatment at week 24 and experienced similar reductions in spinal and SI joint inflammation by week 52.

certolizumab pegol (Cimzia)

RAPID-axSpA is an ongoing multicenter, phase 3, randomized, double-blind, placebo-controlled, parallel-group trial in patients with axial spondyloarthritis (axSpA), including patients with ankylosing spondyloarthritis (AS).[362] While all patients met the criteria for axSpA, at least 50% of the patients had to

meet the modified New York (mNY) criteria for radiographic diagnosis of AS. Patients were randomized to placebo or certolizumab pegol (CZP) 400 mg SC at weeks 0, 2, and 4 (loading dose) followed by either CZP 200 mg SC every 2 weeks or CZP 400 mg every 4 weeks. The doses were administered by unblinded, trained personnel at each site. All patients received injections every 2 weeks, either CZP or placebo, to maintain blinding. Patients were stratified by prior TNF inhibitor exposure. Patients assigned to placebo who did not achieve an Assessment of Spondyloarthritis International Society 20 (ASAS20) response at weeks 14 and 16 underwent mandatory escape at week 16 and were randomized to active treatment in a double blind fashion. Clinical primary endpoint was ASA20 response at week 12, defined as an improvement of ≥ 20% and ≥ 1 unit on a 0 to 10 scale in greater than or equal to 3 of the following: Patients Global Assessment of Disease Activity (PTGADA), Pain assessment (total spinal pain on a 0 to 10 scale), Function (represented by a Bath Ankylosing Spondylitis Functional Index (BASFI), Inflammation (mean of BASDAI questions relating to morning stiffness) and no deterioration (worsening of > 20% or 1 unit on a 0 to 10 scale) in the remaining area. A total of 325 patients were randomized to 1 of the 3 treatment arms. Of these, 178 patients (54.8%) met the mNY criteria for AS. Concomitant therapy with NSAIDS and DMARDs was allowed on the trial. Improvements in ASAS20 at week 12 in the AS subpopulation were 56.9% for CZP 200 mg every 2 weeks and 64.3% for CZP 400 mg every 4 weeks compared to 36.8% for placebo ($p<0.05$). The most common infectious adverse events were nasopharyngitis (8.8% CZP versus 6.5% placebo) and upper respiratory tract infections (4% CZP versus 2.8% placebo). The most common non-infectious adverse events were headache (6.2% CZP versus 6.5% placebo) and increased blood creatine phosphokinase (5.1% CZP versus 1.9% placebo). Increases in creatine phosphokinase were transient and resolved spontaneously despite continued CZP therapy. No elevations were associated with an ischemic cardiac event or resulted in study discontinuation. Beneficial effects were reported as sustained through 4 years of treatment.[363]

etanercept (Enbrel)

A double-blind study recruited 40 patients with active ankylosing spondylitis symptoms despite standard therapy.[364] Patients were randomly assigned to receive twice-weekly SC injections of etanercept 25 mg or placebo. At 4 months, significant improvement in symptoms, as determined by the primary composite endpoint of at least a 20% improvement in 3 of 5 measures of disease activity, was observed in 80% of etanercept patients compared to 30% of placebo patients ($p=0.004$). Etanercept treatment resulted in significant improvements over baseline in 4 of the 5 measures – duration of morning stiffness, nocturnal spine pain, patient assessment of disease activity and BASFI, the BASFI ($p<0.05$ for all comparisons to placebo) – but not for the mean swollen joint score. The etanercept group also had significant improvement in many of the secondary outcome measures, including Physician's global assessment of disease activity, chest expansion, enthesis, ERS (erythrocyte sedimentation rate), and CRP (C-reactive protein). Placebo patients experienced a similar response to etanercept in an open-label, 6-month extension phase. There was no difference in the rates of adverse events between the 2 groups, nor were there any serious adverse events in either group.

Thirty patients with active ankylosing spondylitis refractory to NSAID therapy were randomized in double-blind fashion into 2 groups, receiving either etanercept 25 mg twice weekly or placebo for 6 weeks, after which both groups were treated with etanercept.[365] All patients received etanercept for a total of 12 weeks and were followed up for at least 24 weeks. At week 6, 57% of patients treated with etanercept achieved the primary endpoint of at least a 50% improvement in the BASDAI compared to 6% of the placebo-treated patients ($p=0.004$). There was ongoing improvement in all parameters in both groups throughout the period of etanercept treatment. Disease relapses occurred at an average of 6.2 weeks

after cessation of etanercept. No severe adverse events, including major infections, were observed during the trial. Four patients withdrew from the study, 3 prior to receiving study drug and 1 after receiving 1 dose.

Two hundred seventy-seven patients with moderate to severe ankylosing spondylitis were recruited into a placebo-controlled, double-blind study of etanercept.[366] Patients were randomized to receive etanercept 25 mg or placebo twice weekly for 24 weeks. By 12 weeks, ASAS20, the primary endpoint, was reached by 59% of patients in the etanercept group compared to 28% of patients in the placebo group ($p<0.0001$). This rate of response was maintained, with 57% and 22% of patients in the etanercept and placebo groups, respectively, achieving ASAS20 at the conclusion of the 24-week treatment period ($p<0.0001$). All components of the ASAS, acute-phase reactant levels, and spinal mobility measures were significantly improved ($p<0.05$ for all comparisons to placebo). Injection-site reactions, accidental injuries, and upper respiratory tract infections are the adverse events that occurred more frequently in the etanercept group. A 168-week open-label extension of the trial enrolled 257 of the 277 patients (92%) to evaluate long-term safety and efficacy of etanercept treatment in patients with ankylosing spondylitis.[367] Safety endpoints included rates of adverse events, infections, and death. Of patients who received etanercept in both the clinical trial and the open-label extension, 71% were ASAS20 responders at week 96, and 81% were responders at week 192. Placebo patients who switched to etanercept in the open-label extension showed similar patterns of efficacy maintenance. After up to 192 weeks of treatment with etanercept, the most common adverse effects were injection site reactions, headaches, and diarrhea. The rate of infections was 1.1 per patient-year, and the rate for serious infections was 0.02 per patient-year. No deaths were reported.

The EMBARK study, a randomized, double-blind clinical trial, assessed the efficacy and safety of etanercept in patients with early active nonradiographic spondyloarthritis (n=215).[368] Patients were assigned to receive double-blind etanercept 50 mg/week or placebo for 12 weeks, followed by open-label etanercept (n=205). At 12 weeks, the proportion of patients achieving ASAS40, the primary outcome, was significantly higher in the etanercept group than in the placebo group (32% versus 16%, respectively; $p=0.006$). Clinical effects were sustained through 104 weeks in the open-label phase.[369]

golimumab (Simponi)

GO-RAISE study: The safety and efficacy of golimumab were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 356 adult patients with active AS according to modified New York criteria for at least 3 months (Study AS).[370] Patients had symptoms of active disease [defined as a BASDAI ≥ 4 and VAS for total back pain of ≥ 4, on scales of 0 to 10 cm] despite current or previous NSAID therapy. Patients were excluded if they had complete ankylosis of the spine or if they were previously treated with a biologic TNF antagonist. Patients were randomly assigned to golimumab 50 mg (n=138), golimumab 100 mg (n=140), or placebo (n=78) administered SC every 4 weeks. Patients were allowed to continue stable doses of concomitant methotrexate, sulfasalazine, hydroxychloroquine, low dose corticosteroids, and/or NSAIDs during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited. The primary endpoint was the percentage of patients achieving an ASAS20 response at week 14 and was reported as 59.4% for golimumab 50 mg group, 60% for golimumab 100 mg group, and 21.8% for placebo-treated patients ($p<0.001$). Placebo-controlled efficacy data were collected and evaluated through week 24. ASAS40 response rates at week 24 were 43.5% for golimumab 50 mg group, 54.3% for golimumab 100 mg group, and 15.4% for placebo-treated group. There was no clear evidence of improved ASAS response with the higher golimumab dose group 100 mg compared to the lower golimumab dose group 50 mg. Eight golimumab-treated patients and 1 placebo-treated patient had markedly abnormal

liver enzyme values that were transient. Clinical improvements found at week 24 were continued through week 256 (5 years).[371]

golimumab (Simponi Aria)

GO-ALIVE: A multicenter, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of golimumab IV for the treatment of active AS in patients with an inadequate response or intolerance to NSAIDs (n=208).[372,373] Patients were randomized 1:1 to receive either golimumab 2 mg/kg or placebo as a 30-minute IV infusion at weeks 0, 4, and 12. Patients were allowed to continue stable doses of corticosteroids (equivalent to ≤ 10 mg of prednisone per day), hydroxychloroquine, methotrexate, sulfasalazine, and NSAIDs during the trial. The primary endpoint, the percentage of patients achieving an ASAS20 response at week 16, occurred in 73% of patients treated with golimumab compared to 26% treated with placebo (difference, 47%; 95% CI, 35 to 59; p<0.001). In addition, 41% and 14.6% achieved at least a 50% improvement in the BASDAI in those assigned golimumab and placebo, respectively (p<0.001), and mean improvement in BASFI was -2.4 in those treated with golimumab compared to -0.5 in those treated with placebo (p<0.001). Treatment with golimumab resulted in greater improvement from baseline compared with placebo on the SF-36 and health related quality of life determined by the Ankylosing Spondylitis Quality of Life questionnaire (ASQoL).

infliximab (Remicade)

In a multicenter study, 70 patients with active symptoms of ankylosing spondylitis despite therapy with NSAIDs were enrolled in a placebo-controlled, double-blinded trial of infliximab 0.5 mg/kg IV given at 0, 2, and 6 weeks.[374] The primary endpoint, a 50% improvement in BASDAI between baseline and week 12, was achieved by 53% of patients in the active therapy group and 9% in the control group (p<0.05). Significant benefit of treatment with infliximab was observed in each individual parameter of the BASDAI. Significant benefit was also observed in parameters measuring disability, spinal mobility, quality of life (QoL), and acute phase reactants. Three patients on infliximab had serious events (TB, allergic bronchial granulomatosis, transient leukopenia) and were withdrawn from the study, compared to none on placebo (p=NS). In a 12-week open-label extension, placebo patients who then received infliximab showed similar responses.

Of the 54 patients who completed the first year of this study, 52 continued to receive infliximab 5 mg/kg every 6 weeks up to week 102.[375] Forty-nine patients (71% of 69 enrolled patients and 94% of patients who started year 2) completed the study up to week 102. Improvement in signs and symptoms of ankylosing spondylitis seen during the first year of the study was sustained during the second year. Thirty (58%) patients achieved at least a 50% improvement from baseline in the BASDAI score, the primary endpoint, at week 102. Scores for other efficacy assessments were similar at weeks 54 and 102. Median CRP levels remained low at weeks 54 and 102 (3.9 and 4.3 mg/L, respectively). Side effects during the second year of the study were similar to those of the first year of treatment with infliximab.

In the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT), 357 patients with ankylosing spondylitis were randomly assigned to receive infusions of infliximab 5 mg/kg or placebo at weeks 0, 2, 6, 12, and 18.[376] At 24 weeks, 61.2% of patients in the infliximab group were ASAS20 responders compared with 19.2% of patients in the placebo group (p<0.001). Clinical benefit was observed in patients receiving infliximab as early as week 2 and was maintained over the 24-week study period. In addition, 22.4% of infliximab patients achieved partial remission. Patients receiving infliximab also showed significant improvements in the BASDAI, as well as the chest expansion and physical component summary score of the SF-36 short form health survey. Adverse events were reported by

82.2% of patients receiving infliximab and by 72% of patients receiving placebo. Most adverse events in both treatment groups were mild or moderate in severity. After 24 weeks of therapy in the above study, the placebo-treated (n=78) and the infliximab-treated (n=201) patients all received infliximab 5 mg/kg from week 24 to 96.[377] At week 102, the ASAS20 responses for the patients initially assigned to placebo (72.1%) and for patients initially in infliximab (73.9%) were similar.

infliximab-dyyb (Inflectra)

A 54-week, randomized, double-blind, parallel-group study compared European infliximab to infliximab-dyyb in 250 patients with AS.[378] Patients were randomized 1:1 to either product. Efficacy was considered a secondary objective in this study as the study was designed primarily to assess pharmacokinetics. At week 30, ASAS20 was achieved in 71% of participants using infliximab-dyyb compared to 72% using European infliximab (odds ratio [OR], 0.91 [95% CI, 0.51 to 1.62]; treatment difference using ITT population, -4% [95% CI, -16 to 8]). Overall safety findings on both products were comparable.

ixekizumab (Taltz)

Two phase 3, multinational, randomized, double-blind, placebo-controlled studies, COAST-V and COAST-W, established the safety and efficacy of ixekizumab in adults with active ankylosing spondylitis (defined as BASDAI score ≥ 4 despite NSAID, corticosteroid, or traditional DMARD treatment).[379,380,381] In COAST-W patients were required to have had treatment with ≥ 1 but not more than 2 TNF antagonists, but patients were biologic DMARD-naïve in COAST-V. In COAST-V, 341 patients were randomized 1:1:1:1 to ixekizumab 80 mg every 2 or 4 weeks (both following initial starting dose of 160 mg), placebo, or active comparator (adalimumab 40 mg every 2 weeks). In COAST-W, 316 patients were randomized 1:1:1 to ixekizumab 80 mg every 2 or 4 weeks or placebo. In both studies, at week 16, patients assigned ixekizumab continued their treatment and those randomized to other therapies were re-randomized 1:1 to ixekizumab 80 mg every 2 or 4 weeks (both following initial starting dose of 160 mg) through week 52. The primary outcome was ASAS40 in both trials. In COAST-V, ASAS40 was achieved by 48% of those treated with ixekizumab 80 mg every 4 weeks compared to 18% treated with placebo (treatment difference, 30% [95% CI, 16 to 43]; ASAS40 with adalimumab of 36%), and ASAS20 was achieved by 64% of those treated with ixekizumab 80 mg every 4 weeks compared to 40% treated with placebo (treatment difference, 24% [95% CI, 9 to 39]; ASAS40 with adalimumab of 59%). In COAST-W, ASAS40 was achieved by 25% of those treated with ixekizumab 80 mg every 4 weeks compared to 31% treated with placebo (treatment difference, 13%; 95% CI, 3 to 23), and ASAS20 was achieved by ASAS40 was achieved by 48% of those treated with ixekizumab 80 mg every 4 weeks compared to 30% treated with placebo (treatment difference, 18%; 95% CI, 6 to 31). Results in safety and efficacy were similar at 52 weeks. The ixekizumab 80 mg every 2 week dosage is not FDA-approved; therefore, results from this dosage are not reported in this review.

secukinumab (Cosentyx)

Two randomized, double-blind, placebo-controlled trials (MEASURE 1 and 2) assessed the efficacy of secukinumab for adults with AS. Patients with active disease, as defined by a BASDAI ≥ 4 despite NSAID, corticosteroid, or DMARD therapy.[382,383] Concomitant use of methotrexate (14%) or sulfasalazine (26%) were used in some patients, and approximately 33% of patients had discontinued prior treatment with a TNF antagonist due to either intolerance or lack of efficacy. MEASURE 1 (n=371) patients were randomized to IV secukinumab 10 mg/kg (unapproved dose) or placebo on weeks 0, 2, and 4, followed by either SC secukinumab 75 mg or 150 mg or placebo every 4 weeks thereafter. At week 16, the ASAS20,

the primary endpoint, were 61%, 60%, and 29% for secukinumab 150 mg, secukinumab 75 mg, and placebo, respectively (p<0.001 for both secukinumab doses versus placebo). In MEASURE 2 (n=219), patients were randomized to either SC secukinumab 75 mg or 150 mg or placebo on weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks thereafter. The primary endpoint was patients achieving ASAS20 at week 16, at which point placebo patients were re-randomized to either active treatment dose. At week 16, 61% of patients using the 150 mg dose compared to 28% of patients on placebo achieved ASAS20 (difference, 33%; 95% CI, 18 to 48). ASAS20 for the 75 mg dose was 41% (p=0.1 versus placebo). At week 16, 36% of patients using the 150 mg dose compared to 11% of patients on placebo achieved ASAS40 (difference, 25%; 95% CI, 12 to 38). In a 2-year follow up of the MEASURE trials, continued efficacy of secukinumab was seen at 2 years and sustained benefit has been seen in MEASURE 1 at 3 years.[384,385,386] In a prespecified subanalysis of the MEASURE 2 trial, efficacy of secukinumab versus placebo was stratified by prior TNF antagonist use.[387] At week 16, 68.2% of TNF antagonist-naive subjects treated with secukinumab achieved ASAS20 compared with 31.1% treated with placebo (p<0.001). In the TNF antagonist inadequate response or intolerance group, 50% of subjects treated with secukinumab achieved an ASAS20 response compared with 24.1% treated with placebo (p<0.05). A third study (n=226) demonstrated comparable efficacy and safety between secukinumab 150 mg and 300 mg, each given every 4 weeks.[388]

tofacitinib (Xeljanz, Xeljanz ER)

A phase 3, randomized, double-blind, placebo-controlled study assessed the safety and efficacy of tofacitinib for the treatment of AS in 269 adults diagnosed with active AS (defined by BASDAI score and subscores) and an inadequate response or intolerance to ≥ 2 NSAIDs.[389,390] Eligible patients were randomized 1:1 to tofacitinib 5 mg twice daily or placebo for 16 weeks. At week 16, all patients were then assigned open-label tofacitinib through week 48. The primary endpoint was ASAS20 at week 16, and ASAS40 was a secondary endpoint. About 7% and 21% used concomitant methotrexate and sulfasalazine, respectively. Of those included, 22% had reported an inadequate response to 1 to 2 TNF antagonists. After 16 weeks, ASAS20 occurred more frequently in those treated with tofacitinib compared to placebo (56.4% versus 29.4%, respectively; treatment difference, 27 [95% CI, 16 to 38; p<0.0001]). Likewise, ASAS40 occurred more frequently in those treated with tofacitinib compared to placebo (40.6% versus 12.5%, respectively; treatment difference, 28 [95% CI, 16 to 38; p<0.0001]). The researchers noted that no new safety risks were identified.

upadacitinib (Rinvoq)

Two multinational, randomized, double-blind, placebo-controlled trials, SELECT-AXIS 1 (NCT03178487) and 2 (NCT04169373), assessed the effectiveness and safety of upadacitinib in the treatment of adults with AS.[391,392,393,394] In SELECT-AXIS 1, patients with a BASDAI ≥ 4 and Patient's Assessment of Total Back Pain score ≥ 4 who were biological DMARD treatment-naïve and had an intolerance, contraindication, or inadequate response to ≥ 2 NSAIDs were randomized 1:1 to oral upadacitinib 15 mg once daily or placebo for 14 weeks (n=187). Included patients were able to continue select stable doses of conventional DMARDs (16%). At week 14, a significantly higher percentage of upadacitinib-treated patients achieved ASAS40 response, the primary endpoint, compared to those treated with placebo (52% versus 26%, respectively; treatment difference, 26% [95% CI, 13 to 40]; p=0.0003). Participants were able to continue in an open-label extension study of active treatment for 90 weeks (n=178). Interim data from the extension study at 64 weeks demonstrated sustained and similar benefits. In SELECT-AXIS 2, patients with a BASDAI ≥ 4 and Patient's Assessment of Total Back Pain score ≥ 4 who had an inadequate response to

1 or 2 biologic DMARDs were randomized 1:1 to oral upadacitinib 15 mg once daily or placebo for 14 weeks (n=420). Included patients were able to continue select stable doses of conventional DMARDs (31%). At week 14, a significantly higher percentage of upadacitinib-treated patients achieved ASAS40 response, the primary endpoint, compared to those treated with placebo (44.5% versus 18.2%, respectively; treatment difference, 26% [95% CI, 18 to 35]). Participants were able to continue in an open-label extension study of active treatment or a placebo to active treatment switch for 104 weeks, followed by a potential re-treatment phase following time of flare.

Atopic Dermatitis

abrocitinib (Cibinqo)

Two 12-week, randomized double-blind, placebo-controlled trials, JADE MONO-1 (NCT03349060; n=387) and JADE MONO-2 (NCT03575871; n=391), evaluated the efficacy of abrocitinib in patients ≥ 12 years of age with moderate to severe atopic dermatitis (defined as Investigator's Global Assessment [IGA] score ≥ 3, Eczema Area and Severity Index [EASI] score ≥ 16, body surface area [BSA] involvement ≥ 10%, and Peak Pruritus Numerical Rating Scale [PP-NRS] ≥ 4 at the baseline).[395,396,397] Patients enrolled had either trial had an inadequate response to prior topical therapy, or topical therapy was not advised, or had previously received systemic therapies (e.g., dupilumab). More than 40% of enrollees in each trial had previously received systemic agents with 6% of subjects in the trials receiving dupilumab. Both trials were monotherapy studies compared 2 doses of abrocitinib (200 mg once daily or 100 mg once daily) to placebo. In both trials, the coprimary efficacy endpoints were IGA and EASI-75 responses at 12 weeks. An IGA response was a score of clear (0) or almost clear (1) on the 5-point scale and a decrease from baseline of ≥ 2 points; EASI-75 was ≥ 75% improvement in EASI score from baseline. In JADE-MONO-1, significantly more patients treated with abrocitinib 200 mg (44%) or 100 mg (24%) achieved an IGA response at week 12 compared to placebo (8%); the difference from placebo was 36% (95% CI, 26.2 to 45.7; p<0.0001) for the 200 mg group and 15.8% (95% CI, 6.8 to 24.8; p=0.0037) for the 100 mg group. Similar findings were found for the EASI-75 efficacy endpoint with 63% of patients in 200 mg arm achieving EASI-75 (difference from placebo, 51%; 95% CI, 40.5 to 61.5; p<0.0001) and 40% of patients in the 100 mg group achieving EASI-75 (difference from placebo, 27.9%; 95% CI, 17.4 to 38.3; p<0.0001) compared to 12% of placebo patients. In JADE-MONO-2, statistically significant improvements in both coprimary efficacy endpoints with either dose of abrocitinib compared to placebo. For IGA response, 38.1% of patients in the 200 mg group (difference from placebo, 28.7%; 95% CI, 18.6 to 38.8; p<0.001) and 28.4% of patients in the 100 mg group (difference from placebo, 19.3%; 95% CI, 9.6 to 29; p<0.001) met the endpoint compared with 9.1% of placebo patients. For EASI-75, 61% of 200 mg abrocitinib-treated patients achieved the endpoint (difference from placebo 50.5%; 95% CI, 40 to 60.9; p<0.001) and 44.5% of 100 mg abrocitinib-treated patients reached the endpoint (difference from placebo 33.9%; 95% CI, 23.3 to 44.4; p<0.001) compared with 10.4% of placebo patients.

The JADE COMPARE rial (NCT03720470; n=838) was a 16-week trial and compared abrocitinib (200 mg once daily or 100 mg once daily) with placebo or dupilumab SC 600 mg on day 1, followed by 300 mg every 2 weeks in adults with all individuals receiving background topical corticosteroids.[398,399] A significantly greater proportion of patients in the abrocitinib study arms achieved IGA response and EASI-75 at week 12 compared to placebo. For IGA response, 48.4% of patients in the 200 mg group (difference from placebo, 34.8%; 95% CI, 26.1 to 43.5; p<0.001), 36.6% of patients in the 100 mg group (difference from placebo, 23.1%; 95% CI, 14.7 to 31.4; p<0.001), 36.5% of patients in the dupilumab group achieved this endpoint compared with 14% of patients in the placebo group. For EASI-75, 70.3% of patients in the

200 mg group (difference from placebo, 43.2%; 95% CI, 33.7 to 52.7; p<0.001), 58.7% of patients in the 100 mg group (difference from placebo, 31.9%; 95% CI, 22.2 to 41.6; p<0.001), and 58.1% of patients in the dupilumab arm achieved the endpoint compared to 27.1% of placebo patients. The secondary endpoints assessing itching in all 3 trials also demonstrated numerical improvements with either dose of abrocitinib compared to placebo.

upadacitinib (Rinvoq)

The safety and efficacy of upadacitinib were established in three phase 3, multicenter, randomized, double-blind trials (AD-1 [Measure Up 1], AD-2 [Measure Up 2], AD-3 [AD Up]; NCT03569293, NCT03607422, and NCT03568318, respectively) in 2,584 patients with moderate to severe atopic dermatitis not controlled by topical medications and who were ages 12 years and older.[400,401,402] Included patients had a validated Investigator's Global Assessment (vIGA-AD) score ≥ 3 in the overall assessment (range, 0 to 4), an Eczema Area and Severity Index (EASI) score ≥ 16, a minimum involvement of ≥ 10% BSA, and weekly average Worst Pruritus Numerical Rating Scale (NRS) score ≥ 4. In all trials, patients were randomized to upadacitinib 15 mg or 30 mg or placebo for 16 weeks. The AD-1 and AD-2 trials were monotherapy trials, while patients in AD-3 also received concomitant topical corticosteroids. The co-primary endpoints were the proportion of patients with a vIGA-AD score of 0 (clear) or 1 (almost clear) with a ≥ 2-point improvement and the proportion of patients with improvement of ≥ 75% in EASI score from baseline (EASI-75) at 16 weeks. Baseline characteristics across all 3 trials were 57% male, 69% White, and a mean age of 34 years (range, 12 to 75 years; 13% were < 18 years). At baseline, 49% had a vIGA-AD score of 3 (moderate), 51% had a vIGA-AD score of 4 (severe), a baseline mean EASI score of 29, a baseline weekly Worst Pruritus NRS score of 7, and 52% had a prior exposure to systemic AD treatment. At week 16, the placebo subtracted difference in patients achieving a vIGA-AD score of 0 or 1 in patients treated with upadacitinib 15 mg was 40% (95% CI, 33 to 46) in AD-1 and 34% (95% CI, 28 to 40) in AD-2.[403,404,405] The placebo subtracted difference in those treated with 30 mg was 54% (95% CI, 47 to 60) in AD-1 and 47% (95% CI, 41 to 54) in AD-2. At week 16, the placebo subtracted difference in patients achieving EASI-75 in patients treated with upadacitinib 15 mg was 53% (95% CI, 46 to 60) in AD-1 and 47% (95% CI, 40 to 54) in AD-2. The placebo subtracted difference in those treated with 30 mg was 63% (95% CI, 57 to 70) in AD-1 and 60% (95% CI, 53 to 66) in AD-2. In AD-3 at week 16, the placebo subtracted difference in patients achieving a vIGA-AD score of 0 or 1 in patients treated with upadacitinib 15 mg was 29% (95% CI, 22 to 35) and was 48% (95% CI, 41 to 54) in those treated with upadacitinib 30 mg. The placebo subtracted difference in patients achieving EASI-75 treated with upadacitinib 15 mg was 38% (95% CI, 31 to 45) and 51% (95% CI, 44 to 57) in those treated with upadacitinib 30 mg.

When evaluating the pediatric patient population alone at week 16, the placebo subtracted difference in patients achieving a vIGA-AD score of 0 or 1 in patients treated with upadacitinib 15 mg was 31% (95% CI, 14 to 47) in AD-1 and 40% (95% CI, 22 to 57) in AD-2.[406,407,408] The placebo subtracted difference in those treated with 30 mg was 62% (95% CI, 45 to 78) in AD-1 and 60% (95% CI, 42 to 77) in AD-2. At week 16, the placebo subtracted difference in patients achieving EASI-75 in patients treated with upadacitinib 15 mg was 63% (95% CI, 47 to 79) in AD-1 and 53% (95% CI, 33 to 72) in AD-2. The placebo subtracted difference in those treated with 30 mg was 75% (95% CI, 61 to 89) in AD-1 and 61% (95% CI, 42 to 79) in AD-2. In AD-3 at week 16, the placebo subtracted difference in pediatric patients achieving a vIGA-AD score of 0 or 1 in patients treated with upadacitinib 15 mg was 23% (95% CI, 7 to 40) and was 57% (95% CI, 40 to 75) in those treated with upadacitinib 30 mg. The placebo subtracted difference in patients achieving EASI-75 treated with upadacitinib 15 mg was 26% (95% CI, 5 to 47) and 46% (95% CI, 26 to 65) in those treated with upadacitinib 30 mg.

Axial Spondyloarthritis (nonradiographic)

certolizumab pegol (Cimzia)

A multicenter, randomized, double-blind, placebo controlled study established the safety and efficacy of certolizumab for the treatment of nonradiographic axial spondyloarthritis (nr-axSpA).[409] Patients ≥ 18 years with adult-onset active axial spondyloarthritis for ≥ 12 months, objective signs of inflammation (e.g., CRP > ULN) and/or sacroiliitis on MRI indicative of inflammatory disease but without radiographic evidence of sacroiliac structural damage, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4, and spinal pain ≥ 4 (10-point Numerical Rating Scale [NRS]) (n=317). In addition, included patients were required to have been intolerant to or had an inadequate response to ≥ 2 NSAIDs. Patients were randomized to certolizumab pegol 400 mg at weeks 0, 2, and 4 weeks or placebo, followed by 200 mg every 2 weeks or placebo. Use of concomitant medications (e.g., NSAIDs, DMARDs, corticosteroids, opioids) was permitted, and participants could transition to open-label certolizumab pegol at any time based on the discretion of the investigator (no occurrences prior to week 12). The primary outcome was the Ankylosing Spondylitis Disease Activity Score-Major Improvement (ASDAS-MI) response at week 52, a composite weighted score incorporating disease activity, CRP, and patient-reported outcomes with major improvement (MI) defined as a change from baseline of ≥ 2 or reaching the lowest possible ASDAS value. A greater proportion of patients in the certolizumab pegol group achieved ASDAS-MI at week 52 compared to that in the placebo group (47% versus 7%, respectively; OR, 15.2 [95% CI, 7.3 to 31.6]. In addition, the ASAS40 response (40% improvement of ASAS) was higher in those treated with certolizumab pegol compared to placebo at weeks 12 (48% versus 11%, respectively; OR, 7.4 [95% CI, 4.1 to 13.4]) and 52 (57% versus 16%, respectively; OR, 7.4 [95% CI, 4.3 to 12.6]). In addition, in a study of axial spondyloarthritis patients that included ankylosing spondylitis patients leading to the approval of certolizumab pegol in ankylosing spondylitis, at week 12, patients with nr-axSpA treated with certolizumab pegol 200 mg every 2 weeks and 400 mg every 4 weeks had ASAS20 responses (20% improvement of ASAS) of 42% and 47%, respectively, compared to 20% of those treated with placebo. Likewise, patients with nr-axSpA treated with certolizumab pegol 200 mg every 2 weeks and 400 mg every 4 weeks had ASAS40 responses of 30% and 37%, respectively, compared to 11% of those treated with placebo at 12 weeks.

ixekizumab (Taltz)

A 52-week, multinational, randomized, double-blind, placebo-controlled study assessed the safety and efficacy of ixekizumab for the treatment of nr-axSpA in adults with active disease (defined as BASDAI ≥ 4 and spinal pain ≥ 4/10) for ≥ 3 months (COAST-X; n=303).[410,411] Included patients had objective signs of inflammation (e.g., CRP > 5 mg/L) and/or sacroiliitis on MRI but no radiographic evidence of structural damage. Included patients were also intolerant or had an inadequate response to ≥ 2 NSAIDs. Patients were randomized 1:1:1 to ixekizumab 80 mg every 2 weeks or 4 weeks (following an initial dose) or to placebo. Initiating treatment or dose adjustment with concomitant medications for nr-axSpA (e.g., NSAIDs, conventional DMARDs, corticosteroids, analgesics) was permitted beginning at week 16, at which point open-label ixekizumab 80 mg every 2 weeks could also be used. At baseline, approximately 39% of patients were on a concomitant conventional DMARD, and the mean duration of disease was 11 years. At 16 weeks, ASAS40 response, a primarily endpoint, was achieved in 35.4% of those treated with ixekizumab 80 mg every 4 weeks compared to 19% with placebo (treatment difference versus placebo, 16.4%; 95% CI, 4.2 to 28.5). At week 52, ASAS40 response was achieved in 30.2% of those treated with

ixekizumab 80 mg every 4 weeks compared to 13.3% with placebo (treatment difference, 16.9%; 95% CI, 5.6 to 28.1). The authors concluded that ixekizumab was superior to placebo at weeks 16 and 52.

secukinumab (Cosentyx)

The safety and efficacy of secukinumab for the treatment of nr-axSpA were established in a phase 3, randomized, double-blind, placebo-controlled study (nr-axSpA1) in 555 adults with active nr-axSpA.[412,413] Included patients had active disease, defined as BASDAI ≥ 4 and pain ≥ 40/100 despite NSAID therapy with objective signs of inflammation (e.g., CRP elevated or sacroiliitis). Patients were randomized to secukinumab SQ every 4 weeks, with or without the FDA-approved loading dose regimen or to placebo for 52 weeks, with dose adjustments or concomitant DMARD or NSAID beginning at week 16 and an option for open-label secukinumab or other biologic at week 20. The primary endpoint, ASAS40 at week 52, was met in 38% of those treated with secukinumab without a loading dose (difference versus placebo, 19%; 95% CI, 10 to 28), 34% of those treated with secukinumab with a loading dose (difference versus placebo, 14%; 95% CI, 5 to 23), and 19% treated with placebo. ASAS40 at week 16 was met in 41% of those treated with secukinumab without a loading dose (difference versus placebo, 13%; 95% CI, 3 to 22), 40% of those treated with secukinumab with a loading dose (difference versus placebo, 12%; 95% CI, 2 to 22), and 28% treated with placebo.

upadacitinib (Rinvoq)

The safety and efficacy of upadacitinib for the treatment of nr-axSpA were established in a phase 3, randomized, double-blind, placebo-controlled study (SELECT AXIS 2) in 313 adults with active nr-axSpA.[414,415] Patients enrolled had active disease, defined by BASDAI ≥ 4 and Patient Assessment of Total Back Pain score ≥ 4 (out of 10). Patients had objective signs of inflammation (e.g., elevated CRP) and/or sacroiliitis). Patients were required to have an inadequate response to ≥ 2 NSAIDs or intolerance to or contraindication to NSAIDs. Patients were randomized to oral upadacitinib 15 mg once daily (n=156) or placebo (n=157). At baseline, about 29% of the patients were receiving a concomitant conventional DMARD, and nearly a third of patients had an inadequate response or intolerance to biologic DMARD therapy. The primary endpoint, ASAS40 response at week 14, was significantly higher with upadacitinib (45%) compared to placebo (23%) (treatment difference, 22%; 95% CI, 12 to 32, p<0.0001). Total back pain (p=0.0004) and BASFI (p<0.0001) were also significantly improved with upadacitinib at week 14 compared to placebo. Other measures of disease activity as well as patients' quality of life were also significantly improved with upadacitinib compared to placebo. The overall rate of adverse events was comparable between study arms (48% versus 46%, respectively); however, slightly more patients in the upadacitinib arm experienced a serious adverse event and adverse event leading to discontinuation (3% versus 1%, respectively). Three percent of patients in the upadacitinib arm experienced neutropenia (compared with none in the placebo arm); however, there were no malignancies, MACE, venous thromboembolic events, opportunistic infections, or deaths in the upadacitinib study group.

Crohn's Disease (CD)

adalimumab (Humira)

A study measured the efficacy and safety of adalimumab in the maintenance of response and remission of CD.[416] Patients (n=778) received open-label induction therapy with adalimumab 80 mg (week 0) followed by 40 mg (week 2). At week 4, patients were stratified by response (decrease in Crohn's Disease Activity Index [CDAI] ≥ 70 points from baseline) and randomized to double-blind treatment with placebo, adalimumab 40 mg every other week, or adalimumab 40 mg weekly through week 56. CDAI is used in

clinical trials to measure disease activity. CDAI scores < 150 indicate a clinical remission, and scores > 450 indicate severely active disease. The primary endpoints were the percentages of randomized responders who achieved clinical remission (CDAI score < 150) at weeks 26 and 56. The percentage of randomized responders in remission was significantly greater in the adalimumab every other week and adalimumab weekly groups versus placebo at week 26 (40%, 47%, and 17%, respectively; p<0.001) and week 56 (36%, 41%, and 12%, respectively; p<0.001). There were no significant differences in efficacy between the 2 adalimumab groups. Adverse events requiring discontinuation occurred more frequently in the placebo group (13.4%) than those receiving adalimumab every week (4.7%) or every other week (6.9%). Adalimumab every other week and weekly maintenance therapies were associated with 52% and 60% relative reductions in 12-month, all-cause hospitalization risk, and 48% and 64% reductions in 12-month risk of Crohn's Disease-related hospitalization.[417] Fewer Crohn's Disease-related surgeries occurred in the adalimumab every other week, weekly, and combined groups compared with placebo (0.4%, 0.8%, and 0.6% versus 3.8%, respectively; all p<0.05).[418]

A double-blind, placebo-controlled trial was designed to determine whether adalimumab induces remissions more frequently than placebo in 325 adult patients with Crohn's disease who have symptoms despite infliximab therapy or who cannot take infliximab because of adverse events.[419] Patients were included if they had a history of Crohn's disease for 4 months or more that was moderate to severe at baseline (CDAI score, 220 to 450 points). Patients were randomized to receive induction doses of adalimumab, 160 mg and 80 mg, at weeks 0 and 2, respectively, or placebo at the same time points. The primary endpoint was induction of remission at week 4. A total of 301 patients completed the trial. Remission was achieved at week 4 by 21% versus 7% for adalimumab group versus placebo (p<0.001). The absolute difference in clinical remission rates was 14.2 percentage points (95% CI, 6.7 to 21.6 percentage points). A 70-point response occurred at week 4 in 52% of patients in the adalimumab group versus 34% of patients in the placebo group (p=0.001). Discontinuations due to adverse effects occurred in 2 patients in the adalimumab group and 4 patients in the placebo group. Serious infections were reported in 4 patients receiving placebo and none of the patients receiving adalimumab.

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy of adalimumab in the healing of draining fistulas in 117 patients with active CD.[420] Patients were adults with moderate to severely active CD (CD activity index 220-450) for at least 4 months who had draining fistulas at baseline. All patients received open-label adalimumab induction therapy with 80 mg initially then 40 mg at week 2. At week 4, all patients were randomly assigned to receive double-blind placebo or adalimumab 40 mg every other week or weekly to week 56. Complete fistula healing/closure was defined as no drainage, either spontaneous or with gentle compression, by week 56. The mean number of draining fistulas per day was significantly decreased in adalimumab-treated patients compared with placebo-treated patients during the double-blind treatment period (0.88 with either dose of adalimumab versus 1.34 with placebo; p=0.002).

A 52-week, randomized, double-blind clinical trial assessed the safety and efficacy of adalimumab in pediatric patients 6 years and older with moderately to severely active Crohn's disease, defined as Pediatric Crohn's Disease Activity Index (PCDAI) score > 30, with an inadequate response to corticosteroids or traditional immunomodulators to reduce signs and symptoms of inducing and maintaining clinical remission (n=192).[421] Weight based dosing was initiated and, ultimately, at week 4, patients within the body weight categories were randomized 1:1 to two different maintenance dose regimens: high (40 mg every 2 weeks if ≥ 40 kg, 20 mg every 2 weeks if < 40 kg) and low (20 mg every 2 weeks if ≥ 40 kg, 10 mg every 2 weeks if < 40 kg). Stable doses of corticosteroids and traditional DMARDs

were permitted during treatment. Clinical response, defined as reduction in PCDAI of 15 points from baseline, occurred in 48% of patients receiving the low maintenance dose and 59% of those in the high maintenance dose groups at 26 weeks and 28% of patients receiving the low maintenance dose and 42% of those in the high maintenance dose groups at 26 weeks. Clinical remission, defined as PCDAI ≤ 10, occurred in 28% of patients receiving the low maintenance dose and 39% of those in the high maintenance dose groups at 26 weeks and 23% of patients receiving the low maintenance dose and 33% of those in the high maintenance dose groups at 26 weeks. The higher dose regimen is the FDA approved dosing for adalimumab.

certolizumab pegol (Cimzia)

In a randomized, double-blind, placebo-controlled study, the efficacy of certolizumab pegol was evaluated in 662 adults with moderate to severe Crohn's disease (PRECISE-1).[422] Patients who had received any TNF antagonist within the previous 3 months or who had had a severe hypersensitivity reaction or a lack of response to the first dose of another TNF antagonist were ineligible. Patients were stratified by baseline levels of CRP (≥ 10 or < 10 mg/L), use of glucocorticoids, and use of concurrent immunosuppressive drugs. Patients were randomized to certolizumab pegol 400 mg or placebo SC at weeks 0, 2, and 4 weeks, and then every 4 weeks following that. Response was defined as a decrease of at least 100 points in the CDAI score at week 6 and 26. Remission was defined as an absolute CDAI ≤ 150. In patients with a baseline CRP level ≥ 10 mg/L, 37% of patients in the certolizumab pegol group had a response at week 6, as compared with 26% in the placebo group (p=0.04). Twenty-two percent of patients in the certolizumab pegol group compared to 12% of patients in the placebo group had a response at both weeks 6 and 26 (p=0.05). In the overall population, the response rates at week 6 for certolizumab pegol and placebo were 35% and 27%, respectively (p=0.02). For both weeks 6 and 26, response rates were 23% and 16% for certolizumab pegol and placebo groups, respectively (p=0.02). At weeks 6 and 26, the rates of remission in the 2 groups did not differ significantly (p=0.17). A total of 154 patients assigned to placebo and 145 assigned to certolizumab pegol completed the study. Serious infections were reported in 2% of patients receiving certolizumab pegol and less than 1% of those patients who received placebo. In the certolizumab group, antibodies to the drug developed in 8% of patients and antinuclear antibodies developed in 2%. The study was supported by the manufacturer of certolizumab pegol.

In the double-blind PRECISE-2 study, efficacy of certolizumab pegol was evaluated in 668 adults with moderate to severe Crohn's disease as maintenance therapy.[423] Open-label induction therapy with certolizumab pegol 400 mg SC at weeks 0, 2, and 4 was administered. Baseline CDAI scores were 220-450. Thirty-eight percent of patients in each group were not receiving either glucocorticoids or immunosuppressives. A total of 428 patients had a clinical response at week 6. Patients with a clinical response at week 6 were stratified by baseline CRP level and were randomized to certolizumab pegol 400 mg (n=216) or placebo (n=212) every 4 weeks through week 24 with 2 weeks of additional follow-up. The study was completed by 109 patients assigned to the placebo group and 151 patients assigned to certolizumab pegol. The response was maintained through week 26 in 62% of the patients with a baseline CRP level of at least 10 mg/L, who were receiving certolizumab, compared to 34% in the placebo group (p<0.001). Patients with a response to induction at week 6 and remission (defined as CDAI score ≤ 150) at week 26 was achieved in 48% and 29% of the certolizumab pegol and placebo groups, respectively (p<0.001). Infectious serious adverse events (including 1 case of pulmonary tuberculosis) were reported in 3% of patients receiving certolizumab pegol and less than 1% of the patients receiving placebo. The study was supported by the manufacturer of certolizumab pegol.

infliximab (Remicade)

ACCENT l was a randomized study of the benefit of maintenance therapy with infliximab in patients with active Crohn's disease who respond to a single IV infusion of infliximab.[424] In this study, 573 patients received infliximab 5 mg/kg. They were assessed 2 weeks later, at which time responders, defined as seeing a decrease in CDAI score of at least 70 points and 25% from baseline, were randomized into 1 of 3 groups: high-dose infliximab (5 mg/kg at weeks 2 and 6 followed by 10 mg/kg every 8 weeks until week 46), low-dose infliximab (5 mg/kg at the same time points), or placebo. The primary endpoints were: 1) the proportion of patients who responded at week 2 and were in remission at week 30, and 2) the time to loss of response up to week 54. Fifty-eight percent of the patients responded to the single infusion of infliximab at 2 weeks. At 30 weeks, 21% of the placebo patients were in remission, compared to 45% of high-dose (p=0.0002) and 39% of low-dose (p=0.003) infliximab patients. Throughout the 54-week trial, the median time to loss of response was > 54 weeks and 38 weeks for high- and low-dose infliximab patients, respectively, compared with 19 weeks for the placebo group (p=0.0002 and 0.002, respectively). The safety profile of infliximab was similar to other studies; the incidence of serious infections was similar across treatment groups. ACCENT I substudies showed that infliximab improved health-related quality of life.[425]

An ACCENT II substudy examined the effect of infliximab maintenance treatment on hospitalizations, surgeries, and procedures in patients with fistulizing Crohn's disease.[426] After receiving infliximab 5 mg/kg at weeks 0, 2, and 6, patients were separately randomized at week 14 as responders (195 patients) or nonresponders (87 patients) to receive placebo or to continue with infliximab maintenance therapy every 8 weeks. Among patients randomized as responders, those who received infliximab maintenance had significantly fewer mean hospitalization days (0.5 versus 2.5 days; p<0.05), mean number of hospitalizations (11/100 patient versus 31/100 patients; p<0.05), total surgeries and procedures (65 versus 126; p<0.05), inpatient surgeries and procedures (7 versus 41; p<0.01), and major surgeries (2 versus 11; p<0.05), compared with those who received placebo maintenance.

The REACH study evaluated the safety and efficacy of infliximab in children with moderately to severely active Crohn's disease.[427] Patients (n=112) received infliximab 5 mg/kg at weeks 0, 2, and 6. Patients responding to treatment at week 10 were randomized to infliximab 5 mg/kg every 8 or 12 weeks through week 46. A concurrent immunomodulator was required. Clinical response (decrease from baseline in the pediatric Crohn's disease activity index (PCDAI) score ≥ 15 points; total score ≤ 30) and clinical remission (PCDAI score ≤ 10 points) were evaluated at weeks 10, 30, and 54. At week 10, 88.4% patients responded to infliximab (95% CI, 82.5% to 94.3%) and 58.9% patients achieved clinical remission (95% CI, 49.8% to 68%). At week 54, 63.5% and 55.8% patients receiving infliximab every 8 weeks did not require dose adjustment and were in clinical response and clinical remission, respectively, compared with 33.3% and 23.5% patients receiving treatment every 12 weeks (p=0.002 and p<0.001, respectively).

infliximab-dyyb (Inflectra) versus infliximab originator (Remicade)

A phase 3, multicenter, randomized, double-blind noninferiority study compared the efficacy of infliximab-dyyb to originator infliximab in 220 patients with active CD who had not responded to, or were intolerant to, non-biological treatments.[428] Included patients were randomized 1:1:1:1 to receive infliximab-dyyb then infliximab-dyyb, infliximab-dyyb then infliximab originator, infliximab originator then infliximab originator, or infliximab originator then infliximab-dyyb, with the switch occurring at week 30. All doses were 5 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter to week 54. The primary endpoint was the proportion in each group who had a decrease in CDAI by ≥ 70 points at week 6, with

the noninferiority margin set at -20%. At 6 weeks, responses were similar (infliximab-dyyb 69.4% [95% CI, 59.9 to 77.8] versus infliximab originator 74.3% [95% CI, 65.1 to 82.2]; difference, -4.9% [95% CI, -16.9 to 7.3]), establishing noninferiority. Treatment-emergent adverse effects were similar.

risankizumab-rzaa (Skyrizi)

Two 12-week, double-masked, induction studies (ADVANCE; NCT03105128 and MOTIVATE; NCT03104413) evaluated risankizumab-rzaa in patients 16 to 80 years of age with moderately to severely active Crohn's disease and an inadequate response, loss of response, or intolerance to oral aminosalicylates, corticosteroids, immunosuppressants (ADVANCE), or to biologics (MOTIVATE).[429,430] Patients were randomized to risankizumab-rzaa 600 mg (ADVANCE, n=373; MOTIVATE, n=206) or placebo (ADVANCE, n=186; MOTIVATE, n=207) as an IV infusion at weeks 0, 4, and 8. The co-primary endpoints in both studies were clinical remission (defined based on the Crohn's disease activity index [CDAI] or patient-reported outcome criteria [average daily stool frequency and abdominal pain score]) and endoscopic response at week 12. In ADVANCE, CDAI clinical remission was achieved in 45% and 25% of patients treated with risankizumab-rzaa and placebo respectively (p≤0.0001), and endoscopic response was reported in 40% and 12%, respectively, (p≤0.0001). In MOTIVATE, CDAI clinical response rates were 42% and 20%, respectively (p≤0.0001), and endoscopic response rates were 29% and 11%, respectively (p≤0.0001). A risankizumab-rzaa dose of 1,200 mg was also studied but did not provide additional benefit and is not FDA approved.

In the double-blind, multinational, FORTIFY (NCT03105102) maintenance withdrawal trial, 712 patients who achieved a clinical response with risankizumab-rzaa in the ADVANCE and MOTIVATE trials were re-randomized 1:1:1 to SC risankizumab-rzaa 180 mg or 360 mg or to placebo every 8 weeks.[431] The co-primary endpoints were clinical remission (per CDAI in US protocol, or stool frequency in non-US protocol) and endoscopic response. Higher rates of clinical remission and endoscopic response were achieved with risankizumab-rzaa 360 mg compared to placebo (CDAI clinical remission, 52% versus 41%, respectively; adjusted difference 15% [95% CI, 5 to 24]; stool frequency and abdominal pain score clinical remission, 52% versus 40%, respectively; adjusted difference 15% [95% CI, 5 to 25]; endoscopic response, 47% versus 22%, respectively; adjusted difference 28% [95% CI, 19 to 37]). Higher rates of CDAI clinical remission and endoscopic response, but not stool frequency and abdominal pain score clinical remission (p=0.124) were also achieved with risankizumab-rzaa 180 mg versus placebo (CDAI clinical remission adjusted difference, 15% [95% CI, 5 to 24]; endoscopic response adjusted difference, 26% [95% CI, 17 to 35]).

ustekinumab (Stelara)[432,433]

Three randomized, double-blind, placebo-controlled trials evaluated the role of ustekinumab for the treatment of adults with moderately to severely active CD (CDAI score of 220 to 450). In study 1 (UNITI-1; n=741 in final analysis), patients were randomized to a single dose of ustekinumab 6 mg/kg or 130 mg or placebo. At baseline, 29% patients had an inadequate initial response to a TNF antagonist, 69% responded but subsequently lost response, and 36% were intolerant to a TNF antagonist. Of these patients, 48% failed or were intolerant to a single TNF antagonist while 52% had failed 2 to 3 prior TNF antagonists. Approximately 46% were receiving corticosteroids and 31% were receiving traditional oral immunomodulators (e.g., 6-mercaptopurine, azathioprine, methotrexate). Clinical response, defined as CDAI score decrease of ≥ 100 points or a CDAI < 150, was higher with ustekinumab 130 mg and 6 mg/kg than placebo at week 6 (34.3% and 33.7% versus 21.5%, respectively; p≤0.003 for both versus placebo). Clinical remission, defined as CDAI < 150, was higher with ustekinumab 130 mg and 6 mg/kg than placebo at week 8 (15.9% and 20.9% versus 7.3%, respectively; p≤0.003 for both versus placebo]).

In study 2 (UNITI-2; n=627 in final analysis), patients also were randomized to a single dose of ustekinumab 6 mg/kg or 130 mg or placebo. At baseline, 81% of patients had failed or were intolerant to prior treatment with corticosteroids, and 68% of patients had failed or were intolerant to at least 1 traditional oral immunomodulators. Approximately 69% of patients had never received a TNF antagonist, and 31% had received, but not failed, a TNF antagonist. Approximately 39% were receiving corticosteroids and 35% were receiving traditional oral immunomodulators. Clinical response (as defined above) was higher with ustekinumab 130 mg and 6 mg/kg than placebo at week 6 (51.7% and 55.5% versus 28.7%, respectively; p≤0.01 for both versus placebo). Clinical remission (as defined above) was higher with ustekinumab 130 mg and 6 mg/kg than placebo at week 8 (30.6% and 40.2% versus 19.6%, respectively; p≤0.009 for both versus placebo). Notably, the 130 mg dose studied in both trials is not an FDA-approved dose.

In study 3 (IM-UNITI; n=388), patients with clinical response in studies 1 or 2 were randomized to continue ustekinumab 90 mg every 8 weeks or every 12 weeks or placebo for 44 weeks. Clinical remission at 44 weeks occurred in 35.9% of those treated with placebo compared to 53.1% and 48.8% of those treated with ustekinumab every 8 and 12 weeks, respectively (p=0.005 every 8 weeks versus placebo; p=0.04 every 12 weeks versus placebo). Clinical response at 44 weeks occurred in 44.3% of those treated with placebo compared to 59.4% and 58.1% of those treated with ustekinumab every 8 and 12 weeks, respectively (p=0.02 every 8 weeks versus placebo; p=0.03 every 12 weeks versus placebo). Likewise, 47% of those in the ustekinumab group were corticosteroid-free and in clinical remission compared to 30% in the placebo group.

vedolizumab (Entyvio)[434]

Three randomized, double-blind, placebo-controlled clinical trials (CD Trials I, II, and III) were conducted to evaluate the safety and efficacy of vedolizumab in adult patients with moderately to severely active CD (CDAI score of 220 to 450). Enrolled patients in the US had over the previous 5-year period an inadequate response or intolerance to immunomodulator therapy (e.g., thiopurines [azathioprine or mercaptopurine] or methotrexate) and/or an inadequate response, loss of response, or intolerance to one or more TNF antagonists. Outside the US, prior treatment with corticosteroids was sufficient for entry if, over the previous 5-year period, the patients were corticosteroid dependent or had an inadequate response or intolerance to corticosteroids. Patients that had ever received natalizumab and patients that had received a TNF antagonist in the past 60 days were excluded from enrollment.

In CD Trial I, 368 patients were randomized in a double-blind fashion (3:2) to receive vedolizumab 300 mg or placebo by IV infusion at 0 and 2 weeks with efficacy assessments at 6 weeks. Concomitant stable dosages of aminosalicylates, corticosteroids, and immunomodulators were permitted through week 6. At baseline, patients were receiving corticosteroids (49%), immunomodulators (35%), and/or aminosalicylates (46%). A total of 48% of the patients had an inadequate response, loss of response, or intolerance to a TNF antagonist therapy. The median baseline CDAI score was 324 in the vedolizumab group and 319 in the placebo group. In the trial, a statistically significantly higher percentage of patients treated with vedolizumab achieved clinical remission (defined as CDAI ≤ 150) as compared to placebo (15% versus 7%, p=0.041) at week 6. The difference in the percentage of patients who demonstrated clinical response (defined as a ≥ 100 point decrease in CDAI score from baseline) was not, however, statistically significant at week 6.

In CD Trial II, 416 patients were randomized in a double-blind fashion (1:1) to receive either vedolizumab 300 mg or placebo at 0, 2, and 6 weeks and efficacy assessments occurred at 6 and 10 weeks. The trial

enrolled a higher number of patients who had over the previous 5-year period had an inadequate response, loss of response, or intolerance to 1 or more TNF antagonists (76%) than CD Trial I. Concomitant aminosalicylates, corticosteroids, and immunomodulators were permitted through week 10. At baseline, patients were receiving corticosteroids (54%), immunomodulators (34%), and aminosalicylates (31%). The median baseline CDAI score was 317 in the vedolizumab group and 301 in the placebo group. For the primary endpoint of clinical remission at week 6, treatment with vedolizumab did not result in statistically significant improvement over placebo.

In CD Trial III, 461 patients who had a clinical response to vedolizumab at week 6 were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at week 6: vedolizumab 300 mg every 8 weeks, vedolizumab 300 mg every 4 weeks, or placebo every 4 weeks. Concomitant aminosalicylates and corticosteroids were permitted through week 52 and efficacy assessments were conducted at week 52. Concomitant immunomodulators were permitted outside the US but were not permitted beyond week 6 in the US. At week 6, patients were receiving corticosteroids (59%), immunomodulators (31%), and aminosalicylates (41%). A total of 51% of patients had an inadequate response, loss of response, or intolerance to a TNF antagonist therapy. At week 6, the median CDAI score was 322 in the vedolizumab every 8 week group, 316 in the vedolizumab every 4 week group, and 315 in the placebo group. Patients who had achieved clinical response at week 6 and were receiving corticosteroids were required to begin a corticosteroid tapering regimen at week 6. In the trial, a greater percentage of patients in groups treated with vedolizumab as compared to placebo (39% versus 22%, p=0.001) were in clinical remission at week 52. A greater percentage of patients in groups treated with vedolizumab, as compared to placebo (44% versus 30%, p=0.013), had a clinical response at week 52. The vedolizumab every 4-week dosing regimen did not demonstrate additional clinical benefit over the every-8-week dosing regimen and is not the recommended dosing regimen.

Cytokine Release Syndrome (CRS)

tocilizumab (Actemra)

Efficacy of tocilizumab for the treatment of CRS was assessed in a retrospective analysis of pooled outcome data in 45 patients from clinical trials of CAR T-cell therapies.[435] In the analysis, 69% of patients (95% CI, 53 to 82) achieved a response in their first episode of CRS with tocilizumab.

Deficiency of Interleukin-1 Receptor Antagonist (DIRA)

anakinra (Kineret)

A long-term natural history study of 9 DIRA patients established the safety and efficacy of anakinra for the treatment of DIRA (age range, 1 month to 9 years).[436] Genetically confirmed patients were treated with 1 to 2 mg/kg/day (when dosing reported; 6 patients) of anakinra, adjusted to a stable efficacious dose to control inflammation (highest dose, 7.5 mg/kg/day; ending dose range, 2.2 to 6.1 mg/kg/day). All patients achieved inflammatory remission while treated with anakinra, defined as CRP ≤ 5 mg/L, no inflammatory bone disease, no pustulosis, and no concomitant steroid use.

rilonacept (Arcalyst)

A 2-year, open-label study of rilonacept established its efficacy and safety for the maintenance of remission of DIRA (n=6; median age, 4.8 years [range, 3.3 to 6.2]).[437,438] Patients discontinued anakinra treatment 24 hours prior to the initiation of rilonacept, which was started at 4.4 mg/kg as a loading dose followed by 2.2 mg/kg once weekly. A dose increase to 4.4 mg/kg once weekly was allowed. All met the

primary endpoint, which was remission at 6 months and sustained remission throughout the 2 years (steroid use was not required). Five of the 6 patients required dose escalation. No patient needed steroid therapy.

Giant Cell Arteritis (GCA)

tocilizumab (Actemra)

GiACTA, a 1-year, multicenter, randomized, double-blind, placebo-controlled trial, assessed the safety and efficacy of tocilizumab in the treatment of GCA.[439,440] Included patients were randomized 2:1:1:1 to SC tocilizumab 162 mg weekly plus a 26-week prednisone taper, SC tocilizumab 162 mg every other week plus a 26-week prednisone taper, placebo plus a 26-week prednisone taper, or placebo plus a 52-week prednisone taper. The primary outcome was the rate of sustained glucocorticoid-free remission at week 52. Sustained remission at week 52 occurred in 56% of the patients treated with tocilizumab weekly, 53% of those treated with tocilizumab every other week, 14% of those in the placebo group plus the 26-week taper, and 18% of those in the placebo group plus the 52-week taper ($p<0.001$ for both tocilizumab groups versus placebo groups). The cumulative median prednisone dose was also higher in the 26-week taper placebo group and 52-week taper placebo group compared to the tocilizumab groups (3,296 mg and 3,818 mg versus 1,862 mg, respectively; $p<0.001$ for both comparisons). Serious adverse effects occurred in 15% of those on weekly tocilizumab, 14% on every other week tocilizumab, 22% in the 26-week taper placebo group, and 25% in the 52-week taper placebo group. This study was funded by the manufacturer of tocilizumab.

IV administration of tocilizumab 6 mg/kg for GCA is based on pharmacokinetic exposure and extrapolation to efficacy with tocilizumab SC.[441]

Hidradenitis Suppurativa (HS)

adalimumab (Humira)

Two randomized, double-blind, placebo-controlled studies evaluated the safety and efficacy of adalimumab in adults with moderate to severe HS, defined as those with Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules (PIONEER I, PIONEER II; n=633).[442,443] Patients were randomized to placebo or adalimumab 160 mg on week 0, 80 mg on week 2, and 40 mg on week 4 and every week thereafter through week 11. Concomitant oral antibiotic use was allowed in study 2 (occurred in 19.3% of patients), and patients used topical antiseptic wash daily in both studies. The primary endpoint in both trials was Hidradenitis Suppurativa Clinical Response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula compared to baseline. HS-related pain was assessed on a numeric 11-point scale in patients with a score of ≥ 3 at baseline. At week 12, 41.8% of patients treated with adalimumab and 26% of patients on placebo in PIONEER 1 (n=307; p=0.003) and 58.9% of patients treated with adalimumab and 27.6% of patients on placebo in PIONEER 2 (n=326; p<0.001) achieved response (HiSCR). From week 12 to 35, patients assigned to adalimumab were re-randomized to 40 mg weekly, 40 mg every other week, or placebo. In those reassigned to placebo following adalimumab treatment, 22% (22 of 100) developed flares, defined as ≥ 25% increase in abscess and inflammatory nodule count (minimum of 2 additional lesions) from baseline. Of those receiving weekly adalimumab, 52.3% achieved HiSCR, which was maintained in 52.3% at week 158.[444]

Juvenile Idiopathic Arthritis (JIA)/Still's Disease (Pediatric-Onset)

abatacept (Orencia)

A double-blind, randomized controlled withdrawal trial enrolled 190 patients ages 6 to 17 years with active JIA in at least 5 active joints with an inadequate response or intolerance to at least 1 DMARD.[445] All 190 patients were given 10 mg/kg of abatacept IV in the open-label period of 4 months. Of the 170 patients who completed the lead-in course, 47 did not respond to the treatment according to predefined American College of Rheumatology (ACR) pediatric criteria and were excluded. An ACR30 response requires a patient to have a 30% reduction in the number of swollen and tender joints, and a reduction of 30% in 3 of the following 5 parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, CRP, or erythrocyte sedimentation rate. Of the patients who responded to abatacept, 60 were randomly assigned to receive abatacept 10 mg/kg every 28 days for 6 months, or until a flare of the arthritis, and 62 were randomly assigned to receive placebo at the same dose and timing. The primary endpoint was time to flare of arthritis. Flare was defined as worsening of 30% or more in at least 3 of 6 core variables, with at least 30% improvement in no more than 1 variable. Flares of arthritis occurred in 33 of 62 (53%) patients who were given placebo and 12 of 60 (20%) abatacept patients during the double-blind treatment (p=0.0003). Median time to flare of arthritis was 6 months for patients given placebo; insufficient events had occurred in the abatacept group for median time to flare to be assessed (p=0.0002). The risk of flare in patients who continued abatacept was less than a third of that for controls during that double-blind period (HR, 0.31; 95% CI, 0.16 to 0.95). During the double-blind period, the frequency of adverse events did not differ in the 2 treatment groups. Adverse events were recorded in 37 abatacept recipients (62%) and 34 (55%) placebo recipients (p=0.47); only 2 serious adverse events were reported, both in controls (p=0.5). The manufacturer of abatacept funded the study. Of the 190 enrolled patients, 153 patients entered the long-term extension phase. By day 589 (≥ 21 months), the percentage of patients reaching various ACR criteria in the double-blind and long-term extension phases were the following: ACR Pedi 30 (90%), ACR Pedi 50 (88%), ACR Pedi 70 (75%), ACR Pedi 90 (57%), and ACR Pedi 100 (39%).[446] Similar response rates were observed by day 589 among patients previously treated with placebo. Among patients who had not achieved an ACR Pedi 30 response at the end of the open-label lead-in phase and who proceeded directly into the long term extension phase, 73%, 64%, 46%, 18%, and 5% achieved ACR Pedi 30, Pedi 50, Pedi 70, Pedi 90, and Pedi 100 responses, respectively, by day 589. Tuberculosis and malignancies were not reported during the long term extension phase.

Approval of abatacept for use in patients 2 to < 6 years of age was based on an evaluation of the pharmacokinetics in this population.[447]

adalimumab (Humira)

A randomized, double-blind, placebo-controlled, multi-center, medication-withdrawal study with a 16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase enrolled patients ages 4 to 17 years with active JIA.[448] Patients who had previously received treatment with NSAIDs underwent stratification according to methotrexate use. Patients received adalimumab 24 mg/m^2 of body surface area (maximum dose 40 mg) SC every other week for 16 weeks. Patients with an ACR Pedi 30 response at week 16 were randomized to adalimumab or placebo every other week in a double-blind manner for up to 32 weeks. More patients on methotrexate (94%, 80/85 patients) achieved ACR Pedi 30 response at week 16 compared to those not on methotrexate (74%, 64/86 patients). Patients not receiving methotrexate, disease flares occurred in 43% of adalimumab-treated

patients and 71% of placebo-treated patients (p=0.03). Among patients receiving methotrexate, flares occurred in 37% adalimumab-treated patients and 65% of placebo-treated patients (p=0.02). At 48 weeks, the percentages of patients treated with methotrexate who had ACR Pedi 30, 50, 70, or 90 responses were significantly greater for those receiving adalimumab than for those receiving placebo; the differences between patients not treated with methotrexate who received adalimumab and those who received placebo were not significant. The most frequently reported adverse events were infections and injection site reactions.

canakinumab (Ilaris) [449]

Two phase 3, randomized, double-blind, placebo-controlled trials established the efficacy of canakinumab for the treatment of JIA. In Study 1, 84 patients (ages 2 to 20 years) were randomized to a single SC dose of either canakinumab 4 mg/kg or placebo. The primary outcome was the percent of patients achieving ACR 30 at day 15, and measures were also taken at day 29. ACR 30 occurred in 84% of patients treated with canakinumab compared to 10% treated with placebo on day 15 (weighted difference, 70%; 95% CI, 56 to 74). ACR 50 occurred in in 67% of patients treated with canakinumab compared to 5% treated with placebo (weighted difference, 65%; 95% CI, 50 to 80). ACR70 occurred in in 60% of patients treated with canakinumab compared to 2% treated with placebo (weighted difference, 64%; 95% CI, 49 to 79). On day 29, ACR 30 occurred in 81% of patients treated with canakinumab compared to 10% treated with placebo (weighted difference, 70%; 95% CI, 56 to 84). ACR50 occurred in in 79% of patients treated with canakinumab compared to 5% treated with placebo (weighted difference, 76%; 95% CI, 63 to 88). ACR70 occurred in in 67% of patients treated with canakinumab compared to 2% treated with placebo (weighted difference, 67%; 95% CI, 52 to 81).

In study 2, a treatment withdrawal study, 107 patients received 4 mg/kg canakinumab SC every 1 weeks in part 1 (open-label), and 100 patients continued into part 2, in which patients were randomized to either continue canakinumab as previously dosed or to placebo every 4 weeks. During part 1, of the 92 patients who attempted to taper corticosteroids, 62% of patients were successful and 46% discontinued corticosteroids. Kaplan-Meier estimates were used to compare the risk of flare with each treatment during part 2. A 64% relative reduction in flare risk was found with canakinumab compared to placebo (HR, 0.36; 95% CI, 0.17 to 0.75).

etanercept (Enbrel)

A long-term, open-label extension study evaluated etanercept in 58 patients with JIA for up to 8 years.[450] A total of 42 of the 58 patients (72%) entered the fourth year of continuous etanercept treatment, and 26 patients (45%) entered the eighth year. Efficacy endpoints included the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30), 50, 70, 90, and 100 criteria for improvement. The degree of disability in Health Assessment Questionnaire (HAQ) score was also evaluated. An ACR Pedi 70 response or higher was achieved by 100% of patients (n=11) with 8 years of data and by 61% of patients (28 of 46) according to the last observation carried forward data. The overall rate of adverse events (0.12 per patient-year) did not increase with long-term exposure to etanercept.

golimumab (Simponi Aria)

Approval of IV golimumab in pediatric patients with pJIA is based on pharmacokinetic data and extrapolation of efficacy in adults with RA.[451] A multicenter, open-label, single-arm study in 124 patients (ages 2 years to < 18 years) with active pJIA despite ≥ 2 months of methotrexate was also used to establish efficacy and safety (n=124). All patients received golimumab 80 mg/m^2 as an IV infusion at weeks 0 and 4

and every 8 weeks for 1 year (with stable doses of methotrexate through week 28). Efficacy was consistent with results seen in adults with RA.

tocilizumab (Actemra)

Tocilizumab was assessed in a 3-part study in children 2 to 17 years of age with active polyarticular juvenile idiopathic arthritis (pJIA), who had an inadequate response to methotrexate or inability to tolerate methotrexate.[452,453] Patients had at least 6 months of active disease, with at least 5 joints with active arthritis and/or at least 3 active joints having limitation of motion. JIA subtypes at disease onset included Rheumatoid Factor Positive or Negative Polyarticular JIA, or Extended Oligoarticular JIA. Treatment with a stable dose of methotrexate was permitted but DMARDs, other than methotrexate, or other biologics (e.g., TNF antagonists or T cell costimulation modulator) were not permitted. Part 1 of the study was a 16-week active IV tocilizumab treatment lead-in period (n=188), part 2, a 24-week randomized double-blind placebo-controlled withdrawal period, and part 3, a 64-week open-label period. Patients weighing 30 kg or more received tocilizumab 8 mg/kg IV once every 4 weeks. Patients weighing less than 30 kg received either tocilizumab 8 mg/kg or 10 mg/kg IV in a randomized 1:1 ratio every 4 weeks. At the end of part I, 91% of patients taking background methotrexate in addition to tocilizumab and 83% of patients on tocilizumab monotherapy achieved an ACR 30 response at week 16 and entered the blinded withdrawal period (part 2). In part 2, patients (intent-to-treat population [ITT], n=163) were randomized to tocilizumab (same dose as in Part 1) or placebo in a 1:1 ratio that was stratified by concurrent methotrexate use and concurrent corticosteroid use. Each patient continued in part II until week 40 or until they showed JIA ACR 30 flare criteria (relative to week 16) and the subject qualified for escape. The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16. JIA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% relative to week 16. Tocilizumab-treated patients experienced fewer disease flares compared to placebo-treated patients (26% [21/82] versus 48% [39/81]; with an adjusted difference in proportions of -21%; 95% CI, -35 to -8%). A 2 year follow up demonstrated continued effectiveness and a safety profile consistent with findings assessed earlier.[454]

The efficacy of SC tocilizumab for the treatment of pJIA in pediatric patients 2 to 17 years old was demonstrated in a 52-week, open-label, multicenter, pharmacokinetic/pharmacodynamic and safety study and is based on pharmacokinetic exposure and extrapolation of the established efficacy of IV tocilizumab in pJIA patients.[455]

The efficacy of tocilizumab was assessed in active systemic JIA (sJIA) in a 12-week randomized, double-blind, placebo-controlled, parallel group study in children aged 2 and older.[456] One hundred and twelve patients, treated with or without methotrexate, were randomized 2:1 to receive to IV tocilizumab (n=75) or placebo (n=37). Every 2 weeks, patients less than 30 kg received tocilizumab or placebo infusions at 12 mg/kg and those above 30 kg received tocilizumab or placebo infusions at 8 mg/kg. The primary endpoint was the proportion of patients at week 12 with at least a 30% improvement in American College of Rheumatology Juvenile Idiopathic Arthritis (JIA ACR30) in 3 of 6 core outcome variables compared to baseline and absence of fever during the preceding 7 days. After 6 weeks, patients who achieved a JIA ACR70 response could begin corticosteroid tapering. The JIA ACR30 response rates with absence of fever at week 12 were 85% for tocilizumab and 24% for placebo, with a weighted difference between the tocilizumab and placebo response rates stratified for weight, disease duration, background oral corticosteroid dose, and background methotrexate use of 62% (95% CI, 45% to 78%).

The efficacy of SC tocilizumab for the treatment of systemic JIA in pediatric patients 2 to 17 years old was demonstrated in a 52-week, open-label, multicenter, pharmacokinetic/pharmacodynamic and safety study and is based on pharmacokinetic exposure and extrapolation of the established efficacy of IV tocilizumab in systemic JIA patients.[457]

tofacitinib (Xeljanz)

A 44-week, 2-part clinical trial, consisting of an 18-week, open-label, run-in phase, followed by a 26-week placebo-controlled, double-blind, randomized withdrawal phase, established the efficacy and safety of tofacitinib in pediatric patients ≥ 2 years old with active polyarticular course JIA.[458] Polyarticular course JIA included patients with active rheumatoid factor negative or positive polyarthritis, extended oligoarthritis, and sJIA without systemic manifestations. These patients were included if they had an inadequate response or intolerance to ≥ 1 DMARD (methotrexate or biologic). Other included patients considered to have polyarticular course JIA had active juvenile PsA and enthesitis-related arthritis (ERA) and were required to have an inadequate response to NSAIDs. All 225 patients received tofacitinib 5 mg twice daily or body weight-based equivalent during the run-in phase. They were then randomized 1:1 to continue treatment or to placebo for the remaining 26 weeks if they had achieved ACR Pedi 30 at week 18 (n=173). Continued current methotrexate use, but not biologics or other DMARDs, was permitted. At 18 weeks, the ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 responses were 77%, 70%, and 49%, respectively. The primary endpoint was the occurrence of disease flare at 44 weeks, defined as worsening of ≥ 30% in 3 or more of the 6 JIA core response variables and ≤ 1 of the remaining JIA core response variables improving by ≥ 30% based on the Pediatric Rheumatology Collaborative Study Group (PRCSG)/Pediatric Rheumatology International Trials Organization (PRINTO) Disease Flare criteria. Patients assigned to continue treatment with tofacitinib had fewer disease flares compared to placebo-treated patients at 44 weeks (31% versus 55%, respectively; treatment difference in proportions, -25% [95% CI, -39 to -10; p=0.0007]).

Neuromyelitis Optica Spectrum Disorder (NMOSD)

inebilizumab-cdon (Uplizna)

The N-MOmentum trial, a multinational, double-blind, randomized, placebo-controlled phase 2/3 study, was comprised of 2 parts: part 1 was a double-blind, randomized, placebo-controlled phase, while part 2 was an open-label phase that enrolled eligible participants from part 1.[459,460] The trial involved eligible participants (n=230) who were randomized 3:1 to receive 300 mg IV inebilizumab-cdon (n=174) or placebo (n=56) on days 1 and 15. Patients who had laboratory abnormalities or a significant number of comorbidities were excluded. Eligible participants included adults (≥ 18 years old) with NMOSD (with no regard to AQP4-IgG serostatus), an Expanded Disability Status Scare (EDSS) score of ≤ 8, and a history of ≥ 1 attack that required the use of rescue therapy in the prior year or ≥ 2 attacks requiring the use of rescue therapy in the 2 years prior to screening. Rescue therapy included the use of IV corticosteroids, IV immunoglobulin, or plasma exchange. During the randomized controlled period, which lasted up to 197 days or until the occurrence of an attack, participants were not permitted to use any immunosuppressant, with the exception of prednisone 20 mg (or equivalent), given to all patients between days 1 and 14. Prednisone was given to lower the likelihood of an attack after the first dose of inebilizumab-cdon and was tapered to day 21. An attack was defined as the presence of a NMOSD-related new symptom(s) or the worsening of an existing symptom that met ≥ 1 of the predefined criteria for an attack upon neurological evaluation. Participants were evaluated on days 1, 8, 15, 29, 57, 85, 113, 155, and 197 for adjudicated attacks. Participants in the placebo group were allowed to cross over to inebilizumab-cdon

open-label therapy once they experienced an attack or passed day 197 and experienced no adverse effects. All participants in the open-label phase (n=213) received 300 mg inebilizumab-cdon every 26 weeks after the initial doses given on days 1 and 15 of the open-label phase and participated in follow-up visits for 12 months following the final dose. At baseline, the mean age of the population studied was 43 years (range, 18 to 74 years), and the mean EDSS score was 4. The primary endpoint, which analyzed the time to onset of an NMOSD attack (in days) on or before day 197, was met, as participants utilizing inebilizumab-cdon experienced a significant increase in the time of onset of NMOSD attacks compared to those on placebo therapy. A total of 12% of those on inebilizumab-cdon therapy experienced an attack, while 39% of those on placebo experienced an attack, corresponding with a relative risk reduction of 73% (HR, 0.272; 95% CI, 0.15 to 0.496; p<0.0001). In the AQP4-IgG seropositive group, of the 161 participants who received inebilizumab-cdon, 18 (11%) experienced an attack, while 22 (42%) experienced an attack in the placebo group (HR, 0.227; 95% CI, 0.121 to 0.423; p<0.0001). The use of inebilizumab-cdon did not have a benefit in those who were anti-AQP4 antibody negative. For the ITT population (n=230) and the subpopulation of AQP4-IgG who were seropositive (n=213), there was significant improvements with inebilizumab-cdon in the secondary endpoints of worsening in EDSS score from baseline at last visit, the cumulative number of active MRI lesions from baseline, and the cumulative number of NMOSD-related inpatient hospitalizations since baseline. The enrollment was stopped early with a 6.5 month randomized controlled phase, as the study provided evidence regarding the efficacy of inebilizumab-cdon in NMOSD with a power of more than 99%.

satralizumab-mwge (Enspryng)

The SAkuraSky, double-blind, parallel-group, multicenter, phase 3, randomized controlled trial, included 83 patients between the ages of 12 to 74 years with either AQP4-IgG seropositive (66% of participants) or AQP4-IgG seronegative (33% of participants) NMOSD.[461] All study participants were required to have had ≥ 2 NMOSD relapses in the 2 years prior to screening with ≥ 1 relapse within the preceding year. Study inclusion criteria also required that patients have an EDSS score ≤ 6.5. Participants were randomized 1:1 to receive either SC satralizumab 120 mg (n=41) at weeks 0, 2, and 4, with subsequent doses every 4 weeks thereafter, or matching placebo (n=42). SAkuraSky allowed satralizumab and placebo to be added on to stable immunosuppressant therapy (IST) with either azathioprine, mycophenolate mofetil, or oral glucocorticoids. Therapy with an anti-CD20 agent was not allowed in the 6 months prior to study inclusion or during the study. The primary outcome was the time to first NMOSD relapse. In total, 8 patients (20%) in the satralizumab group and 18 patients (43%) in the placebo group experienced a primary event of relapse (HR, 0.38; 95% CI, 0.16 to 0.88; p=0.02), demonstrating a significantly longer time to first relapse for those treated with satralizumab. Within the AQP4-IgG seropositive patient population, 3 patients (11%) experienced a relapse in the satralizumab group compared to 12 patients (43%) in the placebo group (HR, 0.21; 95% CI, 0.06 to 0.75). Differences between the satralizumab and placebo groups were not significant within the AQP4-IgG seronegative population, with 5 and 6 patients (36% and 43%) experiencing relapses, respectively (HR, 0.66; 95% CI, 0.2 to 2.24).

SAkuraStar, also a double-blind, parallel-group, multicenter, phase 3, randomized controlled trial, included 95 participants with either AQP4-IgG seropositive (67% of patients) or seronegative (33% of patients) NMOSD.[462] Included participants were 18 to 74 years of age with ≥ 1 attack or relapse of NMOSD in the previous year. Participants were also required to have an EDSS score of ≤ 6.5. In total, 77 (81%) of the study participants were female. Study participants were randomized 2:1 to receive monotherapy with either SC satralizumab 120 mg (n=63) at weeks 0, 2, and 4 with subsequent doses every 4 weeks thereafter, or matching placebo (n=32). Notably, concurrent IST was not allowed during the study. The

primary outcome was defined as the time to first NMOSD relapse. At study conclusion, 19 (30%) relapses were reported for satralizumab-treated patients compared to 16 (50%) of placebo patients (HR, 0.45; 95% CI, 0.23 to 0.89; p=0.018). Satralizumab-treated patients demonstrated a significantly longer time to first relapse than those receiving placebo. At 96 weeks, 72% of satralizumab patients were relapse free compared to 51% of those taking placebo. Within the AQP4-IgG seropositive population, 9 patients (22%) in the satralizumab group experienced relapse compared to 13 patients (57%) receiving placebo (HR, 0.26; 95% CI, 0.11 to 0.63). There was no statistically significant difference in relapses seen between groups in AQP4-IgG seronegative patients.

Oral Ulcers Associated with Behçet's Disease

apremilast (Otezla)

A multicenter, randomized, placebo-controlled trial established the efficacy and safety of apremilast for the treatment of oral ulcers associated with Behçet's disease in adults (n=207).[463,464] Included patients met the International Study Group (ISG) Criteria for Behçet's disease, had previously been treated with ≥ 1 nonbiologic medication for oral ulcers, were candidates for systemic therapy, had ≥ 2 oral ulcers at screening and randomization, and did not have current active major organ involvement. Concomitant treatment for Behçet's disease was not permitted. Patients were randomized 1:1 to apremilast 30 mg twice daily or placebo for 12 weeks, and outcomes included the number of and pain associated with oral ulcers at week 12. The change in pain score (as measured by a visual analog scale; range, 0 to 100, with higher numbers indicating more pain) was -18.7 in the placebo group and -42.7 in the apremilast group (treatment difference, -24.1; 95% CI, -32.4 to -15.7). The proportion of patients achieving oral ulcer complete response (free of oral ulcers) was 22.3% in the placebo group and 52.9% in the apremilast group (treatment difference, 30.6%; 95% CI, 18.1 to 43.1). The proportion of patients achieving oral ulcer complete response (free of oral ulcers) at 6 weeks who remained ulcer-free at 12 weeks was 4.9% in the placebo group and 29.8% in the apremilast group (treatment difference, 25.1%; 95% CI, 15.5 to 34.6). The daily average number of oral ulcers during the treatment period was 2.6 in the placebo group and 1.5 in the apremilast group (treatment difference, -1.1; 95% CI, -1.6 to -0.7). Benefits were sustained up to 64 weeks, and apremilast was generally well-tolerated.[465]

Periodic Fever Syndromes

anakinra (Kineret)[466]

The efficacy of anakinra was evaluated in a prospective, long-term, open-label and uncontrolled study which incorporated a withdrawal period in a subset of 11 patients. This study included 43 Neonatal-Onset Multisystem Inflammatory Disease (NOMID) patients 0.7 to 46 years of age treated for up to 60 months. Patients were given an initial anakinra dose of 1 to 2.4 mg/kg body weight. During the study, the dose was adjusted by 0.5 to 1 mg/kg increments to a protocol-specified maximum of 10 mg/kg daily, titrated to control signs and symptoms of disease. The average maintenance dose was 3 to 4 mg/kg daily. In general, the dose was given once daily, but for some patients, the dose was split into twice daily administrations for better control of disease activity. NOMID symptoms were assessed with a disease-specific Diary Symptom Sum Score (DSSS), which included the prominent disease symptoms fever, rash, joint pain, vomiting, and headache. Mean change in DSSS score was -3.5 (95% CI, -3.7 to -3.3) at months 3 to 6 and -3.5 (95% CI, -3.8 to -3.1) at month 60. For the 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of anakinra therapy.

In a long-term, open-label and uncontrolled study, 43 NOMID patients 0.7 to 46 years of age were treated for up to 60 months. Patients were given an initial dose of anakinra 1-2.4 mg/kg, which was titrated by 0.5 to 1 mg/kg increments to control signs and symptoms of disease to a maximum of 10 mg/kg daily. The actual maximum dose studied was 7.6 mg/kg/day. The average maintenance dose was 3 to 4 mg/kg daily. The dose was given once daily, in general, but, for some patients, the dose was split into twice daily administrations for better control of disease activity. NOMID symptoms were assessed with a disease-specific Diary Symptom Sum Score (DSSS), which included the prominent disease symptoms fever, rash, joint pain, vomiting, and headache. Improvements occurred in all individual disease symptoms comprising the DSSS and the estimated changes from baseline in DSSS were -3.5 (95% CI, -3.7 to -3.3) which was seen as early as month 3 and continued through month 60. In addition, improvements in serum markers of inflammation (e.g., serum amyloid A [SAA], high-sensitivity CRP [hsCRP], and erythrocyte sedimentation rate [ESR]) were also evident. For 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of anakinra therapy. Upon withdrawal of treatment, the median time until disease flare criteria were met was 5 days.

canakinumab (Ilaris) [467]

The efficacy and safety of canakinumab for the treatment of CAPS was demonstrated in a 3-part trial in patients in 31 patients 9 to 74 years of age with the Muckle-Wells Syndrome (MWS) phenotype of CAPS.[468] Throughout the trial, patients weighing more than 40 kg received canakinumab 150 mg and patients weighing 15 kg to 40 kg received 2 mg/kg. Part 1 was an 8-week open-label, single-dose period where all patients received canakinumab. Patients who achieved a complete clinical response and did not relapse by week 8 were randomized into part 2, a 24-week randomized, double-blind, placebo-controlled withdrawal period. Patients who completed part 2 or experienced a disease flare entered part 3, a 16-week open-label active treatment phase. A complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and had serum levels of CRP and Serum Amyloid A (SAA) less than 10 mg/L. A disease flare was defined as a CRP and/or SAA values greater than 30 mg/L and either a score of mild or worse for PHY or a score of minimal or worse for PHY and SKD. In Part 1, a complete clinical response was observed in 71% of patients 1 week following initiation of treatment and in 97% of patients by week 8. In Part Two, 16 patients were randomized to the placebo group and 15 were randomized to the canakinumab group. A total of 13 patients (81%) of the patients randomized to placebo flared as compared to none of the patients randomized to canakinumab (95% CI, 53% to 96%). At the end of Part 2, all 15 patients treated with canakinumab had absent or minimal disease activity and skin disease. CRP and SAA values subsequently normalized in the placebo group after reintroduction of canakinumab in Part 3.

The efficacy and safety of canakinumab for the treatment of TRAPS, HIDS/MKD, and FMF were demonstrated in a 4-part study consisting of 3 separate, disease cohorts (TRAPS [n=46], HIDS/MKD [n=72], and FMF [n=63]) including 185 patients ages 28 days and older.[469,470] Following a 12-week screening period (Part 1), patients (ages 2 to 76 years) were randomized at flare onset into a 16-week double-blind, placebo-controlled treatment period (Part 2) where they received either 150 mg canakinumab (or 2 mg/kg if < 40 kg) SC or placebo every 4 weeks. Parts 3 and 4 consisted of an open-label randomized withdrawal open-label treatment phase. In those treated with canakinumab, if the flare did not resolve or the patient had persistent disease activity from day 8 to 14 and/or during day 15 to 28, the patient was given an additional dose. At or following day 29, those assigned canakinumab without optimal response were up-titrated to 300 mg canakinumab (or 4 mg/kg if < 40 kg) per dose. Patients in the FMF

cohort were allowed to continue their stable dose of colchicine. The primary endpoint at the end of Part 2 was the proportion of complete responders within each cohort, defined as resolution of their index disease flare at day 15 (as assessed by the Physician's Global Assessment [PGA]) and those did not experience a new flare during the remainder of the treatment period. The key signs and symptoms assessed in the PGA for each condition were the following: abdominal pain, skin rash, musculoskeletal pain, and eye manifestations for TRAPs; abdominal pain; lymphadenopathy, and aphthous ulcers for HIDS/MKD; and abdominal pain, skin rash, chest pain, and arthralgia/arthritis for FMF.

In the TRAPS cohort, 50% of patients randomized to canakinumab received up-titration.[471,472] Complete response (resolution by day 15 and maintained through week 16) was found in 45.5% of patients treated with canakinumab compared to 8.3% treated with placebo (OR, 9.17; 95% CI, 1.51 to 94.61; p=0.005). Flare resolution at day 15 occurred in 63.6% of patients treated with canakinumab compared to 20.8% treated with placebo. PGA less than 2 and CRP ≤ 10 mg/L occurred more frequently with canakinumab versus placebo (OR, 4.06 [95% CI, 1.12 to 14.72] and OR, 3.88 [95% CI, 1.05 to 14.26], respectively). No statistically significant difference was seen in SAA ≤ 10 mg/L (OR, 5.06; 95% CI, 0.92 to 27.91).

In the HIDS/MKD cohort, 51.4% of patients randomized to canakinumab received up-titration.[473,474] Complete response was found in 35.1% of patients treated with canakinumab compared to 5.7% treated with placebo (OR, 8.94; 95% CI, 1.72 to 86.41; p=0.002). Flare resolution at day 15 occurred in 64.9% of patients treated with canakinumab compared to 37.1% treated with placebo. PGA less than 2 and CRP ≤ 10 mg/L occurred more frequently with canakinumab versus placebo (OR, 3.42 [95% CI, 1.28 to 9.16] and OR, 6.05 [95% CI, 2.14 to 17.12], respectively). No statistically significant difference was seen in SAA ≤ 10 mg/L (OR, 2.94; 95% CI, 0.82 to 10.53).

In the FMF cohort, 32.3% of patients randomized to canakinumab received up-titration, and 87.3% were taking concomitant colchicine.[475,476] Complete response was found in 61.3% of patients treated with canakinumab compared to 6.3% treated with placebo (OR, 23.75; 95% CI, 4.38 to 227.53; p<0.001). Flare resolution at day 15 occurred in 80.7% of patients treated with canakinumab compared to 31.3% treated with placebo. PGA less than 2, CRP ≤ 10 mg/L, and SAA ≤ 10 mg/L occurred more frequently with canakinumab versus placebo (OR, 10.07 [95% CI, 2.78 to 36.49]; OR, 22.51 [95% CI, 5.41 to 93.62]; and OR, 3.73 [95% CI, 1.11 to 12.52], respectively). In a 72-week long-term, open-label follow up study, minimal flares were reported and no new safety concerns were reported.[477]

rilonacept (Arcalyst)[478]

The safety and efficacy of rilonacept for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study with 2 parts (A and B) conducted sequentially in the same patients with FCAS (Familial Cold Autoinflammatory Syndrome) and MWS phenotypes of CAPS. Part A was a 6-week, randomized, double-blind, parallel-group period comparing rilonacept at a dose of 160 mg weekly after an initial loading dose of 320 mg to placebo. Part B followed immediately after Part A and consisted of a 9-week, patient-blind period during which all subjects received rilonacept 160 mg weekly, followed by a 9-week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on rilonacept 160 mg weekly or to receive placebo. Using a daily diary questionnaire, patients rated the following 5 signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue, each on a scale of 0 (none, no severity) to 10 (very severe). The study evaluated the mean symptom score using the change from baseline to the end of treatment. The patients in the rilonacept group had a larger reduction than the placebo (-2.4 versus -0.5; 95% CI, -2.4 to -1.3) in the mean symptom score in Part A. In Part B, mean symptom scores increased

more in patients withdrawn to placebo compared to patients who remained on rilonacept (0.9 versus 0.1; 95% CI, -1.3 to -0.4).

Six pediatric patients with CAPS between the ages of 12 and 16 were treated with rilonacept at a weekly, SC dose of 2.2 mg/kg (up to a maximum of 160 mg) for 24 weeks during the open-label extension phase. These patients showed improvement from baseline in their symptom scores and in objective markers of inflammation (e.g., SAA and CRP). The adverse events included injection site reactions and upper respiratory symptoms as were commonly seen in the adult subjects.

Plaque Psoriasis

For this indication, the Psoriasis Area and Severity Index (PASI) is the measure of efficacy. The PASI score is a composite score that takes into consideration both the fraction of the body surface area (BSA) affected and the nature and severity of psoriatic changes within the affected regions (erythema, infiltration/plaque thickness, and desquamation). The PASI 75, which reflects a 75% or greater improvement in symptoms, is often considered the "gold standard" and is reported when available. When the PASI is not specified, it may be useful to consider that a median reduction in PASI score of 68% correlates to approximately 40% of patients achieving the PASI 75.

adalimumab (Humira)

A multicenter, randomized, double-blind, placebo-controlled trial of 147 patients with moderate to severe plaque psoriasis were treated with adalimumab 40 mg every other week, 40 mg every week, or placebo for 12 weeks and then could continue in a 48-week extension trial.[479] Patients taking placebo were switched to adalimumab for the extension trial. After 12 weeks of adalimumab treatment, 53% of patients taking adalimumab every other week, 80% of patients taking weekly adalimumab, and 4% of patients receiving placebo achieved 75% improvement in PASI score ($p<0.001$). These responses were sustained for the full 60 weeks. The study was insufficiently powered to detect rare adverse effects associated with adalimumab treatment.

A 52-week, multicenter, randomized, placebo-controlled study investigated the efficacy and safety of adalimumab 40 mg for the treatment of moderate to severe psoriasis.[480] A total of 1,212 patients were randomized to adalimumab 40 mg or placebo every other week for the first 15 weeks. Patients were evaluated at week 16; 71% of the adalimumab-treated and 7% of placebo-treated patients showed at least a 75% improvement in PASI score. During weeks 33 to 52, the percentage of patients re-randomized to placebo who lost adequate response (defined as < 50% improvement in the PASI response relative to baseline and at least a 6-point increase in PASI score from week 33) was 28% compared with 5% of patients treated continuously with adalimumab.

The CHAMPION study was a 16-week study to compare adalimumab and methotrexate in 271 patients with psoriasis.[481] Patients with moderate to severe plaque psoriasis were randomized to adalimumab (80 mg SC at week 0, then 40 mg every other week, n=108), methotrexate (7.5 mg orally, increased as needed and as tolerated to 25 mg weekly; n=110) or placebo (n=53) for 16 weeks. The primary efficacy endpoint was the proportion of patients achieving at least a 75% improvement in the PASI 75 after 16 weeks. After 16 weeks, the percent of patients achieving PASI 75 was 79.6% of adalimumab-treated patients, 35.5% for methotrexate ($p<0.001$ versus adalimumab), and 18.9% for placebo ($p<0.001$ versus adalimumab). Statistically significantly more adalimumab-treated patients (16.7%) than methotrexate-treated patients (7.3%) or placebo-treated patients (1.9%) achieved complete clearance of disease. Adverse events were similar in all the groups.

A phase 3, randomized, double-blind, placebo-controlled study assessed the efficacy of adalimumab for the treatment of psoriasis affecting fingernails (n=217).[482] Adult with both chronic, moderate to severe plaque psoriasis (≥ 6 months) and psoriasis in at least 1 fingernail were randomized 1:1 to 40 mg adalimumab every other week or placebo. The primary endpoint was the response rate at week 26 in ≥ 75% improvement in total-fingernail modified Nail Psoriasis Severity Index (mNAPSI75), which occurred in 3.4% of those assigned placebo and 46.6% assigned adalimumab (p<0.001). Benefits were also seen in several secondary endpoints, including nail pain, Nail Psoriasis Physical Functioning Severity, Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis Index, and PGA-fingernail psoriasis.

apremilast (Otezla)

Two multicenter, randomized, double-blind, placebo-controlled trials (Studies PSOR-1 and PSOR-2, also referred to as ESTEEM 1 and ESTEEM 2) enrolled a total of 1,257 subjects 18 years of age and older with moderate to severe plaque psoriasis.[483,484] Subjects were allowed to use low-potency topical corticosteroids on the face, axilla, and groin. Subjects with scalp psoriasis were allowed to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions. Study PSOR-1 enrolled 844 subjects and Study PSOR-2 enrolled 413 subjects. In both studies, subjects were randomized 2:1 to apremilast 30 mg twice daily or placebo for 16 weeks. Both studies assessed the proportion of subjects who achieved PASI 75 at week 16 and the proportion of subjects who achieved a static Physician Global Assessment (sPGA) score of clear (0) or almost clear (1) at week 16. Across both studies, subjects ranged in age from 18 to 83 years, with an overall median age of 46 years. The mean baseline BSA involvement was 25.19% (median 21%), the mean baseline PASI score was 19.07 (median 16.8), and the proportion of subjects with sPGA score of 3 (moderate) and 4 (severe) at baseline were 70% and 29.8%, respectively. In both studies (PSOR-1 and PSOR-2), the PASI 75 and sPGA were statistically significantly higher in the apremilast group when compared to placebo (PSOR-1 PASI 75 33.1% versus 5.3% and sPGA 21.7% versus 3.9%, PSOR-2 PASI 75 28.8% versus 5.8% and sPGA 20.4% versus 4.4%; p values < 0.05). In an *a priori* subgroup analysis of ESTEEM 1 and ESTEEM 2, improvement in nail and moderate to very severe scalp psoriasis at week 16 was also significantly superior to placebo; however, the groups were not stratified by these conditions.[485] Continued safety, but a high dropout rate, was seen at 156 weeks.[486] Another clinical trial, the UNVEIL study, assessed the efficacy and safety of apremilast in systemic- and biologic-naïve patients with moderate plaque psoriasis.[487] In the double-blind 16-week phase, patients were randomized to placebo. After 16 weeks, all patients received open-label treatment on apremilast through week 52. Improvements in efficacy measures were maintained from week 16 to week 52. No new safety signals were seen after 52 weeks of treatment.

STYLE, a randomized, double-blind, placebo-controlled trial, assessed the efficacy and safety of apremilast for the treatment of moderate to severe plaque psoriasis of the scalp (n=303).[488,489] Included patients have a scalp PGA (ScPGA) score ≥ 3, scalp surface area (SSA) involvement ≥ 20%, and an intolerance or inadequate response to ≥ 1 topical treatment, as well as moderate to severe plaque psoriasis. Patients were randomized 2:1 to apremilast 30 mg twice daily or placebo for 16 weeks. The mean age was 46.9 years. Most had moderate scalp psoriasis and were biologic-naïve, and a majority had failed ≥ 1 topical agent. At 16 weeks, 43.3% of apremilast-treated patients achieved a ScPGA response, defined as a score of 0 or 1 with a ≥ 2-point reduction from baseline, compared to 13.7% of those treated with placebo (difference, 29.6%; 95% CI, 19.5 to 39.7). In addition, 45.5% of apremilast-treated patients achieved a Whole Body Itch NRS score reduction ≥ 4 compared to 22.5% of those treated with placebo (difference, 23%; 95% CI, 11.5 to 34.6), and 47.1% of apremilast-treated patients achieved a Scalp Itch NRS score reduction ≥ 4 compared to 21.1% of those treated with placebo (difference, 26.2%; 95% CI, 13.9 to 38.5).

The ADVANCE (NCT03721172) study, a multicenter, randomized, double-blind, placebo-controlled trial, assessed the efficacy and safety of apremilast in 595 adults with mild to moderate plaque psoriasis (defined as a BSA involvement of 2% to 15%, sPGA score of 2 to 3, and PASI score of 2 to 15) who were intolerant to ≥ 1 topical therapy and had not received a prior biologic treatment.[490,491] Included patients were randomized 1:1 to receive either apremilast 30 mg twice daily or placebo for 16 weeks. Patients were able to use unmedicated emollients and shampoos for non-scalp and scalp lesions, respectively. The primary endpoint was the proportion of patients who achieved an sPGA response (defined as an sPGA score of clear [0] or almost clear [1] with a ≥ 2-point reduction from baseline) at week 16. At baseline, the mean BSA involvement was 6.4% and the mean PASI score was 6.5. At 16 weeks, a greater proportion of those treated with apremilast achieved a sPGA response than with placebo (21.6% versus 4.1%, respectively; treatment difference, 17.5% [95% CI, 12.2 to 22.8; p<0.0001]). A significant difference was also demonstrated in Whole Body Itch response. No new safety risks were identified by the investigators.

brodalumab (Siliq) [492,493,494]

Three multicenter, randomized, double-blind, controlled trials (AMAGINE-1, -2, and -3) enrolled adult patients (n=4,373) with moderate to severe plaque psoriasis for ≥ 6 months. Patients were required to have a minimum affected BSA of 10%, a PASI score that was ≥ 12, a sPGA score of ≥ 3, and be eligible for systemic therapy or phototherapy. Patients were randomized to either SC placebo or brodalumab 210 mg at weeks 0, 1, and 2 and every 2 weeks thereafter for 12 weeks. The AMAGINE-2 and -3 trials were active comparator trials that also included an ustekinumab group dosed as either 45 mg or 90 mg (weight based) at weeks 0, 4, and 16 followed by the same dose every 12 weeks. The trials had 2 co-primary endpoints assessed from baseline to week 12: PASI 75 and the proportion of patients with a sPGA of 0 or 1 and ≥ 2 point improvement from baseline. Other evaluated outcomes were the proportion of patients achieving an sPGA of 0 (clear) and the proportion of patients achieving a Psoriasis Symptom Inventory (PSI) score of 0 or 1 (not at all or mild, respectively). At week 12, 83%, 86%, and 85% of those treated with brodalumab in the AMAGINE-1, -2, and -3 trials achieved PASI 75, respectively, compared to 3%, 8%, and 6% in the placebo groups of these trials, respectively (p<0.001 for all comparisons). PASI 75 was achieved by 70% and 69% of ustekinumab-treated patients in AMAGINE-2 and -3, respectively. Similarly, 76%, 79%, and 80% of those treated with brodalumab in the AMAGINE-1, -2, and -3 trials achieved SPGA 0/1, respectively, compared to 1%, 4%, and 4% in the placebo groups of these trials, respectively (p<0.001 for all comparisons). As a reference comparator, sPGA was achieved by 61% and 57% of ustekinumab-treated patients in AMAGINE-2 and -3, respectively. Significant differences in all treatment groups (brodalumab or ustekinumab) were also seen in PASI 100 and sPGA of 0 in all eligible trials when compared to placebo.

All 3 trials also had a re-randomization phase at week 12 where patients originally prescribed brodalumab during the first 12 weeks were re-randomized to brodalumab 210 mg every 2 weeks or an alternative 140 mg dosing regimen. In AMAGINE-1, patients were also eligible for re-randomization to placebo. Patients originally taking placebo received brodalumab 210 mg every 2 weeks and patients originally taking ustekinumab (AMAGINE-2 and -3 only) continued to take ustekinumab every 12 weeks until week 52 when they were switched to brodalumab 210 mg every 2 weeks. At week 52, the percent of patients who maintained a sPGA of 0 or 1 and PASI 100 score was 83.1% and 67.5%, respectively, for those treated with brodalumab 210 mg every 2 weeks in the AMAGINE-1 trial. The percent of patients who maintained a sPGA of 0 or 1 and PASI 100 score was 63% and 56%, respectively, for those treated with constant brodalumab 210 mg in the AMAGINE-2 trial. Finally, the percent of patients who maintained a sPGA of 0 or 1 and PASI 100 score was 61% and 53%, respectively, for those treated with constant brodalumab 210 mg in the AMAGINE-3 trial. Notably, 30% and 29% of those with constant ustekinumab treatment

achieved PASI 100 at week 52 in the AMAGINE-2 and AMAGINE-3 trials, respectively. The authors concluded brodalumab therapy provided significant improvements in patients with moderate to severe psoriasis.

certolizumab pegol (Cimzia)

Two phase 3, multicenter, randomized, double-blind, placebo-controlled studies assessed the efficacy and safety of certolizumab pegol in adult patients with moderate to severe chronic plaque psoriasis who were eligible for systemic therapy or phototherapy (CIMPASI-1: n=234; CIMPASI-2: n=227).[495,496] Included patients were required to have a PGA ≥ 3, a PASI score ≥ 12, and BSA involvement of ≥ 10% and were randomized 2:2:1 to certolizumab 400 mg, certolizumab 200 mg, or placebo every 2 weeks. At week 16, certolizumab-treated patients achieving a PASI 50 continued treatment through week 48. The coprimary endpoints were those with a response at week 16, as measured by a PASI 75 and a PGA of 0 or 1 with a ≥ 2-point improvement. Response based on PASI 75 occurred in 6.5%, 66.5%, and 75.8% of the placebo, certolizumab 200 mg, and certolizumab 400 mg groups, respectively, in CIMPASI-1 and in 11.6%, 81.4%, and 82.6%, respectively, in CIMPASI-2 (p<0.0001 for active treatments versus placebo). Response based on PGA occurred in 4.2%, 47%, and 57.9% of the placebo, certolizumab 200 mg, and certolizumab 400 mg groups, respectively, in CIMPASI-1 and in 2%, 66.8%, and 71.6%, respectively, in CIMPASI-2 (p<0.0001 for active treatments versus placebo). PASI 90 was achieved in 0.4%, 35.8%, and 43.6% of the placebo, certolizumab 200 mg, and certolizumab 400 mg groups, respectively, in CIMPASI-1 and in 4.5%, 52.6%, and 55.4%, respectively, in CIMPASI-2 (p<0.0001 for active treatments versus placebo). At week 48, PASI 75 was achieved by 87.1% and 67.2% of those treated with certolizumab 400 mg and 200 mg, respectively, in CIMPASI-1 and 81.3% and 78.7%, respectively, in CIMPASI-2. At week 48, PGA 0/1 was achieved by 69.5% and 52.7% of those treated with certolizumab 400 mg and 200 mg, respectively, in CIMPASI-1 and 66.6% and 72.6%, respectively, in CIMPASI-2. A *post-hoc* subgroup analysis, stratified by ≤ 90 kg or > 90 kg, determined that patients with both lower body weight and lower disease severity may have an acceptable response at a lower dosage of 200 mg every other week. Extension study 3-year results have demonstrated sustained efficacy.[497]

certolizumab pegol (Cimzia) versus placebo and etanercept (Enbrel)

Another phase 3, multicenter, randomized, double-blind study compared the efficacy of certolizumab pegol to placebo and etanercept in adults with moderate to severe chronic plaque psoriasis who were eligible for systemic therapy or phototherapy (CIMPACT; n=559).[498,499] Included patients had the same requirements as in the CIMPASI trials but were randomized 3:3:1:3 to 16 weeks of certolizumab pegol 200 mg every other week (following 400 mg at weeks 0, 2, and 4), certolizumab pegol 400 mg every other week, placebo, or etanercept 50 mg twice weekly (through 12 weeks). The primary endpoint was the proportion of patients achieving PASI 75 at week 12. At week 12, 53.3%, 5%, 61.3% and 66.7% achieved PASI 75 in the etanercept, placebo, certolizumab 200 mg, and certolizumab 400 mg groups, respectively (p<0.0001 for both certolizumab groups versus placebo; not significant [NS] versus etanercept); 1.9%, 39.8%, and 50.3% achieved PGA 0/1 in the placebo, certolizumab 200 mg, and certolizumab 400 mg groups, respectively (p<0.001 for both versus placebo); and 0.2%, 31.2%, and 34% achieved PASI 90, respectively (p<0.0001 for both versus placebo). Those who achieved PASI 75 response at week 16 were then re-randomized to either continue treatment with certolizumab or to placebo (discontinue active therapy). At 48 weeks, 98% of those who continued certolizumab 400 mg achieved PASI 75 compared to 36% who were re-randomized to placebo and 79.5% of those who continued certolizumab 200 mg were

PASI 75 responders compared to 45.5% of placebo. PASI response was generally maintained at 144 weeks, and no new safety signals were identified.[500]

etanercept (Enbrel)

A double-blind study enrolled 583 adult patients with active, clinically stable plaque psoriasis involving at least 10% of BSA, with a minimum PASI of 10 at screening and who had received or were a candidate to receive systemic psoriasis therapy or phototherapy.[501] During the first 12 weeks of the study, patients were randomly assigned to receive etanercept 25 or 50 mg or placebo twice weekly as SC injections. During the second 12 weeks, all patients received etanercept 25 mg twice weekly. The primary endpoint, a PASI 75 response at week 12, was achieved by 49% of patients in the etanercept 50 mg group, 34% in the 25 mg group, and 3% in the placebo group ($p<0.0001$ for each etanercept group compared with placebo). At week 24 (after 12 weeks of open-label etanercept 25 mg twice weekly), a PASI 75 was achieved by 54% of patients whose dose was reduced from 50 mg to 25 mg twice weekly, by 45% of patients in the continuous 25 mg twice weekly group, and by 28% in the group that received placebo followed by etanercept 25 mg twice weekly. Etanercept was well tolerated throughout the study.

A 48-week, randomized, double-blind, placebo-controlled trial evaluated the efficacy of etanercept in 211 pediatric patients (ages 4 to 17 years) with moderate to severe plaque psoriasis (sPGA score ≥ 3, ≥ 10% BSA affected, and PASI ≥ 12) who were candidates for phototherapy or systemic therapy or were inadequately controlled on topical therapy.[502,503] Patients were randomized to placebo or etanercept 0.8 mg/kg (maximum, 50 mg/dose) once weekly for 12 weeks. Then all patients were given etanercept 0.8 mg/kg (maximum, 50 mg/dose) once weekly for a 24-week open-label phase, followed by a 12-week withdrawal-retreatment period. Following 12 weeks of treatment, response was defined as a PASI score reduction of at least 75% from baseline and was achieved in 11% of patients treated with placebo compared to 57% of patients with etanercept. PASI 90 (90% reduction in PASI score) was achieved in 7% of placebo patients compared to 27% of etanercept patients. Thirteen percent of placebo patients had sPGA scales considered “clear” or “almost clear” compared to 52% of those treated with etanercept. Maintenance of response was evaluated during the final 12 weeks, and maintenance was higher at week 48 with etanercept compared to placebo (65% versus 49% for PASI 75 in etanercept and placebo groups, respectively).

guselkumab (Tremfya)

The VOYAGE 1 trial, a phase 3, double-blind, placebo- and active-comparator trial, was conducted to assess the efficacy and safety of guselkumab compared to adalimumab in patients ≥ 18 years old for the treatment of moderate to severe plaque psoriasis.[504] Patients were randomized to guselkumab 100 mg (weeks 0 and 4, then every 8 weeks; n=329); placebo then guselkumab (placebo at weeks 0, 4, and 12, then guselkumab weeks 16 and 20 and every 8 weeks thereafter; n=174); or adalimumab (80 mg week 0, 40 mg week 1, then 40 mg every 2 weeks through week 47; n=334). The Investigator Global Assessments (IGA), PASI, Dermatology Life Quality Index (DLQI), Psoriasis Symptoms and Signs Diary (PSSD), and safety were evaluated through week 48. The results demonstrated that guselkumab was superior ($p<0.001$) to placebo at week 16. When using the IGA 0/1 (clear/minimal) and PASI 90 (≥ 90% improvement in PASI score from baseline), guselkumab was superior ($p<0.001$) to adalimumab at week 16 (85.1% versus 65.9% and 73.3% versus 49.7%, respectively), week 24 (84.2% versus 61.7% and 80.2% versus 53%, respectively), and week 48 (80.5% versus 55.4% and 76.3% versus 47.9%, respectively). PASI 100 responses were significantly better in guselkumab treated patients compared to adalimumab at weeks 24 and 48 ($p<0.001$). At week 48, the health related quality of life (HRQOL) measures (mean change, -11.8 versus -

9.2, respectively) and PSSD symptom scores (symptom score of 0 was 41.9% versus 23.1%, respectively) were significantly greater for guselkumab versus adalimumab (p<0.001). Adverse event rates were comparable between treatments and patient reported improvements were significant. An open-label extension study has demonstrated maintained clinical response through week 100 with guselkumab.[505]

The VOYAGE 2 trial was a phase 3, multicenter, randomized, double-blind, placebo and adalimumab comparator-controlled study to assess efficacy and safety of guselkumab in adults with moderate to severe psoriasis.[506] The study included interrupted treatment and changing adalimumab nonresponders to guselkumab. Patients were randomized to guselkumab 100 mg (weeks 0 and 4, then every 8 weeks; n=496); placebo then to guselkumab (weeks 0, 4, and 12 then guselkumab weeks 16 and 20; n=248); or adalimumab (80 mg week 0, then 40 mg week 1, and every 2 weeks through week 23; n=248). At week 28, guselkumab PASI 90 responders were re-randomized to guselkumab or placebo with guselkumab after loss of response. Placebo then to guselkumab responders and adalimumab responders were provided placebo, then guselkumab after they had loss of response; nonresponders received guselkumab. At week 16, a greater proportion of patients achieved an IGA 0/1, PASI 90, and PASI 75 response when treated with guselkumab compared to adalimumab. At week 24, the higher response rates were maintained with the guselkumab versus adalimumab group for IGA 0 (51.8% versus 31.5%), IGA 0/1 (83.5% versus 64.9%), PASI 90 (75.2% versus 54.8%), and PASI 100 (44.2% versus 26.6%). During the randomized withdrawal and retreatment period, PASI 90 patients who remained on guselkumab were better maintained compared to re-randomized placebo patients at week 28 (median time to lose PASI 90 was 15.2 weeks). At week 48 IGA, PASI, DLQI, and PSSD symptom and sign scores from baseline were significantly greater in the maintenance guselkumab group versus the withdrawal placebo group (p<0.001). Patients who were adalimumab nonresponders started guselkumab at week 28. These patients' PASI 90 and PASI 100 response rates increased after switching to guselkumab at 48 weeks, reaching 66.1% and 28.6%, respectively.

Following continued evaluation in the VOYAGE 1 and 2 trials, the 3-year response rates to guselkumab were 82.8% and 77.2%, respectively, for PASI 90.[507] Also at 3 years, 50.8% and 48.8% achieved PASI 100, respectively. Regarding IGA scores, 82.1% and 83%, respectively, achieved a score of 0/1, while 53.1% and 52.9%, respectively, achieved an IGA score of 0. An open-label extension study of VOYAGE 2 has demonstrated maintained clinical response up to 4 years with guselkumab.[508]

The NAVIGATE trial evaluated the efficacy and safety of guselkumab in patients with moderate to severe plaque psoriasis who had an inadequate response to ustekinumab.[509] The study was a randomized, double-blind study with 871 participants receiving ustekinumab (45 mg or 90 mg; open-label) at weeks 0 and 4. At week 16, patients with an inadequate response to ustekinumab were randomized (double-blind) to guselkumab 100 mg or to continue using ustekinumab (67% of patients with IGA 0/1 at week 16 continued open-label ustekinumab). At week 28 and week 52, a greater proportion of guselkumab patients achieved IGA 0/1 and ≥ 2 grade improvement compared to the randomized ustekinumab patients (week 28: 31.1% versus 14.3%, respectively [p=0.001]; week 52: 36.3% versus 17.3% respectively [p<0.001]). At week 52, compared to the randomized ustekinumab patients, a greater proportion of guselkumab treated patients achieved a PASI 90 (51.1% versus 24.1%, respectively; p<0.001), PASI 100 (20% versus 7.5%, respectively; p=0.003), and DLQI 0/1 (38.8% versus 19%, respectively; p=0.002).

The ORION study assessed the efficacy of the One-Press delivery system of guselkumab in a phase 3, multicenter, double-blind, placebo-controlled study in 78 randomized adults with moderate-to-severe psoriasis.[510,511] Patients were randomized 4:1 to guselkumab 100 mg at weeks 0 and 4 and every 8 weeks thereafter with crossover at week 16 in the placebo group. A higher portion of the active-treatment group

achieved an IGA of 0/1 (80.6% versus 0, respectively; p<0.001) or a PASI 90 (75.8% versus 0, respectively; p<0.001) at week 16 compared to the placebo group.

guselkumab (Tremfya) versus secukinumab (Cosentyx)

ECLIPSE, a phase 3, multinational, double-blind, randomized, noninferiority trial, compared the efficacy of guselkumab and secukinumab for the treatment of adults with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy (n=1,048).[512] Patients were randomized 1:1 to either guselkumab 100 mg at weeks 0 and 4 then every 8 weeks thereafter or secukinumab 300 mg at weeks 0, 1, 2, 3, and 4, and then every 4 weeks thereafter. The primary endpoint was the proportion of patients who achieved PASI 90 at week 48, which was found to be higher in those treated with guselkumab (84%) compared to those treated with secukinumab (70%), thus meeting both noninferiority (within the margin of 10%) and superiority requirements (p<0.0001). Noninferiority within the margin of 10% was also established in those achieving PASI 75 at both weeks 12 and 48 (85% guselkumab versus 80% secukinumab); however, guselkumab did not meet superiority requirements (p=0.0616) in this secondary outcome parameter.

ixekizumab (Taltz)

Three multicenter, randomized, double-blind, placebo-controlled trials (UNCOVER-1, -2, and -3) assessed the efficacy if ixekizumab in adult patients with plaque psoriasis who were candidates for phototherapy or systemic therapy (n=3,866).[513,514,515] Patients were required to have a minimum BSA involvement of 10%, sPGA score of ≥ 3 in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 5, and PASI score ≥ 12. In all trials, subjects were randomized to either placebo or ixekizumab (80 mg every 2 weeks for 12 weeks following a 160 mg starting dose. In addition, 2 studies included an active comparator arm (UNCOVER-2 and -3), in which subjects were also randomized to etanercept 50 mg twice weekly for 12 weeks. All the trials evaluated the changes from baseline to week 12 in the 2 co-primary endpoints: 1) PASI 75; and 2) sPGA of "0" (clear) or "1" (minimal), the proportion of subjects with a sPGA 0 or 1 and at least a 2-point improvement. Other evaluated outcomes included the proportion of subjects with a sPGA score of 0 (clear), a reduction of at least 90% in PASI (PASI 90), a reduction of 100% in PASI (PASI 100), and an improvement of itch severity as measured by a reduction of at least 4 points on an 11-point itch Numeric Rating Scale. Median baseline PASI score ranged from approximately 17 to 18. Baseline sPGA score was severe or very severe in 51% of subjects in UNCOVER-1, 50% in UNCOVER-2, and 48% in UNCOVER-3. Of all subjects, 44% had received prior phototherapy, 49% had received prior conventional systemic therapy, and 26% had received prior biologic therapy for the treatment of psoriasis.

At week 12, the percentage of patients that experienced an sPGA score of "0" or "1" in the every 2 week ixekizumab group versus the placebo group was 81.8% versus 3.2% (UNCOVER-1), 83% versus 2% (UNCOVER-2), and 81% versus 7% (UNCOVER-3).[516,517,518] At week 12, the percentage of patients that experienced at least a 75% reduction in their PASI composite score in the every 2 week ixekizumab group versus the placebo group was 89.1% versus 3.9% (UNCOVER-1), 90% versus 2% (UNCOVER-2), and 87% versus 7% (UNCOVER-3). The differences between the ixekizumab group and the placebo group all fell within the 95% confidence interval with a p<0.0001 for the respective endpoints. At week 12, the percentage of patients that experienced an sPGA score of "0" or "1" in the every-2-week ixekizumab group versus the etanercept group was 83% versus 36% (UNCOVER-2), and 81% versus 42% (UNCOVER-3). At week 12, the percentage of patients that experienced at least a 75% reduction in their PASI composite score in the every-2-week ixekizumab group versus the etanercept group was 90% versus 42%

(UNCOVER-2), 87% versus 53% (UNCOVER-3). These differences between the ixekizumab group and the etanercept group all fell within the 95% confidence interval with a p<0.0001 for the respective endpoints. Ixekizumab has been reported as well-tolerated and had continued efficacy reported though 60 weeks in UNCOVER-1 and UNCOVER-2 and through 108 weeks in UNCOVER-3.[519,520]

Patients originally randomized to ixekizumab in UNCOVER-1 and UNCOVER-2 who were responders at week 12 (sPGA of 0 or 1) were re-randomized to an additional 48 weeks of either a maintenance dose of ixekizumab 80 mg every 4 weeks or placebo to evaluate the maintenance and durability of response.[521,522] Furthermore, ixekizumab non-responders (sPGA > 1) and subjects who relapsed (sPGA ≥ 3) during the maintenance period were placed on ixekizumab 80 mg every 4 weeks. For patients who were responders at week 12, the percent who maintained a response (an sPGA of "0" or "1") at the end of week 60 was higher for the ixekizumab group compared to the placebo group (75% versus 7%, respectively). The median time to relapse (sPGA ≥ 3) was 164 days for responders at week 12 who got re-randomized to treatment withdrawal and received placebo. Of the patients re-randomized to receive placebo, 66% regained a response of at least "0" or "1" within 12 weeks of restarting treatment with ixekizumab every 4 weeks. An open-label assessment of UNCOVER-3 at 3 and 5 years did not identify additional safety concerns and demonstrated sustained clinical efficacy.[523,524]

A randomized, double-blind, placebo-controlled trial assessed the effectiveness and safety of ixekizumab for the treatment of plaque psoriasis in adults who genital involvement (IXORA-Q; n=149).[525] Included patients had minimal BSA involvement (1%), a sPGA score of ≥ 3, a sPGA of genitalia score of ≥ 3, and failed to respond to or were intolerant of ≥ 1 topical therapy used for treatment of genital psoriasis. In addition, they were required to be candidates for phototherapy and/or systemic therapy. Patients were randomized to ixekizumab 160 mg followed by 80 mg every 2 weeks for 12 weeks or placebo, and the primary endpoint evaluated with the proportion of patients at week 12 who achieved a 0 or 1 the on sPGA of genitalia. At 12 weeks, 73% of ixekizumab patients achieved this endpoint, compared to 8% of those assigned placebo. In addition, 73% of ixekizumab patients achieved a sPGA score of 0 or 1, compared to 8% of those assigned placebo. Also, a higher proportion of patients with a baseline Genital Psoriasis Symptoms Scale (GPSS) itch score ≥ 4 achieved a ≥ 4 point improvement in the ixekizumab group compared to placebo (55% versus 6%, respectively). Likewise, a higher proportion of those with a baseline Genital Psoriasis Sexual Frequency Questionnaire (GenPs-SFQ) item 2 score ≥ 2 or 1 in the ixekizumab group compared to placebo (78% versus 21%, respectively). In an open-label extension in which all originally randomized patients were eligible for ixekizumab, response results were similar at 52 weeks.[526]

IXORA-Peds, a randomized, double-blind, placebo-controlled study, evaluated the safety and efficacy of ixekizumab in pediatric patients ages 6 to 18 years with moderate to severe plaque psoriasis, defined as a sPGA ≥ 3, > 10% of BSA, and PASI ≥ 12, who were inadequately controlled on topical therapy or were candidates for phototherapy or systemic therapy.[527] Included patients were randomized to weight-based ixekizumab dosing (FDA-approved dosing in this population) or to placebo. At 12 weeks, one of the primary outcomes, the proportion of patients who achieved a PASI ≥ 75%, was 89% of those treated with ixekizumab (n=115) compared to 25% treated with placebo (n=56). At 12 weeks, another primary outcome, the proportion of patients who achieved a sPGA of 0 or 1 with ≥ 2 point improvement from baseline, was achieved in 81% of those treated with ixekizumab compared to 11% treated with placebo.

ixekizumab (Taltz) versus guselkumab (Tremfya)

IXORA-R, a 24-week, multicenter, double-blind, parallel-group, randomized controlled trial, compared the efficacy of ixekizumab and guselkumab for the treatment of moderate to severe chronic plaque psoriasis

(n=1,027).[528] Prior use of biologics was allowed, but patients with prior use of IL-23p19 antagonists and those having failed another IL-17 antagonist were excluded. Eligible adults were randomized 1:1 to ixekizumab or guselkumab (dosing per approved labeling). The primary endpoint was the proportion of patients achieving PASI 100 at week 12, which occurred in 41% of those treated with ixekizumab compared to 25% treated with guselkumab (p<0.001). At 24 weeks, ixekizumab was also noninferior to guselkumab in PASI 100 (50% versus 52%, respectively; p=0.41).[529] In addition, a greater number of ixekizumab-treated patients showed clear nails at week 24 compared to those treated with guselkumab (52% versus 31%, respectively; p=0.007).

ixekizumab (Taltz) versus ustekinumab (Stelara)

IXORA-S, a 52-week, phase 3b, multicenter, double-blind, parallel-group, randomized controlled trial, compared the efficacy of ixekizumab and ustekinumab for the treatment of moderate to severe psoriasis.[530] Patients with moderate to severe psoriasis for ≥ 6 months who had a contraindication or failure to ≥ 1 systemic therapy were randomized to ixekizumab (160 mg, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks) or ustekinumab (45 mg or 90 mg weight-based dosing per approved labeling). The primary endpoint was the proportion of patients achieving PASI 90 at week 12. Key secondary endpoints at week 12 included PASI 75, PASI 100, sPGA 0/1, and sPGA of 0, among others. At week 12, ixekizumab was superior to ustekinumab in PASI 90 response (response difference, 32.1%; 97.5% CI, 19.8 to 44.5; p<0.001). Response rates for PASI 75, PASI 100, and sPGA 0/1 were significantly higher for ixekizumab than for ustekinumab (adjusted p<0.05 for all comparisons). At week 24, more ixekizumab-treated patients than ustekinumab-treated patients achieved PASI 75 (p=0.029) and PASI 90 (p<0.001). Adverse effects were similar between groups. Additional assessments are planned at 52 weeks. At 52 weeks, a higher proportion of ixekizumab-treated patients compared to ustekinumab achieved PASI 90 (76.5% versus 59%, respectively), sPGA of 0 (52.9% versus 36.1%, respectively), or sPGA of 0 or 1 (82.1% versus 65.1%, respectively).[531] Treatment-emergent and serious adverse effects and discontinuation rates were similar; however, injection site reactions occurred more frequently with ixekizumab compared to ustekinumab (16.3% versus 1.2%, respectively).

risankizumab-rzaa (Skyrizi)

Four multicenter, randomized, double-blind studies led to the approval of risankizumab-rzaa: UltIMMa-1, ULTIMMA-2, IMMhance, and IMMvent.[532,533] All trials assessed the efficacy of risankizumab-rzaa in patients ≥ 18 years with moderate to severe plaque psoriasis, a BSA involvement of ≥ 10%, a sPGA score of ≥ 3 (“moderate”) in the overall assessment, and a PASI score ≥ 12. In all studies, 48%, 42%, and 38% of the included patients had received prior non-biologic systemic therapy, biologic therapy, and phototherapy, respectively. UltIMMa-1 and UltIMMa-2 were replicate trials in which eligible patients were stratified by weight and prior TNF treatment and randomized 3:1:1 to risankizumab-rzaa 150 mg SC, ustekinumab 45 mg or 90 mg based on weight, or placebo at weeks 0 and 4 (UltIMMa-1, n=506; UltIMMa-2, n=491). Patients with prior exposure to ustekinumab were excluded. The coprimary endpoints were the proportions of patients achieving a PASI 90 and a sPGA score of 0 or 1 at week 16 in the intent-to-treat population. At week 16 in UltIMMa-1, PASI 90 was achieved in 75.3% of those treated with risankizumab-rzaa versus 4.9% treated with placebo (treatment difference, 70.3%; 95% CI, 64 to 76.7; p<0.0001) and versus 42% with ustekinumab (treatment difference, 33.5%; 95% CI, 22.7 to 44.3; p<0.0001), and sPGA score of 0 or 1 was achieved in 87.8% of those treated with risankizumab-rzaa versus 8% treated with placebo (treatment difference, 79.9%; 95% CI, 73.5 to 86.3; p<0.0001) and versus 63% with ustekinumab (treatment difference, 25.1%; 95% CI, 15.2 to 35; p<0.0001). At week 16 in UltIMMa-

2, PASI 90 was achieved in 74.8% of those treated with risankizumab-rzaa versus 2% treated with placebo (treatment difference, 72.5%; 95% CI, 66.8 to 78.2; p<0.0001) and versus 47.5% with ustekinumab (treatment difference, 27.6%; 95% CI, 16.7 to 38.5; p<0.0001), and sPGA score of 0 or 1 was achieved in in 83.7% of those treated with risankizumab-rzaa versus 5.1% treated with placebo (treatment difference, 78.5%; 95% CI, 72.4 to 84.5; p<0.0001) and versus 61.6% with ustekinumab (treatment difference, 22.3%; 95% CI, 12 to 32.5; p<0.0001). Treatment-emergent adverse effects were similar in all groups. PASI 100 occurred in 36% and 51% of those treated with risankizumab-rzaa in UltIMMa-1 and UltIMMa-2, respectively, and in zero patients treated with placebo. No significant differences in efficacy were found in subgroup analyses of age, gender, race, weight, prior treatment, or baseline PASI score. Patients also reported an improvement in symptoms related to pain, redness, itching, and burning when assessed via the Psoriasis Symptom Scale (PSS). Following 16 weeks of double-blind treatment, patients assigned to placebo were switched to risankizumab-rzaa 150 mg at week 16, while those assigned an active treatment continued that treatment, beginning every 12 weeks starting at 16 weeks. At week 52, 82% and 81% of those in UltIMMa-1 and UltIMMa-2, respectively, achieved PASI 90, 58% and 60% achieved a sPGA of 0 or 1, and 56% and 60% achieved PASI 100. In addition, 88% of those achieving PASI 90 at week 16 had a continued response at week 52.

In IMMhance, patients were randomized 4:1 to risankizumab-rzaa or placebo SC at weeks 0 and 4 and every 12 weeks thereafter (n=507).[534,535,536] Risankizumab-rzaa demonstrated efficacy at week 16 over placebo in both coprimary endpoints of sPGA 0 or 1 (84% versus 7%, respectively) and PASI 90 (73% versus 2%, respectively). PASI 100 was achieved in 47% of those assigned risankizumab-rzaa and 1% of those assigned placebo. At week 28, patients achieving sPGA of 0 or 1 were re-randomized to continue risankizumab-rzaa or assigned to withdrawal of therapy. At 52 weeks, 87% of those with continued risankizumab-rzaa had a continued response compared to 61% of those assigned to treatment withdrawal.

risankizumab-rzaa (Skyrizi) versus adalimumab (Humira)

In the multinational, double-dummy IMMvent trial, 605 patients were randomized 1:1 to risankizumab-rzaa 150 mg SC at weeks 0 and 4 or adalimumab 80mg SC at week 0 and 40 mg SC at weeks 1, 3, 5, and every other week thereafter for the first 16 weeks of the trial (n=605).[537] Patients with prior exposure to adalimumab were excluded. The coprimary endpoints were PASI 90, and sPGA of 0 of 1 at week 16. At week 16, PASI 90 was achieved by 72% and 47% of those assigned risankizumab-rzaa and adalimumab, respectively (absolute difference, 24.9%; 95% CI, 17.5 to 32.4; p<0.0001), and sPGA of 0 or 1 was achieved by 84% and 60% of those assigned risankizumab-rzaa and adalimumab, respectively (absolute difference, 23.3%; 95% CI, 16.6 to 30.1; p<0.0001). In the second part of the study (weeks 16 to 44), adalimumab intermediate responders were re-randomized to either continue adalimumab or switch to 150 mg risankizumab-rzaa. At week 44 in those who were intermediate adalimumab responders in the first part of the study, 66% and 21% of those assigned risankizumab-rzaa and adalimumab, respectively (absolute difference, 45%; 95% CI, 28.9 to 61.1; p<0.0001).

secukinumab (Cosentyx)

Four randomized, double-blind, placebo-controlled, multicenter trials (trials 1, 2, 3, and 4) enrolled 2,403 patients (691 randomized to secukinumab 300 mg, 692 to secukinumab 150 mg, 694 to placebo, and 323 to a biologic active control) 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and PASI ≥ 12, and who were candidates for phototherapy or systemic therapy.[538,539] In all trials, the endpoints were the proportion of subjects who achieved a reduction in PASI

≥ 75% (PASI 75) from baseline to week 12 and treatment success (clear or almost clear) on the Investigator's Global Assessment modified 2011 (IGA). Other evaluated outcomes included the proportion of subjects who achieved a reduction in PASI score of at least 90% (PASI 90) from baseline at week 12, maintenance of efficacy to week 52, and improvements in itching, pain, and scaling at week 12 based on the Psoriasis Symptom Diary. PASI 90 response at week 12 was achieved with secukinumab 300 mg and 150 mg compared to placebo in 59% (145/245) and 39% (95/245) versus 1% (3/248) of subjects, respectively (Trial 1: ERASURE trial) and 54% (175/327) and 42% (137/327) versus 2% (5/326) of patients, respectively (Trial 2: FIXTURE trial). Similar results were seen in Trials 3 and 4. With continued treatment over 52 weeks, subjects in Trial 1 who were PASI 75 responders at week 12 maintained their responses in 81% (161/200) of the subjects treated with secukinumab 300 mg and in 72% (126/174) of subjects treated with secukinumab 150 mg. Trial 1 patients who were clear or almost clear on the IGA at week 12 also maintained their responses in 74% (119/160) of subjects treated with secukinumab 300 mg and in 59% (74/125) of subjects treated with secukinumab 150 mg. Similarly, in Trial 2, PASI 75 responders maintained their responses in 84% (210/249) of subjects treated with secukinumab 300 mg and in 82% (180/219) of subjects treated with secukinumab 150 mg. Trial 2 subjects who were clear or almost clear on the IGA also maintained their responses in 80% (161/202) of subjects treated with secukinumab 300 mg and in 68% (113/167) of patients treated with secukinumab 150 mg. The manufacturer of secukinumab sponsored the study.

GESTURE, a double-blind, randomized, controlled trial, assessed the efficacy of secukinumab for the treatment of moderate to severe palmoplantar psoriasis in adults with plaque psoriasis that was inadequately controlled by topical therapy, phototherapy, and/or systemic therapy (n=205).[540] Patients were randomized 1:1:1 to placebo, secukinumab 150 mg, or secukinumab 300 mg. The primary endpoint was a response of 0 (clear) or 1 (almost clear/minimal) on the Palmoplantar Investigator's Global Assessment (ppIGA) at week 16. At week 16, the percentage of subjects who achieved ppIGA 0/1 with secukinumab 150 mg and 300 mg (33.3% and 22.1%, respectively) was superior to placebo (1.5%; p<0.001). Likewise, Palmoplantar Psoriasis Area and Severity Index (ppPASI) was significantly reduced with secukinumab 150 mg and 300 mg (-35.3% and -54.5%, respectively) compared with placebo (-4%, p<0.001).

A 20-week, multicenter, randomized, double-blind, placebo-controlled study assessed the efficacy of secukinumab in patients with moderate to severe scalp psoriasis (with or without plaque psoriasis elsewhere on the body) of ≥ 6 months (n=102).[541] Eligible patients had prior inadequate control with topical treatments, phototherapy, or systemic therapies and were randomized 1:1 to SC self-administered secukinumab 300 mg or placebo at weeks 0, 1, 2, and 3 and then every 4 weeks thereafter. The primary efficacy variable was 90% improvement of Psoriasis Scalp Severity Index (PSSI 90) score from baseline at week 12. At week 12, PSSI 90 was significantly improved with secukinumab compared to placebo (52.9% versus 2%, respectively; proportional difference, 0.51 [95% CI, 0.37 to 0.65; p<0.001]). In addition, an IGA response of 0 or 1 occurred in more patients treated with secukinumab compared to placebo (56.9% versus 5.9%, respectively; proportional difference, 0.51 [95% CI, 0.36 to 0.66; p<0.001]).

The safety and efficacy of secukinumab in pediatric patients with plaque psoriasis were assessed in a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial (NCT02471144) in patients 6 years to < 18 years of age with severe plaque psoriasis (PASI ≥ 20, IGA 4, and ≥ 10% BSA) who were candidates for systemic therapy.[542,543] Included patients were randomized to placebo, secukinumab (< 25 kg = 75 mg, 25 to 50 kg = 75 mg or 150 mg, ≥ 50 kg = 150 mg or 300 mg), or an active control. Secukinumab was administered at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter. At 12 weeks,

placebo-assigned nonresponders were transitioned to secukinumab (dosing as described beginning at week 12). At baseline, 83% were Caucasian, 60% were female, the mean age was 13.5 years, the mean weight was 50.6 kg, 9% had concomitant psoriatic arthritis, and the mean PASI score was 26. Regarding prior therapy, 43% had prior phototherapy, 55% had conventional systemic therapy, and 3% had used biologics. The co-primary endpoints were the proportion of participants achieving PASI 75 and proportion of participants achieving an IGA score of 0 or 1 (and ≥ 2 point improvement) at week 12. PASI 90 was also reported. At 12 weeks, 56% of those treated with secukinumab compared to 5% of those treated with placebo achieved the IGA endpoint, while 70% and 60% of those treated with secukinumab compared to 15% and 2% of those treated with placebo achieved PASI 75 and PASI 90, respectively.

secukinumab (Cosentyx) versus ustekinumab (Stelara)

CLEAR, a randomized, double-blind, 52-week trial compared the efficacy of secukinumab to ustekinumab in the treatment of adult patients with moderate to severe plaque psoriasis (n=676).[544] Patients with inadequate control from topical treatments, phototherapy, and/or previous systemic therapy, but without prior exposure to biologics targeting IL-17 or IL-12/IL-23, were randomized 1:1 to SC secukinumab 300 mg or ustekinumab dosed based on body weight (both per labeling). The primary endpoint was 90% improvement in PASI (PASI 90) at week 16. At week 16, a greater percentage of patients in the secukinumab group (79%) achieved PASI 90 compared to ustekinumab (57.6%; p<0.0001). A significant difference was also seen between groups in PASI 100 and PASI 75 at week 16 (p≤0.001). Adverse effects were reported in over half the population in each group with infections being the most commonly reported adverse effect; however, most infections were considered to be nonserious and did not lead to discontinuation. The authors concluded that secukinumab was superior to ustekinumab in the treatment of moderate to severe psoriasis. In an analysis of the data at 52 weeks, secukinumab demonstrated superiority to ustekinumab in the proportion of subjects with PASI 90 (76% versus 61%, respectively; p<0.0001), PASI 100 (46% versus 36%, respectively; p=0.0103), and IGA responses of clear/almost clear skin (80% versus 65%, respectively; p<0.0001).[545] Adverse effects were comparable. This trial was funded by the manufacturer of secukinumab.

Another randomized, double-blind, 52-week trial, CLARITY, compared the efficacy and safety of secukinumab and ustekinumab for the treatment of moderate to severe plaque psoriasis.[546] Patients were randomized 1:1 to SC secukinumab 300 mg or ustekinumab dosed as recommended by the manufacturer. At week 12, secukinumab was superior to ustekinumab in PASI 90 (66.5% versus 47.9%, respectively) and IGA score of 0/1 (72.3% versus 55.4%, respectively; p<0.0001 for both). At 52 weeks, secukinumab was superior to ustekinumab in PASI 90 (73.2% versus 59.8%, respectively; OR, 1.84 [95% CI, 1.41 to 2.41; p<0.0001]) and IGA score of 0/1 (76% versus 60.2%, respectively; OR, 2.12 [95% CI, 1.61 to 2.79; p<0.0001]).[547]

tildrakizumab-asmn (Ilumya)

Two, multinational, 3-part, parallel group, double-blind, randomized, placebo-controlled studies assessed the safety and efficacy of tildrakizumab-asmn for the treatment of moderate to severe chronic psoriasis in patients ≥ 18 years (reSURFACE 1 and reSURFACE 2).[548,549] In both trials, moderate to severe chronic psoriasis was defined as BSA involvement ≥ 10%, PGA score ≥ 3, and PASI score ≥ 12. In the first part, participants were randomized to active treatments or placebo. The co-primary endpoints were the proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥ 2 grade score reduction from baseline) at week 12. In reSURFACE 1, 772 patients were randomized 2:2:1 to tildrakizumab-asmn 200 mg, tildrakizumab-asmn 100 mg, or placebo administered at weeks 0 and 4 during part 1 and at week

16 during part 2 (weeks 12 and 16 for participants re-randomized from placebo to tildrakizumab-asmn). At week 12, 62% of patients in the 200 mg group and 64% patients in the 100 mg group achieved PASI 75 versus 6% in the placebo group (p<0.0001 for both active dosing regimens versus placebo), and 59% of the 200 mg group and 58% of the 100 mg group achieved PGA responses versus 7% in the placebo group (p<0.0001 for both active dosing regimens versus placebo). Serious adverse events were similar between groups. In reSURFACE 2, 1,090 patients were randomized 2:2:1:2 to tildrakizumab-asmn 200 mg or tildrakizumab-asmn 100 mg administered at weeks 0 and 4 during part 1 and at week 16 during part 2 (weeks 12 and 16 for participants re-randomized from placebo to tildrakizumab-asmn), placebo, or etanercept 50 mg given twice weekly in part 1 (once weekly during part 2). At week 12, 66% of patients the 200 mg tildrakizumab-asmn group, 61% in the 100 mg tildrakizumab-asmn group, 6% in the placebo group, and 48% in the etanercept group achieved PASI 75 (p<0.0001 for both tildrakizumab-asmn versus placebo; p≤0.001 for tildrakizumab-asmn versus etanercept). Likewise, 59% of patients in the 200 mg tildrakizumab-asmn group, 55% in the 100 mg tildrakizumab-asmn, 4% in the placebo group, and 48% in the etanercept group achieved a PGA response (p<0.0001 for both tildrakizumab-asmn versus placebo; p=0.0031 for tildrakizumab-asmn 200 mg versus etanercept; p=0.0663 for tildrakizumab-asmn 100 mg versus etanercept). Serious adverse events were similar between groups; however, 1 patient died (cause of death undetermined, but the patient did have alcoholic cardiomyopathy and steatohepatitis).

At week 12 in reSURFACE 1 (part 2), those assigned to placebo were reassigned to either active strength of tildrakizumab-asmn, and, by week 28, efficacy was similar to results seen with those who initiated active treatment at baseline.[550,551] At week 28 (part 3), those who did not achieve a PASI 50 were removed from the study. Partial responders assigned tildrakizumab-asmn 200 mg continued treatment and partial responders assigned tildrakizumab-asmn 100 mg were re-randomized to 100 mg or 200 mg tildrakizumab-asmn. Participants assigned tildrakizumab-asmn who achieved PASI 75 were re-randomized to either continue treatment or to placebo until relapse (PASI maximum response reduction of 50%) and were then re-initiated on their active treatment. Those who were initially assigned placebo and randomized to active treatment at week 12 who then achieved PASI 50 continued their treatment. Response was generally maintained through part 3. At week 12 in reSURFACE 2 (part 2), those assigned to placebo were reassigned to either active strength of tildrakizumab-asmn and, by week 28, efficacy was similar to results seen with those who initiated tildrakizumab-asmn at baseline. At week 28 (part 3), participants were also reassigned based on responder status. Nonresponders assigned tildrakizumab-asmn were discontinued from the study while those assigned to etanercept were switched to tildrakizumab-asmn 200 mg. Etanercept responders were discontinued from the study. Those assigned tildrakizumab-asmn 200 mg achieving PASI 75 were randomized to either continue treatment or to a lower dose of 100 mg, and partial responders continued treatment. Those assigned tildrakizumab-asmn 100 mg achieving PASI 75 continued treatment, and partial responders were randomized to either continue treatment or to an increased dose of 200 mg. Response was generally maintained through part 3. Only the 100 mg strength is approved. At 5 years, the investigators found generally sustained disease control in those who responded at 28 weeks, and no additional significant safety concerns were identified.[552]

ustekinumab (Stelara) versus etanercept (Enbrel)

In the treatment of moderate to severe psoriasis, ustekinumab and etanercept were compared in a single-blind, randomized trial with 903 patients.[553] Patients were randomized to either ustekinumab SC 45 or 90 mg at weeks 0 and 4 or etanercept SC 50 mg twice weekly for 12 weeks. The primary endpoint was the proportion of patients with at least 75% improvement in PASI at week 12. The secondary endpoint was

the proportion of patients with cleared or minimal disease based on the physician's global assessment. Assessors were blinded to the treatment. The proportion of patients achieving 75% improvement on PASI at week 12 were 67.5% of ustekinumab 45 mg group, 73.8% of the ustekinumab 90 mg group, and 56.8% of the etanercept group (p=0.01 and p<0.001, respectively). For the physician's global assessment, 65.1%, 70.6%, and 49% of patients had cleared or minimal disease, respectively (p<0.001 for both comparisons). Patients who did not have a response to etanercept were crossed over to ustekinumab therapy for 12 weeks; 48.9% had at least 75% improvement in the PASI within 12 weeks of crossover. Serious adverse events were reported in 1.9, 1.2, and 1.2% of the ustekinumab 90 mg and 45 mg groups and etanercept group, respectively. Safety patterns were similar before and after crossover from etanercept to ustekinumab. The manufacturer of ustekinumab sponsored the study.

ustekinumab (Stelara)

Two multicenter, randomized, double-blind, placebo-controlled trials were conducted to study ustekinumab. Both studies enrolled subjects 18 years of age or older with moderate to severe plaque psoriasis who had a minimum body surface area involved of 10% a PASI of 12 or greater, and who were candidates for phototherapy or systemic therapy. Subjects were randomized to placebo, ustekinumab 45 mg, or ustekinumab 90 mg. Subjects randomized to ustekinumab received the agent at weeks 0, 4, and 16. Subjects randomized to receive placebo crossed over to ustekinumab at weeks 12 and 16. The endpoints of both trials were the proportion of subjects who achieved at least a 75% in PASI score from baseline to week 12 and treatment success on the PGA.

PHOENIX 1 enrolled a total of 766 subjects evaluated through week 52.[554] At week 12, 67.1% of those receiving 45 mg of ustekinumab, 66.4% of those receiving 90 mg of ustekinumab, and 3.1% of those receiving placebo achieved the PASI 75 response (difference in response rate versus placebo 63.9% [95% CI, 57.8 to 70.1; p<0.0001] for 45 mg and 63.3% [95% CI, 57.1 to 69.4; p<0.0001] for 90 mg). At week 12, a total of 59% of those receiving 45 mg of ustekinumab, 61% of those receiving 90 mg of ustekinumab, and 4% of those receiving placebo achieved a PGA score indicating "cleared" or "minimal." Of the patients initially randomized to ustekinumab at week 0 who achieved a long-term response (defined as 75% improvement in PASI 75) at weeks 28 and 40 were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment until loss of response. At week 40, long-term response had been achieved by 150 patients in the 45 mg group and 172 patients in the 90 mg group. Of these, 162 patients were randomly assigned to maintenance ustekinumab and 160 to withdrawal. At 1 year, PASI 75 response was better maintained in those receiving maintenance ustekinumab than those withdrawn from treatment (p<0.0001). Serious adverse events were reported in 1.2% of patients receiving ustekinumab and 0.8% receiving placebo. Long-term safety data demonstrated consistent adverse effects over 3 years.[555]

PHOENIX 2 enrolled a total of 1,230 subjects with moderate to severe psoriasis.[556] At week 12, 66.7% of those receiving 45 mg of ustekinumab, 75.7% of those receiving 90 mg of ustekinumab, and 3.7% of those receiving placebo achieved the PASI 75 response (difference in response rate 63.1% [95% CI, 58.2 to 68; p<0.0001] for the 45 mg group versus placebo and 72% [95% CI, 67.5 to 76.5; p<0.0001] for the 90 mg group versus placebo). At week 12, a total of 68% of those receiving 45 mg of ustekinumab, 73% of those receiving 90 mg of ustekinumab, and 4% of those receiving placebo achieved a PGA score indicating "cleared" or "minimal."

CADMUS: A third study assessed the role of ustekinumab in adolescents 12 to 17 years of age with moderate to severe plaque psoriasis.[557] The phase 3, multicenter, double-blind, placebo-controlled study

included 110 patients who were randomized ustekinumab standard dosing (SD: 0.75 mg/kg for < 60 kg; 45 mg for 60 kg through 100 kg; 90 mg for > 100 kg) or half-standard dosing (HSD: 0.375 mg/kg for < 60 kg; 22.5 mg for 60 kg through 100 kg; 45 mg for > 100 kg) at weeks 0 and 4 and every 12 weeks thereafter or placebo with crossover to 1 of the ustekinumab dosing regimens at week 12. At week 12, the proportion of patients achieving PGA 0/1 was higher in both ustekinumab groups compared to placebo (67.6% and 69.4% for ustekinumab HSD and SD, respectively, compared to 5.4% with placebo; p<0.001 for both comparisons). In addition, greater proportions of patients (p<0.001) treated with ustekinumab achieved PASI 75 (HSD, 78.4%; SD, 80.6%; placebo, 10.8%) or PASI 90 (HSD, 54.1%; SD, 61.1%; placebo, 5.4%) at week 12. Adverse effects through week 12 occurred in 56.8% of placebo-treated patients compared to 51.4% and 44.4% of HSD and SD patients, respectively. Approval of ustekinumab for younger children (ages 6 to 11 years) is based on data from an open-label, single-arm study that evaluated efficacy, safety, and pharmacokinetics.[558]

Psoriatic Arthritis (PsA)

abatacept (Orencia) [559,560]

Two randomized, double-blind, placebo-controlled studies (Studies PsA-I and PsA-II) assessed the efficacy and safety of abatacept in adults with psoriatic arthritis (n=594). Included patients had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) despite prior treatment with DMARD therapy and had 1 qualifying psoriatic skin lesion (≥ 2 cm). In PsA-I, a dose-ranging study that included non-FDA approved dosages, 47.5%, 25%, and 12.5% of those receiving approximately 10 mg/kg IV (dosing as FDA-approved; n=40) compared to 19%, 2.4%, and 0 in the placebo group (n=42) achieved ACR20, ACR50, and ACR70, respectively, at week 24. In PsA-II, 424 patients were randomized 1:1 to receive double-blind weekly doses of SC abatacept 125 mg or placebo without a loading dose for 24 weeks, followed by open-label abatacept 125 mg SC weekly. Patients were allowed to receive stable doses of concomitant traditional DMARDs, low-dose corticosteroids, and/or NSAIDs. Patients who had not achieved at least a 20% improvement from baseline in their swollen and tender joint counts by week 16 were able to transition to open-label abatacept 125 mg SC weekly. The primary endpoint for PsA-II was the proportion of patients achieving ACR20 response at week 24 (day 169). In PsA-II, 61% of patients were treated with a TNF antagonist previously. At week 24, 39.4%, 19.2%, and 10.3% of those receiving abatacept (n=213) compared to 22.3%, 12.3%, and 6.6% in the placebo group (n=211) achieved ACR20, ACR50, and ACR70, respectively. Improvements in enthesitis and dactylitis were also see with abatacept treatment at week 24.

adalimumab (Humira)

Patients with moderately to severely active PsA and a history of inadequate response to NSAIDs were randomized to receive adalimumab 40 mg or placebo SC every other week for 24 weeks.[561] At week 12, 58% of the adalimumab-treated patients achieved an ACR20 response, a primary endpoint, compared with 14% of the placebo-treated patients (p<0.001). An ACR20 response requires a patient to have a 20% reduction in the number of swollen and tender joints, and a reduction of 20% in 3 of the following 5 parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, CRP or erythrocyte sedimentation rate, and degree of disability in Health Assessment Questionnaire (HAQ) score. ACR30, ACR50, ACR70, ACR90, and ACR100 responses follow accordingly. At week 24, similar ACR20 response rates were maintained and the mean change in the modified total Sharp score (mTSS, a measurement of erosion and joint space narrowing) was significantly improved in patients receiving adalimumab compared to those receiving placebo (p<0.001). Of the adalimumab-treated

patients, 59% achieved a PASI 75 response at 24 weeks, compared with 1% of patients treated with placebo (p<0.001). Adalimumab was generally safe and well tolerated.

Patients (n=313) who completed the 24-week, double-blind, Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) study versus placebo in PsA could elect to receive open-label adalimumab 40 mg SC every other week after week 24.[562] After 48 weeks, patients from the adalimumab arm of ADEPT (n=151) had achieved ACR20, ACR50, and ACR70 response rates of 56%, 44%, and 30%, respectively. A total of 69 patients were evaluated with PASI 50, PASI 75, PASI 90, and PASI 100 response rates and results were reported as follows: 67%, 58%, 46%, and 33%, respectively. Improvements in disability, as measured by the Disability Index of the Health Assessment Questionnaire (HAQ-DI), were sustained from week 24 to week 48. The HAQ-DI is a self-administered questionnaire that patients can complete easily and rapidly and that gives important information about prognosis, patient status, and changes in disease course over time. Adalimumab demonstrated clinical and radiographic efficacy regardless of whether patients were receiving methotrexate at baseline and was generally safe and well tolerated through week 48. After 2 years of treatment with adalimumab 40 mg every other week, patients (n=245) continued to exhibit inhibition of radiographic progression and improvements in joint disease were maintained.[563] Long-term adverse effects were similar to those reported in the 24-week study with adalimumab.

In a placebo-controlled, double-blind, randomized, multicenter study, 100 patients with active PsA with an inadequate response to DMARDs were treated for 12 weeks with adalimumab 40 mg every other week or placebo.[564] The primary efficacy endpoint was the percentage of patients who met the ACR20 core criteria at week 12. At week 12, an ACR20 response was achieved by 39% of adalimumab patients versus 16% of placebo patients (p=0.012). At week 12, measures of skin lesions and disability were statistically significantly improved with adalimumab. After week 12, open-label adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR20 response rates of 65% and 57%, respectively, observed at week 24. Adverse effects were similar in frequency.

apremilast (Otezla)

The safety and efficacy of apremilast were evaluated in 3 randomized, double-blind, placebo-controlled, multicenter trials (Studies PsA-1, PsA-2, and PsA-3) of similar design. A total of 1,493 adult patients with active psoriatic arthritis (PsA) (3 swollen joints and 3 tender joints) despite prior or current treatment with DMARD therapy were randomized.[565] Patients enrolled in these studies had a diagnosis of PsA for at least 6 months. Previous treatment with a biologic, including TNF antagonists was allowed (up to 10% could be TNF antagonist therapeutic failures). Across the 3 studies, patients were randomly assigned to placebo (n=496), apremilast 20 mg (n=500), or apremilast 30 mg (n=497) given orally twice daily. Titration was used over the first 5 days. Patients were allowed to receive stable doses of concomitant methotrexate (25 mg/week), sulfasalazine, leflunomide, low dose oral corticosteroids, and/or NSAIDs during the trial. The patients who were therapeutic failures of greater than 3 agents for PsA (small molecules or biologics), or more than 1 biologic TNF antagonist were excluded. The primary endpoint was the percentage of patients achieving ACR20 response at week 16. In all 3 studies (PsA-1, PsA-2, and PsA-3), the week ACR20 response was statistically significantly higher in the apremilast group when compared to placebo (PsA-1 38% versus 19 %, PsA-2 32% versus 19% and PsA-3 41% versus 18%; $p < 0.05$ for both).

certolizumab pegol (Cimzia)

RAPID-PsA is a phase 3, double-blind, placebo-controlled study of certolizumab in patients with psoriatic arthritis.[566] A total of 409 adult ($\geq$ 18 years) patients were randomized to 1 of 3 arms: placebo,

certolizumab pegol (CZP) 200 mg SC every 2 weeks, or CZP 400 mg every 4 weeks. Patients on the active treatment arms also received a loading dose of CZP 400 mg SC at weeks 0, 2, and 4 and then preceded on to the assigned maintenance dose arms. The drug was administered by investigators at each site using a blinded prefilled syringe. Patients at each site were stratified by prior exposure to TNF inhibitor. Placebo patients who failed to achieve a 10% improvement from baseline in both swollen and tender joints at weeks 14 and 16 underwent mandatory escape to active treatment in a blinded manner. A total of 59 (43.4%) of placebo patients were re-randomized to CZP treatment at week 16. The primary clinical endpoint of the study was ACR20 response at week 12. The radiographic primary endpoint of the trial was change from baseline to week 24. Concomitant DMARDS were used by 70.2% of patients at baseline through week 24. At week 12, significantly more patients in the CZP 200 mg SC every 2 weeks and CZP 400 mg SC every 4 weeks achieved an ACR20 response compared to placebo patients (58% and 51.9% versus 24.3%; p<0.001 for both). Patients treated with CZP 200 mg SC every 2 weeks demonstrated greater reduction in radiographic progression compared to placebo-treated patients at week 24 as measured by change in baseline in total modified total Sharp score (mTSS) (0.18 in placebo group compared with -0.02 in CZP 200 mg SC every 2 weeks group (95% CI, -0.38 to 0.04). Patients treated with CZP 400 mg SC every 4 weeks did not demonstrate greater inhibition of radiographic progression compared with placebo-treated patients at week 24. The most common non-infectious adverse events were diarrhea (3.6% CZP versus 2.9% placebo) and headache (3.6% CZP versus 1.5% placebo). The most common infectious adverse effects were nasopharyngitis (8.7% CZP versus 7.4% placebo) and upper respiratory tract infection (7.8% CZP versus 5.1% placebo).

etanercept (Enbrel)

Investigators randomized 205 patients with PsA to receive etanercept 25 mg or placebo twice weekly for 24 weeks.[567] Patients continued to receive blinded therapy in a maintenance phase until all had completed the 24-week phase, at which point they could receive open-label etanercept in a 48-week extension. At 12 weeks, 59% of etanercept patients achieved an ACR20 response (the primary outcome) compared with 15% of placebo patients (p<0.0001); results were sustained at 24 and 48 weeks. At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least a PASI 75 score, compared with 3% of placebo patients (p=0.001). Etanercept was well tolerated. This study confirmed the findings of an earlier, smaller clinical trial that was the first placebo-controlled trial of a TNF antagonist for this indication.[568]

In a continuation of the above study, patients were permitted to continue in an open-label extension where all patients received etanercept 25 mg twice weekly.[569] Radiographic progression was monitored at baseline, 1, and 2 years using the Sharp method, modified to include joints frequently affected by PsA. A total of 169 patients continued therapy and were followed out to 2 years; 141 of them previously randomized to placebo and 70 previously randomized to etanercept,. ACR20, PsARC, and PASI 50 criteria were met by 64%, 84%, and 62%, respectively, of etanercept/etanercept patients at the end of the 48-week open-label period. Placebo/etanercept patients achieved comparable results within 12 weeks that were sustained at 48 weeks (63%, 80%, and 73%, respectively). For the patients who initially received placebo, disease progression was inhibited once patients began receiving etanercept. Adverse effects were similar to the randomized phase.

A total of 618 patients with moderate to severe psoriasis were enrolled in a double-blind treatment with etanercept 50 mg twice weekly or placebo.[570] The primary endpoint, PASI 75 at week 12, was reached by 47% of the etanercept group and 5% of those receiving placebo (p<0.0001). Secondary endpoints were the functional assessment of chronic illness therapy fatigue (FACIT-F) scale and the Hamilton rating scale

for depression (HAM-D). On the HAM-D evaluation, more patients receiving etanercept had at least a 50% improvement at week 12 compared with the placebo group. Fatigue was also improved in the etanercept group (mean FACIT-F improvement 5 versus 1.9; p<0.0001).

golimumab (Simponi)

GO-REVEAL: The safety and efficacy of golimumab were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 405 adult patients with moderately to severely active PsA (≥ 3 swollen joints and ≥ 3 tender joints).[571] Patients in this study had a diagnosis of PsA for at least 6 months with a qualifying psoriatic skin lesion of at least 2 centimeters in diameter. Prior treatment with a biologic TNF antagonist was not allowed. Patients were randomly assigned to golimumab 50 mg (n=146), golimumab 100 mg (n=146), or placebo (n=113) given SC every 4 weeks. Patients were allowed to receive stable doses of concomitant methotrexate (≤ 25 mg/week), low dose oral corticosteroids, and/or NSAIDs during the trial. The use of DMARDs, including sulfasalazine, hydroxychloroquine, cytotoxic agents, or other biologics, was prohibited. The primary endpoint was the percentage of patients achieving ACR20 response at week 14 and was reported as: 51% (golimumab 50 mg), 45% (golimumab 100 mg) versus 9% (placebo), respectively (p<0.001 for all comparisons). Among secondary endpoints, 52% of patients administered golimumab 50 mg and 61% of patient receiving golimumab 100 mg, achieved ACR20 at week 24 versus 12% in the placebo group (p<0.001). There was no clear evidence of improved ACR response with the higher golimumab dose group (100 mg) compared to the lower golimumab dose group (50 mg). ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant methotrexate. Similar ACR20 responses at week 14 were observed in patients with different PsA subtypes. Golimumab 50 mg treatment also resulted in significantly greater improvement in enthesitis and skin manifestations in patients with PsA. Among the 74% of patients in whom at least 3% of the body surface area was affected by psoriasis at baseline, 40% of those in the golimumab 50 mg group and 58% of those in the golimumab 100 mg group had at least 75% improvement in the PASI at week 14, compared with 3% of placebo-treated patients (p<0.001 for both doses). A 2-year follow-up of the GO-REVEAL trial indicated sustained responses at 2 years.[572] At week 104, patients originally randomized to golimumab 50 mg had an ACR20 response of 67.1% and patients originally randomized to golimumab 100 mg had an ACR20 response of 69.9%. Through week 104, 23 (6%) of patients discontinued golimumab because of an adverse event. Serious adverse events were reported for 16 (6.5%) and 18 (8%) of patients receiving golimumab 50 mg and 100 mg, respectively. There were 6 serious infections but, when assessed according to patient-years follow-up, no increase in the incidence of serious infection was observed for either golimumab arm. This analysis was, however, limited by the relatively short duration of placebo treatment and the small number of patients. No patient developed active TB through week 104, including the 44 patients who received TB prophylaxis secondary to detection of latent TB at time of trial participation screening. Eight patients were diagnosed with a malignancy during the 2-year period (1 colon cancer, 1 prostate cancer, 2 squamous cell lung cancers, and 4 basal cell carcinomas). When assessed by patient-years of follow-up, the incidence of malignancies for golimumab-treated patients was numerically higher compared to patients receiving placebo (95% CI, 0 to 0.74). Again, the authors note the analysis was limited by small sample size and the short period of placebo follow-up. When the number of malignancies (excluding the non-melanoma skin cancers) in the trial were compared to the expected rates in the general US population, the numbers were not statistically significantly different.

golimumab (Simponi Aria)

GO-VIBRANT: A phase 3, randomized, double-blind, placebo-controlled trial compared golimumab to placebo for the treatment of PsA (n=480).[573] Included patients were ≥ 18 years and had PsA for ≥ 6 months. They were randomized to either IV placebo or golimumab at 2 mg/kg at weeks 0, 4, 12, and 20. The primary endpoint was the proportion of patients achieving an ACR20 response at week 14, which occurred in 75.1% and 21.8% of patients in the golimumab group and placebo group, respectively (p<0.001). At week 14, greater proportions of golimumab-treated patients also had an ACR50 response (43.6% versus 6.3%), ACR70 response (24.5% versus 2.1%), mean change in HAQ-DI score (-0.6 versus -0.12), and PASI 75 response (59.2% versus 13.6%) (p<0.001 for all comparisons). Adverse effects were comparable to other TNF antagonists. At week 52, 76.8% and 77% of patients in the golimumab and placebo-crossover groups achieved an ACR20 response, respectively, and 58.1% and 53.6%, respectively, achieved an ACR50 response.[574] ACR70 was achieved by 38.6% and 33.9% of the golimumab and placebo-crossover groups, respectively.

Approval of IV golimumab in pediatric patients is based on pharmacokinetic data and extrapolation of efficacy in adults with PsA.[575]

guselkumab (Tremfya)

Two clinical trials, DISCOVER-1 and DISCOVER-2, established the efficacy of guselkumab for the treatment of psoriatic arthritis.[576,577,578] DISCOVER-1, a multinational, phase 3, double-blind, placebo-controlled study, randomized adults with active psoriatic arthritis 1:1:1 to guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, a higher proportion of those treated with guselkumab achieved an ACR20 response compared to placebo (difference versus placebo, 37% [95% CI, 26 to 48; p<0.0001] for the every-4-week group; difference versus placebo, 30% [95% CI, 19 to 41; p<0.0001] for the every-8-weeks group). DISCOVER-2, a multinational, phase 3, double-blind, placebo-controlled study, randomized biologic-naive patients with active psoriatic arthritis 1:1:1 to guselkumab 100 mg every 4 weeks, guselkumab 100 mg every 8 weeks, or placebo. At week 24, a higher proportion of those treated with guselkumab achieved an ACR20 response compared to placebo (difference versus placebo, 31% [95% CI, 22 to 39; p<0.0001] for the every-4-weeks group; difference versus placebo, 31% [95% CI, 23 to 40; p<0.0001] for the every-8-weeks group). Sustained improvements have been seen through 52 weeks.[579]

infliximab (Remicade)

IMPACT I, the Infliximab Multinational Psoriatic Arthritis Controlled Trial, was an investigator-initiated study of 104 patients with active PsA.[580,581] Patients received placebo or infliximab 5 mg/kg at weeks 0, 2, 6, and 14 with open-label infliximab 5 mg/kg every 8 weeks in follow-up. The primary endpoint, ACR20 at week 16, was achieved in 69% of infliximab patients versus 8% on placebo (p<0.001). PASI 75 response in evaluable patients was 70.4% and 0% in the infliximab and placebo groups, respectively (p<0.001). At week 50, the same ACR20 response was maintained.[582] No worsening of radiographic progression was noted in approximately 85% of the remaining patients. At week 98, 62% (48/78 patients) of infliximab-treated patients achieved an ACR20 response.[583] Among patients with baseline PASI scores ≥ 2.5, PASI 75 response was 64% (16/25 patients) at week 98. The average estimated annual radiographic progression with infliximab treatment was significantly reduced versus the estimated baseline rate of progression.

IMPACT II was a randomized, double-blind study of 200 patients with active PsA who had an inadequate response to DMARDs or NSAIDs.[584] Patients received infliximab 5 mg/kg or placebo at weeks 0, 2, 6, 14,

and 22. Significant improvements in both ACR20 and PASI 75 were observed as early as week 2. At week 14, ACR20 was seen in 58% (11% in placebo; p<0.001) and PASI 75 response in 64% (2% in placebo; p<0.001). The median PASI improvement in ACR20 responders was 87.5%, whereas the median improvement in non-responders was 74%.[585] At week 24, 27% of infliximab-treated patients experienced ACR70% versus 2% of placebo-treated patients (p<0.001). At week 24, 60% of infliximab-treated patients experienced PASI 75 versus 1% of placebo-treated patients, and 39% of infliximab-treated achieved PASI 90. There were similar numbers of adverse events in each group, although there were more serious adverse events in the infliximab group (8.7%) than in the placebo group (6.2%). In a continuation of the IMPACT II trial, infliximab therapy given every 8 weeks was continued for 1 year.[586] Placebo-assigned patients crossed over to infliximab at week 24. Patients randomized to infliximab who had no response or who lost response could escalate their dose to 10 mg/kg starting at week 38. Through 1 year of treatment, 58.9% and 61.4% of patients in the randomized infliximab and placebo/infliximab groups, respectively, achieved ACR20; corresponding figures for PASI 75 were 50% and 60.3%. The safety profile of infliximab through week 54 was consistent with that seen through week 24. Two malignancies occurred: basal cell skin cancer (placebo) and stage I Hodgkin's lymphoma (infliximab). Radiographs of hands and feet were obtained at baseline and at weeks 24 and 54.[587] These were evaluated for erosions and joint space narrowing using the Sharp/van der Heijde scoring method modified for PsA. Radiographic progression, measured at week 24, was significantly less in patients initially randomized to infliximab compared with patients randomized to receive placebo (p<0.001). At week 54, slower radiographic progression was observed in patients on infliximab for 1 year compared to patients receiving infliximab for 24 weeks (p=0.001).

One hundred four patients with PsA in whom prior therapy with at least 1 DMARD had failed were recruited into an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled clinical trial.[588] During the initial blinded portion of the study, patients received infusions of infliximab 5 mg/kg or placebo at weeks 0, 2, 6, and 14. After week 16, patients initially assigned to receive placebo crossed over to receive infliximab 5 mg/kg every 8 weeks through week 50, while patients initially randomized to infliximab continued to receive active treatment at the same dose through week 50. The proportion of infliximab-treated patients who achieved the primary endpoint of an ACR20 response at week 16 (65%) was significantly higher than the proportion of placebo-treated patients who achieved the response (10%). In addition, 46% of infliximab-treated patients achieved an ACR50 response and 29% achieved an ACR70 response; no placebo-treated patient achieved these endpoints. Among patients who had PASI scores of $\geq$ 2.5 at baseline, 68% of infliximab-treated patients achieved improvement of at least 75% in the PASI score at week 16 compared with none of the placebo-treated patients. Continued therapy with infliximab resulted in sustained improvement in articular and dermatologic manifestations of PsA through week 50. The incidence of adverse events was similar between the treatment groups.

ixekizumab (Taltz)

SPIRIT-P1: A 3-year, phase 3, randomized, double-blind, placebo- and active-controlled clinical trial assessed the efficacy of ixekizumab for the treatment of active PsA who had not had biologic therapy (n=417).[589] Participants were randomized 1:1:1:1 to SC placebo, adalimumab 40 mg once every 2 weeks (active reference), ixekizumab 80 mg once every 2 weeks (following 160 mg initial dose), or ixekizumab 80 mg once every 4 weeks (following 160 mg initial dose). Both ixekizumab regimens included a 160-mg starting dose. The primary objective was the proportion of patients achieving an ACR20 response at week 24, which was found to be higher in those treated with either ixekizumab dose when compared to placebo (62.1% and 57.9% with every 2 and 4 week ixekizumab dosing, respectively, versus 30.2% with placebo;

p≤0.001 for both). The ACR20 response at 24 weeks was 57.4% with adalimumab. An improvement compared to placebo was also seen with ixekizumab and adalimumab in disease activity, functional disability, and progression of structural damage. Treatment-emergent adverse effects were higher with active treatments (64% to 66%) than placebo (47%) (p<0.05).

SPIRIT-P2: A phase 3, multinational, double-blind, randomized, placebo-controlled trial assessed the efficacy of ixekizumab in adult patients with active PsA (≥ 6 months) and a previous inadequate response to TNF antagonists (n=363).[590] Patients were randomized 1:1:1 SC ixekizumab 80 mg every 4 weeks or every 2 weeks (following a 160 mg starting dose) or placebo. The primary endpoint was the proportion of patients who achieved ACR20 at week 24. At week 24, a larger proportion of patients achieved ACR20 with ixekizumab every 4 weeks (53%) and ixekizumab every 2 weeks (48%) than with placebo (20%) (effect size compared to placebo 33.8% [95% CI, 22.4 to 45.2; p<0.0001] with ixekizumab every 4 weeks and 28.5% [95% CI, 17.1 to 39.8; p<0.0001] with ixekizumab every 2 weeks). Serious adverse events occurred in 3% of patients treated with ixekizumab every 4 weeks, 7% treated with ixekizumab every 2 weeks, and 3% with placebo. At week 52, all patients were assigned open-label ixekizumab every 2 or 4 weeks, and clinical improvement and safety were similar at 52 weeks as were demonstrated at 24 weeks.[591]

risankizumab-rzaa (Skyrizi)

KEEPsAKE 1 (NCT03675308) and KEEPsAKE 2 (NCT03671148), two randomized, double-blind, placebo-controlled studies, assessed the efficacy and safety of risankizumab-rzaa in adults with active PsA.[592,593,594] In both trials, included patients had a diagnosis of PsA (based on the Classification Criteria for Psoriatic Arthritis [CASPAR]) for at least 6 months (median duration, 4.9 years), ≥ 5 tender joints and ≥ 5 swollen joints, and active plaque psoriasis or psoriatic nail disease. In KEEPsAKE 1, included patients had an inadequate response or intolerance to ≥ 1 conventional DMARD but were biologic treatment-naïve. In addition, 67.3% had psoriatic nail disease. Patients were randomized 1:1 to risankizumab-rzaa 150 mg or to placebo, both given at weeks 0, 4, and 16 (n=964). At week 24, a greater proportion of risankizumab-rzaa-treated patients achieved the primary endpoint, ACR20 (57.3% versus 33.5%, respectively; p<0.001). In KEEPsAKE 2, included patients had an inadequate response or intolerance to ≥ 1 conventional DMARD and/or no more than 2 biologic therapies. Patients were randomized 1:1 to risankizumab-rzaa 150 mg or to placebo, both given at weeks 0, 4, and 16 (n=444). Notably, 46.5% of patients had prior failure or intolerance to a biologic agent. At week 24, a greater proportion of risankizumab-rzaa-treated patients achieved the primary endpoint, ACR20 (51.3% versus 26.5%, respectively; p<0.001). In both trials, statistically significant differences were also seen in ACR20 at week 16 and ACR50 and ACR70 at weeks 16 and 24. Statistically significant differences were also seen in several other notable secondary endpoints at 24 weeks, including change in HAQ-DI, PASI 90, select components of the SF-36, and resolution of enthesitis and dactylitis. Similar responses were seen regardless of special population assessed. At 24 weeks, all patients were able to switch to active treatment, with all patients receiving risankizumab-rzaa every 12 weeks beginning at week 28 as part of a long-term extension of each study for up to an additional 204 weeks.

secukinumab (Cosentyx)

A double-blind, phase 3, randomized clinical trial, the FUTURE 1 study, assessed the efficacy of secukinumab compared to placebo for the treatment of psoriatic arthritis in adults and active disease, as defined by > 3 swollen and > 3 tender joints despite NSAID, corticosteroid, or DMARD therapy (n=606).[595,596] Patients were randomly assigned 1:1:1 to placebo or IV secukinumab (10 mg/kg) at weeks 0, 2, and 4 followed by SC secukinumab at a dose of either 75 mg or 150 mg every 4 weeks. At week 16

or 24, patients assigned to placebo were switched to SC secukinumab 75 mg or 150 mg based on clinical response. The primary endpoint was ACR20 at week 24. At 24 weeks, ACR20 response was higher in both secukinumab groups (75 mg: 50.5%; 150 mg: 50%) compared to placebo (17.3%; p<0.001 for both). Secondary endpoints, such as ACR50 and joint structural damage, were also superior in the secukinumab groups compared to placebo. At 52 weeks, the improvements were maintained. Adverse effects, specifically infections (e.g., candida), were more common in the secukinumab group. Four patients and 2 patients in the secukinumab groups had a stroke and myocardial infarction, respectively, while no patients in the placebo group experienced these events. This study was funded by the manufacturer of secukinumab and was used, in part, for FDA approval of this indication. A 2-year follow up study demonstrated sustained improvements.[597]

A second double-blind, phase 3, randomized clinical trial, the FUTURE 2 study, assessed the efficacy of secukinumab compared to placebo for the treatment of psoriatic arthritis in adults and active disease, as defined by > 3 swollen and > 3 tender joints despite NSAID, corticosteroid, or DMARD therapy (n=397).[598,599] In both the FUTURE 1 and 2 trials, approximately 32% of patients had discontinued prior treatment with a TNF antagonist due to either intolerance or lack of efficacy, and approximately 55% were using concomitant methotrexate during the study. Patients were randomized 1:1:1:1 to secukinumab 75 mg, 150 mg, or 300 mg or placebo SC on weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks thereafter. At week 16 or 24, patients assigned to placebo were switched to SC secukinumab 75 mg or 150 mg based on clinical response. The primary endpoint was patients achieving ACR20 at week 24. At week 24, 29% of patients using the 75 mg dose, 51% of patients using the 150 mg dose, and 54% of patients using the 300 mg dose compared to 15% of patients on placebo achieved ACR20 (75 mg difference, 14% [95% CI, not reported]; 150 mg difference, 36% [95% CI, 24 to 48]; and 300 mg difference, 39% [95% CI, 27 to 51]). Significant differences from placebo were also seen with the 150 mg and 300 mg doses at weeks 16 and 24 in ACR50 and ACR70. Data with the 75 mg dose were not reported. No difference was seen in patients over both trials using concomitant methotrexate or those with prior TNF antagonist use. A 2-year follow up study demonstrated sustained improvements.[600]

FUTURE 3 assessed the efficacy and safety of secukinumab administered by an autoinjector in a 52-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial (n=414).[601] Adults with active PsA were randomized 1:1:1 to SC secukinumab 300 mg, secukinumab 150 mg, or placebo at baseline, weeks 1, 2, 3, and 4, and every 4 weeks thereafter. Those with a clinical response were then re-randomized to SC secukinumab 300 or 150 mg at week 16 (nonresponders) or week 24 (responders). The primary endpoint was the proportion of patients achieving ACR20 at week 24, which was significantly higher in secukinumab groups (300 mg: 48.2% [p<0.0001 versus placebo]; 150 mg: 42% [p<0.0001 versus placebo]) compared to placebo (16.1%) and was sustained through 52 weeks.

Another study, FUTURE 5, evaluated the effect of secukinumab on the signs and symptoms of PsA and radiographic progression in adults with active PsA (n=996).[602,603] Included patients were randomized 2:2:2:3 to secukinumab 300 mg or 150 mg with a loading dose (LD), secukinumab 150 mg without an LD, or placebo at baseline, weeks 1, 2, and 3, and then every 4 weeks beginning at week 4. The primary endpoint was the proportion of patients who achieved ACR20 at week 16, which occurred in 62.6% of those assigned secukinumab 300 mg with LD, 55.5% of those assigned secukinumab 150 mg with an LD, and 59.5% of those assigned secukinumab, all of which were higher than those assigned to placebo (27.4%; p<0.0001 for all). In addition, radiographic progression, as measured by van der Heijde-modified total Sharp score (mTSS), was inhibited at week 24 in all secukinumab-treated groups compared to placebo (p<0.05 for all). Also, the percentage of patients with no disease progression (e.g., a change from

baseline in mTSS ≤ 0) at week 24 was 75.7%, 70.9%, 76.5%, and 68.2% in the secukinumab 150 mg without LD, secukinumab 150 mg with LD, secukinumab 300 mg with LD, and placebo groups, respectively. Sustained low rates of radiographic progression continued through 2 years of treatment.[604,605]

A 2-year, 3-part, phase 3, double-blind, placebo-controlled, event-driven, randomized trial assessed the efficacy and safety of secukinumab in 86 pediatric patients ≥ 2 years of age with active enthesitis-related arthritis (60.5%) or juvenile PsA (39.5%) diagnosed based on modified International League of Associations for Rheumatology (ILAR) JIA (NCT03031782). [606] The trial consisted of a 12-week, open-label portion with secukinumab treatment, followed by a randomized (1:1), double-blind withdrawal period of those who were considered responders in the first trial part with treatment to either placebo or secukinumab, and then an open-label secukinumab treatment period. Approximately two-thirds of patients were treated with concomitant methotrexate. Dosing was weight-based (per labeling). The primary endpoint was the time to flare during the treatment withdrawal period, which was defined as a ≥ 30% worsening in ≥ 3 of 6 and ≥ 30% improvement in ≤ 1 of 6 JIA ACR response criteria as well as a ≤ 2 active joints. At the end of the first trial portion, 85% of those with enthesitis-related arthritis and 91% of those with juvenile PsA achieved a JIA ACR30. During the second portion of the trial, 11 patients with PsA treated with placebo compared to 4 with continued secukinumab experienced a flare (85% risk reduction; HR, 0.15 [95% CI, 0.04 to 0.56]). In the enthesitis-related arthritis subgroup, 10 patients treated with placebo compared to 6 with continued secukinumab experienced a flare (53% risk reduction; HR, 0.47 [95% CI, 0.17 to 1.32]).

secukinumab (Cosentyx) versus adalimumab (Humira)

EXCEED, a multicenter phase 3b, parallel-group, double-blind study, assessed the efficacy of secukinumab and adalimumab for the treatment of adults with active psoriatic arthritis (n=853).[607] Included patients were randomized 1:1 to secukinumab 300 mg SC at weeks 0, 1, 2, 3, and 4, followed by every 4 weeks through week 48, or adalimumab 40 mg SC (citrate-free) every 2 weeks through week 50. The primary endpoint, ACR20 at week 52 analyzed by superiority of secukinumab over adalimumab, was not met with 67% in the secukinumab group and 62% in the adalimumab group achieving ACR20 (OR, 1.3; 95% CI, 0.98 to 1.72; p=0.0719).

tofacitinib (Xeljanz)

OPAL Broaden: A phase 3, 12-month, double-blind, active- and placebo-controlled trial assessed the efficacy of tofacitinib for the treatment of PsA in patients who previously had an inadequate response to conventional DMARDs (n=422).[608] Patients were randomized 2:2:2:1:1 ratio to 1 of 5 regimens: oral tofacitinib 5 mg twice daily, oral tofacitinib 10 mg twice daily, SC adalimumab 40 mg every 2 weeks, placebo + switch to oral tofacitinib 5 mg twice daily at 3 months, or placebo + oral tofacitinib 10 mg twice daily at 3 months. The primary endpoints were the proportion of patients with an ACR20 response from baseline and the change from baseline in the HAQ-DI score at month 3. At month 3, ACR20 response was higher in the tofacitinib groups than the placebo groups (50% and 61% in the 5 mg and 10 mg groups, respectively, compared to 33% in the placebo group; p≤0.01 for both comparisons). ACR20 was achieved by 52% of those treated with adalimumab. At month 3, the change in HAQ-DI score was higher in the tofacitinib groups than the placebo groups (-0.35 and -0.4 in the 5 mg and 10 mg groups, respectively, compared to -0.18 in the placebo group; p≤0.006 for both comparisons). The score change was -0.38 in those treated with adalimumab. Adverse effect rates were similar in all groups (64% to 72%).

OPAL Beyond: A phase 3, 6-month randomized, double-blind, placebo-controlled trial compared the efficacy of tofacitinib and placebo in patients with PsA and a prior inadequate response to TNF antagonists

(n=395).[609] Patients were randomized (2:2:1:1) to 1 of 4 regimens: tofacitinib 5 mg orally twice daily; tofacitinib 10 mg twice daily; placebo, followed by a switch to tofacitinib 5 mg twice daily at 3 months; or placebo, followed by a switch to tofacitinib 10 mg twice daily at 3 months. The primary end points were ACR20 response and the change in HAQ-DI at the month 3. At 3 months, ACR20 response occurred more frequently with both tofacitinib groups compared to the pooled placebo group (50% and 47% with tofacitinib 5 mg and 10 mg, respectively, compared to 24% with placebo; p<0.001 for both). In addition, the mean change from baseline in HAQ-DI was -0.39 with tofacitinib 5 mg and -0.35 with tofacitinib 10 mg as versus -0.14 with placebo (p<0.001 for both active treatments versus placebo). At 3 months, the adverse event rate was higher in the tofacitinib groups (53% to 55%) compared to placebo (44%).

upadacitinib (Rinvoq)

SELECT-PsA 1 (NCT03104400): A 24-week, phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of upadacitinib for the treatment of 1,704 adults with moderately to severely active PsA.[610,611] Included patients had PsA ≥ 6 months (based on CASPAR), ≥ 3 tender joints, ≥ 3 swollen joints, a history of or active plaque psoriasis, and an inadequate response or intolerance to ≥ 1 nonbiologic DMARD. Patients were randomized 1:1:1:1 to upadacitinib 15 mg or 30 mg daily, placebo, or an active comparator (adalimumab). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12. Comparisons of upadacitinib to adalimumab were secondary endpoints. At week 12, ACR20 was achieved by 70.6%, 78.5%, 36.2%, and 65% of those treated with 15 mg upadacitinib, 30 mg upadacitinib, placebo, and adalimumab, respectively (p<0.001 for both upadacitinib doses versus placebo; treatment difference of 5.6% [95% CI, -0.6 to 11.8] for upadacitinib 15 mg versus adalimumab [noninferior]). Only the 15 mg dose is approved for this use. ACR50 occurred in 38% of those treated with upadacitinib 15 mg compared to 13% of those treated with placebo (treatment difference, 24%; 95 CI, 19 to 30). ACR70 occurred in 16% of those treated with upadacitinib 15 mg compared to 2% of those treated with placebo (treatment difference, 13%; 95 CI, 10 to 17). Adverse effects occurred more frequently in upadacitinib-treated patients compared to those treated with placebo. Efficacy was generally maintained through 56 weeks with no additional safety signals.[612]

SELECT-PsA 2 (NCT03104374): A 24-week, phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of upadacitinib for the treatment of 642 adults with moderately to severely active PsA.[613,614] Like SELECT-PsA 1, included patients had PsA ≥ 6 months (based on CASPAR), ≥ 3 tender joints, ≥ 3 swollen joints, a history of or active plaque psoriasis, and an inadequate response or intolerance to ≥ 1 nonbiologic DMARD. Patients were randomized 2:2:2 to upadacitinib 15 mg or 30 mg daily or to placebo. Those assigned placebo were further subdivided 1:1 to treatment with upadacitinib 15 mg or 30 mg at 24 weeks. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12. At week 12, ACR20 was achieved by 56.9%, 63.8%, and 24.1% of those treated with 15 mg upadacitinib, 30 mg upadacitinib, and placebo, respectively (p<0.001 for both upadacitinib doses versus placebo). Only the 15 mg dose is approved for this use. ACR50 occurred in 32% of those treated with upadacitinib 15 mg compared to 5% of those treated with placebo (treatment difference, 27%; 95 CI, 20 to 34). ACR70 occurred in 9% of those treated with upadacitinib 15 mg compared to 1% of those treated with placebo (treatment difference, 8%; 95 CI, 4 to 12).

ustekinumab (Stelara)

A total of 927 adult patients with active PsA (≥ 5 swollen joints and ≥ 5 tender joints) were enrolled in 2 randomized, double-blind, placebo-controlled studies.[615,616] Patients in both trials had ongoing symptoms despite therapy with NSAIDs or DMARDs. In study 1 (PSUMMIT 1 trial), 615 patients were randomized to

placebo, 45 mg SC ustekinumab, or 90 mg SC ustekinumab at weeks 0 and 4 and every 12 weeks thereafter. Patients with prior history of treatment with a TNF antagonist were excluded from this trial. Early escape was allowed at week 16 for patients on placebo or ustekinumab 45 mg if they had a less than 5% improvement from baseline in both tender and swollen joints. Primary efficacy endpoint was the proportion of patients with ACR20 at week 24. A significantly higher proportion of patients in the ustekinumab groups than in the placebo group achieved an ACR20 response at week 24 (difference in response rate 19.6% [95% CI, 10.8 to 28.5, p<0.0001] for the 45 mg group versus placebo and 26.7% [95% CI, 17.8 to 35.6, p<0.0001] for the 90 mg group versus placebo). ACR20 treatment effects at week 24 were numerically lower for patients receiving concomitant methotrexate than for those patients who were not but tests of significance were not reported. The most common adverse events in the ustekinumab-treated patients were nasopharyngitis (4.6%), upper respiratory tract infection (3.4%), and headache (3.4%). In an open-label expansion study of the PSUMMIT 1 trial, clinical benefits were maintained through week 100.[617] In PsA Study 2 (n=312), the trial design was identical to the PSUMMIT 1 trial except PsA Study 2 included patients who had been previously treated with a TNF antagonist (58% of study participants).[618] Seventy percent of the patients previously treated with a TNF antagonist had discontinued their TNF antagonist for lack of efficacy or intolerance. The ACR20 response at week 24 in this trial was 44% in patients receiving ustekinumab 45 mg, 44% in patients receiving ustekinumab 90 mg, and 20% for patients receiving placebo. Responses were similar in patients regardless of prior TNF antagonist exposure.

Recurrent Pericarditis (RP)

rilonacept (Arcalyst)

RHAPSODY (NCT03737110), a multinational, phase 3, double-blind, placebo-controlled randomized treatment withdrawal study, assessed the effectiveness and safety of rilonacept for the treatment of 86 patients at least 12 years of age with symptomatic RP (mean age, 45 years; 57% female).[619,620] The study consisted of a 12-week run-in period, in which rilonacept was dosed per its approved labeling and patients tapered and discontinued standard of care therapies, following by a 1:1 randomized withdrawal period in which 61 patients continued maintenance dosing or were assigned to placebo. This period continued until the pre-specified number of primary events, cases of RP, was met. Notably, 48% of patients were receiving treatment with corticosteroids at baseline. Those who then experienced RP were eligible for open-label rilonacept. At baseline, 85% had a diagnosis of idiopathic pericarditis, while the remainder had a diagnosis of post-cardiac injury pericarditis (mean duration, 2.4 years; mean of 4.4 events per year). The primary endpoint was the time to first adjudicated pericarditis recurrence based on pain, clinical symptoms, and CRP, and the median time to recurrence was not estimable due to too few events (7%); however, this was found to be 8.6 weeks on placebo (95% CI, 4 to 11.7; HR, 0.04 [95% CI, 0.01 to 0.18; p<0.0001]) with 74% experiencing cases on placebo. Furthermore, the cases occurring on rilonacept were associated with temporary treatment regimen interruptions (1 to 3 weeks). All patients with cases in the placebo group subsequently received rilonacept and then had resolution of the episode. After 16 weeks, 17/21 patients in the rilonacept group compared to 4/20 in the placebo group maintained a response (p=0.0002). In addition, fewer patients treated with rilonacept experienced pain, as measured by an NRS ≤ 2 (range, 0 to 10; p<0.0001).

Rheumatoid Arthritis (RA)

abatacept (Orencia)

Patients with active RA despite therapy with methotrexate were randomized to receive, in addition to the methotrexate, abatacept 2 mg/kg, abatacept 10 mg/kg, or placebo for 6 months.[621] In the 339-patient study, those treated with the higher dose of abatacept were more likely to have an ACR20 response than were patients who received placebo (60% and 35%, respectively; p<0.001). Significantly higher rates of ACR50 and ACR70 responses were seen in both active treatment groups. Abatacept was well tolerated, with an overall safety profile similar to that of placebo.

Patients with active RA and an inadequate response to at least 3 months of TNF antagonist therapy were randomly assigned to receive abatacept (n=258) or placebo (n=133) every 2 weeks for 1 month, then every 4 weeks for 6 months.[622] Patients discontinued TNF antagonist therapy before randomization but were given at least 1 other DMARD. After 6 months, the rates of ACR20 responses were 50.4% in the abatacept group and 19.5% in the placebo group (p<0.001). The rates of ACR50 and ACR70 responses were also significantly higher in the abatacept group (20.3% and 10.2%, respectively) than in the placebo group (3.8 and 1.5%; p<0.003 for both comparison). At 6 months, significantly more patients in the abatacept group (47.3%) had a clinically meaningful improvement from baseline in the Health Assessment Questionnaire Disability Index (placebo 23.3%; p<0.001). The incidence of adverse events and serious infections were similar in each group.

Due to a lack of other data for therapy for 2 years with abatacept, this open-label extension study has been included. Patients completing the 6-month trial were eligible to enter the long-term open-label extension trial to evaluate the safety and efficacy of abatacept during 2 years of the ATTAIN (Abatacept Trial in Treatment of Anti-TNF INadequate responders) trial in patients with RA.[623] A total of 317 patients (218 from the abatacept and 99 from the placebo group) entered, and 222 (70%) completed 18 months of long-term extension treatment. The ACR20 responses at 6 months and 2 years were 59.4 and 56.2%; ACR50, 23.5 and 33.2%; ACR70, 11.5 and 16.1%, respectively. Safety data were consistent with adverse effects reported in the 6-month trial.

In a double-blind study, 652 patients with active chronic RA despite treatment with methotrexate were randomized to abatacept (10 mg/kg) or placebo once monthly.[624] After 6 months in the abatacept in Inadequate Responders to methotrexate (AIM) study, ACR20 (68% versus 40%), ACR50 (40% versus 17%), and ACR70 (20% versus 7%) responses occurred more frequently in the active treatment group than in the group receiving placebo (p<0.05 for all comparisons). These differences were maintained at 1 year with ACR20 (73% versus 40%), ACR50 (48% versus 18%), and ACR70 (29% versus 6%) responses, all occurring more frequently with abatacept (p<0.001 for all comparisons). Physician function and progression of joint damage also favored abatacept. The incidence of adverse events was similar in both groups. There was, however, a higher incidence of infusion reactions with abatacept (8.8%) than with placebo (4.1%; p<0.05). The manufacturer of abatacept, which also employs several of the authors, funded this study. At the end of 1 year, 539 patients remained.[625] Patients who received placebo for 1 year were switched to abatacept and followed for 1 additional year with 488 patients completing the 2 years of evaluation. After the second year, ACR20 scores from year 2 were similar to year 1. Further inhibition of radiographic progression during year 2 of abatacept treatment was observed (57% reduction in mean change of total score in year 2 versus year 1; p<0.0001), and minimal radiographic progression was observed (mean change in total score from baseline was 1.1 and 1.6 at year 1 and 2, respectively).[626]

The efficacy and safety of abatacept in methotrexate-naïve patients with early RA were investigated in a double-blind phase 3 study.[627] Patients had RA for less than 2 years and had a mean DAS28 of 6.3. Inclusion criteria also required patients to have erosions and be seropositive for rheumatoid factor and/or anti-CCP2 that are associated with poor radiologic outcomes. Patients were randomized to abatacept 10 mg/kg plus methotrexate (n=256) or placebo plus methotrexate (n=253). The co-primary endpoints were the portion of patients achieving disease activity score in 28 joints (DAS-28)-defined remission and joint damage progression measured by Genant-modified Sharp total score at 1 year. After 1 year, a significantly greater proportion of abatacept plus methotrexate-treated patients achieved remission (41.4% versus 23.3%; p<0.001). Less radiographic progression occurred in the combination treatment group (mean change in total Sharp score, 0.63 versus 1.06; p=0.04). Adverse effects were comparable between groups for frequency of adverse effects, serious adverse events, serious infections, and malignancies.

The efficacy and safety of abatacept administered SC in 1,457 RA patients who had an inadequate response to methotrexate was studied in a randomized, double-blind, double-dummy, non-inferiority study (Study SC-I).[628] Patients were randomized with stratification by body weight (< 60 kg, 60 to 100 kg, > 100 kg) to receive abatacept 125 mg SC injections weekly, after a single IV loading dose of abatacept based on body weight or abatacept IV on days 1, 15, 29, and every 4 weeks thereafter. Patients continued taking their current dose of methotrexate from the day of randomization. The main outcome measure was ACR20 at 6 months. The pre-specified non-inferiority margin was a treatment difference of -7.5%. The percentage of patients achieving ACR response in the abatacept SC and IV treatment arms at 6 months was as follows: ACR20 (76% SC, 76% IV); ACR50 (52% SC, 50% IV); ACR70 (26% SC, 25% IV). Non-inferiority of abatacept SC relative to IV infusions of abatacept with respect to ACR20 responses up to 6 months of treatment was demonstrated. No major differences in ACR responses were observed between IV and SC treatment groups in subgroups based on weight categories.

abatacept (Orencia) versus infliximab (Remicade)

A double-blind trial compared the efficacy and safety of abatacept and infliximab in 431 adults with RA.[629] Patients were randomized to abatacept approximately 10 mg/kg every 4 weeks (n=156), infliximab 3 mg/kg every 8 weeks (n=165), placebo every 4 weeks (n=110), and background methotrexate. The primary objective of the study was to evaluate the mean change from baseline in Disease Activity Score (based on erythrocyte sedimentation rates; DAS28 [ESR]) for the abatacept versus placebo groups at day 197. At 6 months, mean changes in DAS28 (ESR) were significantly greater for abatacept versus placebo (-2.53 versus -1.48; p<0.001) and infliximab versus placebo (-2.25 versus -1.48; p<0.001). At day 197, ACR20 responses were significantly greater with abatacept versus placebo (ACR20, 66.7% versus 41.8%; p<0.001). ACR20 responses were also significantly higher in the infliximab group versus placebo (ACR20, 59.4% versus 41.8%; p=0.006). For abatacept versus infliximab treatment at day 365, reductions in the DAS28 (ESR) were -2.88 versus -2.25. At day 365, the ACR20 response rates were 72.4% for abatacept and 55.8% for infliximab. The DAS28-defined remission rates were 18.7% and 12.2% for abatacept and infliximab, respectively. Adverse events and discontinuations related to adverse events were lower with abatacept than infliximab. The manufacturer of abatacept funded the study.

abatacept (Orencia) versus adalimumab (Humira)

AMPLE (Abatacept versus Adalimumab Comparison in Biologic-Naïve RA Subjects with Background Methotrexate) was a phase 3, randomized, prospective study.[630] Patients with active RA (n=646) who had never received a biologic agent and had an inadequate response to methotrexate were randomized to abatacept 125 mg SC weekly or adalimumab 40 SC biweekly, both given in combination with

methotrexate for the 2-year study period. Patients were not blinded, but the independent clinical assessors, as well as the radiologists interpreting the radiographs, were blinded with regard to each patient's treatment. The primary endpoint was treatment inferiority based on ACR20 at 1 year. Other comparisons measured were radiographic response (of the hands and feet taken at baseline and on day 365), as well as overall safety. At 1 year, 274 (86.2%) of the abatacept-treated patients and 269 (82%) of the adalimumab-treated patients completed the study. The main reasons for discontinuation were lack of efficacy (3.8% of abatacept-treated patients versus 4.6% of adalimumab-treated patients) and adverse events (3.5% of abatacept-treated patients versus 6.1% of adalimumab-treated patients). The proportion of patients achieving an ACR20 response at 1 year was 64.8% (95% CI, 59.5% to 70%) in the abatacept group and 63.4% (95% CI, 58.2% to 68.6%) in the adalimumab group. The difference in ACR20 response rates between groups was 1.1% (95% CI, -6.5% to 8.7%), demonstrating noninferiority of abatacept compared to adalimumab. The rate of radiographic non-progression from baseline to 1 year was observed to be 84.8% in the abatacept group and 88.6% in the adalimumab group (difference between groups was 4.1% (95% CI, -1.5% to 9.6%). The rate of serious adverse events was 10.1% in the abatacept group and 9.1% in the adalimumab group. Discontinuations due to adverse effects occurred at almost twice the rate in the adalimumab group (6.1%) than in the abatacept group (3.5%). The incidences of infection (63.2% versus 61.3%) and malignancies (1.6% versus 1.2%) were similar between the 2 groups; however, the rate of autoimmune events was higher in the abatacept group (3.1%) compared to the adalimumab group (1.2%). Statistical analyses were not reported on these safety measures. Local injection site reactions occurred in significantly fewer patients in the abatacept group than in the adalimumab group (3.8% versus 9.1%; 95% CI, -9.13 to -1.62; p=0.006). A follow-up publication reported 79.2% of abatacept and 74.7% of adalimumab patients completed year 2 of the AMPLE trial. At year 2, efficacy outcomes, including radiographic results, remained comparable between groups and with year 1 results. The ACR20 at year 2 was 59.7% for abatacept and 60.1% for adalimumab. Overall, the rates of adverse events and serious adverse events were similar between the 2 groups; however, there were more serious infections with adalimumab (3.8% versus 5.8%), including 2 cases of tuberculosis with adalimumab. There were fewer discontinuations due to adverse events (3.8% versus 9.5%) or serious adverse events (1.6% versus 4.9%) in the abatacept group. Injection site reactions occurred less frequently with abatacept (4.1% versus 10.4%).[631]

adalimumab (Humira) with methotrexate versus placebo + methotrexate

The Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Rheumatoid Arthritis (ARMADA) trial was a 24-week, double-blind study of 271 patients with active RA despite treatment with methotrexate.[632] Patients were randomly assigned to receive adalimumab 20, 40, or 80 mg or placebo SC every other week while continuing to take their long-term stable dosage of methotrexate. The proportion of patients achieving ACR20 at 24 weeks was significantly greater in the adalimumab 20 mg (47.8 %), 40 mg (67.2%), and 80 mg (65.8%) groups than in the placebo group (14.5%; p<0.001 for all comparisons with placebo). Most patients receiving adalimumab achieved an ACR20 response at week 1. Compared with the ACR50 response rate of 8.1% in the placebo group, ACR50 response rates were higher in the groups receiving adalimumab 20 mg (31.9% p=0.003), 40 mg (55.2%; p<0.001), and 80 mg (42.5%; p<0.001). Near-remission, defined as an ACR70 response rate, occurred in 4.8% of the placebo group (p<0.001), 10.1% of the 20 mg group (p=NS), 26.9% of the 40 mg group (p<0.001), and 19.2% of the 80 mg group (p=0.02). The incidence of adverse events was similar in all groups.

A randomized trial of adalimumab evaluated 619 patients with active RA who had average disease duration of more than 10 years and who had inadequate response to methotrexate.[633] Patients received

adalimumab 40 mg every other week, 20 mg every week, or placebo. All patients received stable doses of methotrexate. The primary efficacy endpoints were radiographic progression at week 52 (total Sharp score by a modified method [TSS]), clinical response at week 24 (ACR20), and physical function at week 52 (HAQ-DI). Radiographs were assessed using a modified version of the Sharp method. Digitized images were scored by physicians who were blinded to the treatment, chronological order, and clinical response of each patient. Erosion scores were recorded for each hand/wrist and each forefoot on a 6-point scale (0 = no erosions; 1 = 1 discrete erosion or ≤ 20% joint involvement; 2 = 2 separate quadrants with erosion or 21 to 40% joint involvement; 3 = 3 separate quadrants with erosion or 41 to 60% joint involvement; 4 = all 4 quadrants with erosion or 61 to 80% joint involvement; and 5 = extensive destruction with > 80% joint involvement). Joint space narrowing scores were recorded for each hand/wrist and each forefoot on a 5-point scale (0 = no narrowing; 1 = up to 25% narrowing; 2 = 26 to 65% narrowing; 3 = 66 to 99% narrowing; and 4 = complete narrowing). To determine the modified TSS for each patient, the total erosion score (scale 0 to 230) and the joint space narrowing score (scale 0 to 168) were added (TSS scale 0 to 398). At weeks 24 and 52, adalimumab-treated patients had significantly less disease progression than placebo-treated patients. Patients receiving adalimumab plus methotrexate experienced significantly less radiographic progression than those taking methotrexate only ($p \leq 0.001$). At week 52, no new erosions were observed in significantly more patients receiving adalimumab 40 mg every other week (61.8%) than in those taking placebo (46%). In addition, joint erosion scores improved in almost twice as many patients receiving adalimumab 40 mg every other week than placebo (38.2% versus 19.3%, respectively). At 52 weeks, ACR20 responses were achieved by 59% of patients receiving adalimumab 40 mg every other week (placebo 24%) and ACR50 responses were achieved by 41.5% (placebo 9.5%). ACR70 was achieved by 23.2% of patients treated with adalimumab 40 mg every other week compared to 4.5% in the placebo group. Physical function improved significantly more for patients receiving adalimumab 40 mg every other week than for patients on placebo ($p \leq 0.001$). The rate of adverse events was similar among patients treated with adalimumab and placebo, although the proportion of patients reporting serious infections was higher in patients receiving adalimumab (3.8%) than placebo (0.5%; $p \leq 0.002$). The most common adverse events occurring in adalimumab 40 mg and placebo-treated patients, respectively, included injection-site reaction (26.1% versus 24%), upper-respiratory infection (19.8% versus 13.5%), rhinitis (16.4% versus 16.5%), and sinusitis (15.9% versus 13%). Forty-two adalimumab patients and 13 placebo patients withdrew from the study due to adverse events.

A double-blind study enrolled 799 patients with RA with active disease of less than 3 years duration to compare the efficacy and safety of adalimumab plus methotrexate versus either monotherapy over 2 years – the PREMIER study.[634] Patients had previously not received methotrexate. Patients were randomized to adalimumab 40 mg every other week plus methotrexate or either monotherapy. Co-primary endpoints at year 1 were ACR50 and mean change from baseline in the modified TSS. The combination therapy had a superior ACR50 response at 1 year (62%) compared to those receiving methotrexate (46%) or adalimumab monotherapy (41%; both $p<0.001$). The combination group had less radiographic progression ($p \leq 0.002$), as measured by the modified TSS, at both year 1 and 2 than patients on methotrexate and adalimumab monotherapy. Adverse events were similar in all groups.

adalimumab (Humira) in DMARD-nonresponders

In a 26-week, double-blind, placebo-controlled trial, 544 patients with RA who had failed therapy with other DMARDs were randomized to monotherapy with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, 40 mg weekly, or placebo.[635] After 26 weeks, patients treated with adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, and 40 mg weekly had

significantly better response rates than those treated with placebo: ACR20 (35.8%, 39.3%, 46%, and 53.4%, respectively versus 19.1%; p≤0.01); ACR50 (18.9%, 20.5%, 22.1%, and 35% versus 8.2%; p≤0.05); ACR70 (8.5%, 9.8%, 12.4%, and 18.4% versus 1.8%; p≤0.05). Patients treated with adalimumab achieved better improvements in HAQ-DI scores than those receiving placebo (p≤0.01 for all comparisons). There were no significant differences between treatment groups in the occurrence of serious adverse events, serious infections, or malignancies. Injection site reaction occurred in 10.6 and 0.9% of adalimumab- and placebo-treated patients, respectively (p≤0.05).

adalimumab (Humira) versus certolizumab pegol (Cimzia)

EXXELERATE: A 104-week multinational, randomized, single-blind, parallel-group, superiority trial compared the efficacy of adalimumab and certolizumab pegol, both with background methotrexate therapy in adult patients with RA (n=915).[636] Eligible patients were biologic DMARD-naïve with active disease despite ≥ 12 weeks of methotrexate therapy and were randomly assigned 1:1 to certolizumab 200 mg every 2 weeks (following titration) or adalimumab 40 mg every 2 weeks while continuing methotrexate in a double-blind 12-week phase. Stable doses of NSAIDs and oral glucocorticoids (≤ 10 mg prednisone equivalent) were allowed. Following 12 weeks of therapy, patients were considered either responders (DAS28 [ESR] ≤ 3.2 or DAS28 [ESR] reduction of ≥ 1.2 from baseline) or nonresponders. Responders continued the originally assigned treatment while nonresponders (65 with certolizumab pegol, 57 with adalimumab) were immediately switched to the alternate treatment group following titration per manufacturer dosing recommendations if needed. Those who still did not respond at 24 weeks despite 12 weeks of secondary treatment (38% with adalimumab second, 42% with certolizumab second) were considered nonresponders to TNF inhibitors and were withdrawn from the study. Following 12 weeks of therapy, no statistically significant difference was found between adalimumab and certolizumab pegol in ACR20 response (71% versus 69%, respectively; OR, 0.9; 95% CI, 0.67 to 1.2; p=0.467) or in DAS28 (ESR) low disease activity achievement (30% in both groups; OR, 1; 95% CI, 0.75 to 1.34). Likewise, following 104 weeks of therapy, no difference was found in DAS28 (ESR) low disease activity achievement (33% with adalimumab versus 35% with certolizumab pegol; OR, 1.09; 95% CI, 0.82 to 1.45; p=0.532). A similar number of treatment-emergent adverse effects were reported in each group (74% to 75%).

anakinra (Kineret)

In a 24-week extension of a 24-week, randomized, double-blind study of anakinra in 472 patients with RA, patients who had received placebo were randomized to receive anakinra 30 mg, 75 mg, or 150 mg SC daily.[637] Patients who had been initially randomized to 1 of the 3 anakinra dosages continued to receive the same dosage. Radiographs of the hands were obtained at baseline and at 24 and 48 weeks. The radiographs were evaluated using a modified TSS. The mean change in the modified TSS of 178 patients who completed 48 weeks treatment with active drug was significantly less than the change observed in the 58 patients who received placebo for 24 weeks and anakinra for 24 weeks (p=0.015). Significant reductions in the second 24-week period were observed in patients receiving anakinra 75 mg/day (p=0.006) and 150 mg/day (p=0.008). The modified TSS was reduced significantly more during the second 24-week treatment period compared to the first (p<0.001).

anakinra (Kineret) and etanercept (Enbrel) combination therapy

Two hundred forty-four patients in whom RA was active despite methotrexate therapy were treated with etanercept 25 SC mg twice weekly, etanercept 25 mg SC twice weekly plus anakinra 100 mg daily, or

etanercept 25 mg SC once weekly plus anakinra 100 mg daily for 6 months in a double-blind multicenter study.[638] Patients were naïve to anticytokine therapy. Thirty-one percent of the patients treated with twice weekly etanercept plus anakinra achieved an ACR50 response, compared with 41% of the patients treated with etanercept only (p=NS). The incidence of serious infections (0% for etanercept alone and 3.7% to 7.4% for combination therapy), injection-site reactions, and neutropenia was increased with combination therapy.

anakinra (Kineret) with methotrexate versus placebo + methotrexate

A total of 419 patients with moderate to severe active RA, despite at least 6 months of methotrexate therapy, received either placebo or anakinra 0.04 to 2 mg/kg SC daily in addition to methotrexate.[639] At 12 weeks, the proportion of patients who achieved an ACR20 response was significantly higher among those who received anakinra 1 mg/kg (46%; p=0.001) and 2 mg/kg (38%; p=0.007) than among those who received placebo (19%). At 24 weeks, the percentage of responders remained significantly higher among anakinra 1 mg/kg recipients (42%) than among placebo recipients (23%; p=0.004). Similar improvements in anakinra-treated subjects were noted in individual ACR components, onset of ACR20 response, sustainability of ACR20 response, and magnitude of ACR response. This study was supported by a grant from the manufacturers of anakinra.

In a double-blind study, 506 patients with active RA despite treatment with methotrexate were randomized to receive anakinra 100 mg or placebo SC daily in addition to continued treatment with methotrexate.[640] At the first study assessment (4 weeks), twice as many patients achieved an ACR20 response with anakinra as with placebo (p<0.005). The primary outcome, ACR20 at week 24, was achieved by 38% of the anakinra group and by 22% of the placebo group (p<0.001). A greater proportion of patients treated with anakinra also achieved ACR50 (17% versus 8%; p<0.01) and ACR70 (6% versus 2%; p<0.05) responses. Compared with placebo, anakinra also resulted in significant responses in individual components of the ACR response, pain, CRP levels, and ESR. The safety profile for anakinra was similar to placebo, except for more frequent mild to moderate injection site reactions (65% versus 24%). The manufacturer of anakinra supported the study.

baricitinib (Olumiant)

The efficacy and safety of baricitinib 2 mg once daily was assessed in 2 phase 3, randomized, double-blind, multicenter studies in adult patients with active RA diagnosed according to the ACR/European League Against Rheumatism (EULAR) 2010 criteria.[641,642,643] RA-BUILD (n=684) and RA-BEACON (n=527) were 24-week trials conducted in patients who had moderately to severely active RA and an inadequate response or intolerance to conventional DMARDs (cDMARDs) (RA-BUILD) or TNF inhibitors with or without other biologic DMARDs (RA-BEACON). Patients who were over 18 years of age were eligible if they had at least 6 tender and 6 swollen joints, present at baseline. In both trials, patients were randomized 1:1:1 to receive baricitinib 2 mg or 4 mg once daily or placebo in addition to their existing cDMARD treatment. The primary endpoint of each study was the proportion of patients who achieved an ACR20 response at week 12, which occurred in 62% versus 39% of those treated with baricitinib and placebo, respectively, in RA-BUILD (p≤0.001) and 55% versus 27%, respectively, in RA-BEACON (p<0.001). Any non-responding patients by week 16 could be rescued with the baricitinib 4 mg once daily. At week 24, the results of both studies revealed higher ACR20 response rates with baricitinib compared to placebo (RA-BUILD: 61% versus 42%; RA-BEACON: 45% versus 27%), as well as improvements in the DAS28-joint count CRP (DAS28-CRP), defined as DAS28-CRP < 2.6 (RA-BUILD: 31% versus 11%, respectively; RA-BEACON: 11% versus 6%, respectively). Secondary outcomes that also demonstrated greater

effectiveness in the baricitinib 2 mg group versus placebo were improvements in physical function as measured by the HAQ-DI and general health status assessed by the SF-36.

certolizumab pegol (Cimzia)

The FAST4WARD (eFficAcy and Safety of cerTolizumab pegol – 4 weekly dosAge in RheumatoiD arthritis) study was a 24-week, multicenter, double-blind trial that evaluated the efficacy and safety of certolizumab pegol as monotherapy in patients with active RA.[644] Patients who had not received a biologic therapy for RA within 6 months and had previously failed at least 1 DMARD (n=220) were randomized 1:1 to receive certolizumab pegol 400 mg or placebo every 4 weeks. ACR20 response at week 24, the primary endpoint, was 45.5% for certolizumab pegol and 9.3% for placebo (p<0.001). Most adverse events in both groups were mild or moderate. There were no reports of tuberculosis, opportunistic infections, malignancy, demyelinating disease, or congestive heart failure in either group. However, 2 cases (1.8%) of serious infection and 2 cases (1.8%) of benign tumors were reported in the certolizumab pegol group. This study was funded by the manufacturer of certolizumab pegol.

certolizumab pegol (Cimzia) + methotrexate versus methotrexate monotherapy

RAPID 2 was a 24-week, phase 3, multicenter, double-blind study that evaluated the efficacy and safety of SC certolizumab pegol plus methotrexate compared with placebo plus methotrexate.[645] Patients (n=619) with active adult-onset RA were randomized 2:2:1 to certolizumab pegol 400 mg at weeks 0, 2, and 4 followed by 200 mg or 400 mg plus methotrexate, or placebo plus methotrexate, every 2 weeks for 24 weeks. The primary endpoint, ACR20 response at week 24, was achieved by 57.3% of the low-dose certolizumab pegol group, 57.6% of the high-dose certolizumab pegol group, and 8.7% of the placebo-treated group (p≤0.001). Certolizumab pegol low- and high-dose groups also significantly inhibited radiographic progression; mean changes from baseline in mTSS at week 24 were 0.2 and -0.4, respectively, versus 1.2 for placebo (rank analysis p≤0.01). Physical function improved rapidly with certolizumab pegol compared to placebo based on mean changes from baseline in HAQ-DI at week 24 (p≤0.001). Most adverse events were mild or moderate, with low incidence of withdrawals due to adverse events. Five patients treated with certolizumab pegol developed tuberculosis. The RAPID 2 study was fully funded by the manufacturer of certolizumab pegol.

Certolizumab pegol plus methotrexate and placebo plus methotrexate were compared in 982 patients with active RA with an inadequate response to methotrexate therapy alone.[646] The 52-week, phase 3, randomized, double-blind trial evaluated ACR20 response rates at week 24 and the mean change from baseline in the modified total Sharp score at week 52. Certolizumab pegol was given as an initial dosage of 400 mg at weeks 0, 2, and 4, with a subsequent dosage of 200 mg or 400 mg given every 2 weeks, plus methotrexate, or placebo plus methotrexate. At week 24, ACR20 response rates using nonresponder imputation for the certolizumab pegol 200 mg and 400 mg groups were 58.8% and 60.8%, respectively, as compared with 13.6% for the placebo group. Differences in ACR20 response rates versus placebo were significant at week 1 and were sustained to week 52 (p<0.001). At week 52, mean radiographic progression from baseline was reduced in patients treated with certolizumab pegol 200 mg (0.4 Sharp units) or 400 mg (0.2 Sharp units) as compared with that in placebo-treated patients (2.8 Sharp units) (p<0.001 by rank analysis). Adverse effects were mild or moderate.

The C-EARLY trial, a multicenter, double-blind, placebo-controlled trial, compared the efficacy of methotrexate monotherapy versus certolizumab pegol with methotrexate in DMARD-naïve patients with moderate to severe RA over 52 weeks (n=879).[647] Patients were randomized 3:1 to certolizumab pegol (400 mg at weeks 0, 2, and 4, then 200 mg every 2 weeks thereafter) with methotrexate, or placebo with

methotrexate. The primary outcomes were sustained remission (sREM) and sustained low disease activity (sLDA), as defined by DAS28 scores ≤ 3.2) at week 52. After 52 weeks, significantly more patients assigned to the certolizumab group compared with placebo achieved sREM (28.9% versus 15%, p<0.001) and sLDA (43.8% versus 28.6%, p<0.001). The incidence of adverse events, including serious adverse effects, was similar between treatment groups. In an expansion of this study, 293 were re-randomized 2:3:2 certolizumab pegol at a standard dose, certolizumab pegol at a reduced frequency (every 4 weeks), or placebo plus methotrexate (certolizumab pegol discontinued).[648] The primary endpoint was the percentage of patients who maintained benefit without flares throughout weeks 52 through 104. A higher proportion of patients treated with certolizumab pegol maintained a benefit compared to those who discontinued certolizumab pegol (48.8% and 53.2% versus 39.2%, respectively; p=0.112 and p=0.041, respectively).

etanercept (Enbrel) plus methotrexate versus methotrexate monotherapy

The combination of methotrexate and etanercept in active early RA (COMET) study compared remission and radiographic non-progression in patients treated with methotrexate monotherapy or combination of etanercept with methotrexate.[649] A total of 542 methotrexate-naïve patients with early moderate to severe rheumatoid arthritis for 3 to 24 months were randomized to methotrexate monotherapy (n=268) titrated up from 7.5 mg per week to a maximum of 20 mg per week by week 8 or methotrexate with the same titration schedule plus etanercept 50 mg weekly (n=274). In the double-blind study, remission was measured with the DAS28 and radiographic non-progression measured with modified total Sharp score. Fifty percent of patients on combination therapy achieved clinical remission compared to 28% receiving methotrexate monotherapy (effect difference, 22.05%; 95% CI, 13.96 to 30.15; p<0.0001). The manufacturer of etanercept funded the study.

The COMET study continued to evaluate the outcomes of patients who completed the first year of the 2 year study.[650] The original combinations group either continued etanercept plus methotrexate (n=111) or received etanercept monotherapy (n=111) in year 2. The original methotrexate group received either methotrexate plus etanercept (n=90) or continued methotrexate monotherapy (n=99) in year 2. Efficacy endpoints were DAS28 remission and radiographic nonprogression at year 2. DAS28 remission was achieved by 62/108 patients of the etanercept plus methotrexate group continuous group, 54/108 patients for the etanercept plus methotrexate group then switched to etanercept only, 51/88 patients of the methotrexate group switched to combination therapy, and 33/94 patients in the methotrexate monotherapy group (p<0.01 for the etanercept plus methotrexate for 2-year group, and methotrexate monotherapy for year 1 then combination therapy for year 2 versus the methotrexate monotherapy for 2-years group). The proportions of subjects achieving radiographic nonprogression (n=360) were 89/99 of the combination therapy over 2 years group, 74/99 of the combination therapy then etanercept monotherapy group, 59/79 methotrexate then combination therapy group, and 56/83 methotrexate monotherapy over 2-years group (p<0.01 versus each of the other groups). No new safety issues or differences in serious adverse events were reported.

etanercept (Enbrel) plus methotrexate versus methotrexate monotherapy versus etanercept monotherapy

The TEMPO study evaluated the combination of etanercept plus methotrexate versus each of the single treatments in 686 patients with RA.[651] In the double-blind study, patients were randomized to etanercept 25 mg twice weekly, oral methotrexate up to 25 mg weekly or the combination. In the 682 patients that received study drug, the combination was more efficacious than methotrexate or etanercept alone in

retardation of joint damage over 52 weeks (mean total Sharp score, -0.54 [95% CI, -1 to -0.07] versus 2.8 [95% CI, 1.08 to 4.51; p<0.0001] and 0.52 [95% CI, -0.1 to 1.15; p=0.0006], respectively). The primary efficacy endpoint was the numeric index of the ACR response (ACR-N) area under the curve (AUC) over the first 24 weeks. ACR-N AUC at 24 weeks was greater for the combination group compared with etanercept alone and methotrexate alone (18.3%-years [95% CI, 17.1 to 19.6] versus 14.7%-years [13.5 to 16; p<0.0001] and 12.2%-years [95% CI, 11 to 13.4; p<0.0001], respectively). The mean difference in ACR-N AUC between combination and methotrexate alone was 6.1 (95% CI, 4.5 to 7.8; p<0.0001) and between etanercept and methotrexate was 2.5 (95% CI, 0.8 to 4.2; p=0.0034). To evaluate the clinical response between 12 and 24 weeks in subjects with RA, 12-week non-responders from the above TEMPO study were assessed at 24 weeks according to ACR response criteria. The proportion of subjects who successfully maintained response to 52 weeks was analyzed as were radiographic outcomes. Over 80% of the week 24 ACR20/50/70 responders in the etanercept plus methotrexate arm sustained their response to 52 weeks.[652] In the etanercept arms, a delayed clinical response was not associated with increased radiographic progression at week 52. The number of patients reporting infections or adverse events was similar in all groups.

golimumab (Simponi) SC

GO-AFTER: This was a phase 3, multicenter, double-blind trial that included 461 patients with moderately to severely active rheumatoid arthritis who had previously received TNF-α therapy.[653] Eligible patients had been treated with at least 1 dose of a TNF antagonist previously. Patients continued stable doses of methotrexate, sulfasalazine, hydroxychloroquine, oral corticosteroids, and NSAIDs. Patients were randomized to receive SC injections of placebo (n=155), 50 mg golimumab (n=153), or 100 mg golimumab (n=153) every 4 weeks. The primary endpoint was achievement of ACR20 at week 14. At week 16, patients who did not achieve ACR20 were given rescue therapy and changed treatment from placebo to 50 mg golimumab, or from 50 mg to 100 mg golimumab. At week 14, 18% of patients on placebo, 35% of patients on 50 mg golimumab (OR, 2.5; 95% CI, 1.5 to 4.2; p=0.0006), and 38% of patients on 100 mg golimumab (OR, 2.8; 95% CI, 1.6 to 4.7; p=0.0001) achieved ACR20. Serious adverse events were recorded in 7% of patients on placebo, 5% on 50 mg golimumab, and 3% on 100 mg golimumab.

GO-FORWARD: This was a phase 3, multicenter, double-blind, placebo controlled-trial.[654] All patients were diagnosed with moderate to severe RA and had been on a stable methotrexate dose of 15 to 25 mg/week immediately prior to screening. Patients (n=444) were randomized to receive placebo plus methotrexate, golimumab 100 mg SC plus placebo, golimumab 50 mg SC plus methotrexate, or golimumab 100 mg SC plus methotrexate every 4 weeks. Primary endpoints were proportion of patients that achieved ACR20 at week 14 and the change from baseline in the HAQ-DI at week 24. The proportion of patients who achieved an ACR20 response at week 14 was 33.1% in the placebo/methotrexate group, 44.4% (p=0.059) in the golimumab 100 mg/placebo group, 55.1% (p=0.001) in the golimumab 50 mg/methotrexate group and 56.2% (p<0.001) in the golimumab 100 mg/methotrexate group. At week 24, median improvements from baseline in HAQ-DI scores were 0.13, 0.13 (p=0.24), 0.38 (p<0.001), and 0.5 (p<0.001), respectively. At week 52, the ACR20 response rates were 44% for the placebo/methotrexate group, 45% for the golimumab 100 mg plus placebo, 64% for the golimumab 50 mg/methotrexate, and 58% for the golimumab 100 mg/methotrexate group.[655] The golimumab 100 mg/methotrexate group had a higher rate of serious adverse effects and infections. A 2-year follow-up of this trial reported that 392 patients continued from week 52 through week 104. Clinical improvement was maintained through week 104; 75% of golimumab 50 mg + methotrexate patients achieved an ACR20 response and 72% of patients randomized to golimumab 100 mg + methotrexate achieved an ACR20

response. Incidences of serious infections were 2.24, 4.77, and 5.78 per 100 patient-years of follow-up for golimumab 50 mg plus methotrexate, golimumab 100 mg plus placebo, and 100 mg plus methotrexate, respectively.[656]

GO-BEFORE: This study evaluated 637 patients with moderately to severely active RA who were methotrexate-naive and had not previously been treated with a biologic TNF antagonist.[657,658] Patients were randomized to receive methotrexate, golimumab 50 mg SC plus methotrexate, golimumab 100 mg SC plus methotrexate, or golimumab 100 mg SC monotherapy. For patients receiving methotrexate, the methotrexate dose was 10 mg per week beginning at week 0 and increased to 20 mg per week by week 8. Golimumab dose or placebo was administered every 4 weeks. The use of other DMARDs or other biologics was prohibited. The primary endpoint was the percentage of patients achieving an ACR50 response at week 24. The combination groups of golimumab 50 mg or 100 mg plus methotrexate in the intent-to-treat population did not show a significant difference on proportion of patients achieving ACR50 response from the placebo plus methotrexate group (38.4% and 29.4%, respectively; p=0.053). When 3 untreated patients were excluded in a post-hoc modified ITT analysis, the ACR50 response showed statistically significant differences between the combined group and placebo plus methotrexate (38.5% versus 29.4%; p=0.049) and between golimumab 50 mg plus methotrexate (40.5%; p=0.038) but not golimumab 100 mg plus methotrexate (36.5%; p=0.177) and placebo plus methotrexate. Golimumab 100 mg plus placebo was non inferior to placebo plus methotrexate for the ACR50 response at week 24 (33.1%; 95% CI, -5.2% to -10%). The combination of golimumab plus methotrexate demonstrated a significantly better response compared with placebo plus methotrexate in most other efficacy parameters, including response/remission, according to the Disease Activity Score in 28 joints.

In a multicenter, double-blind, randomized controlled trial, golimumab was evaluated in 172 patients with RA despite treatment with methotrexate.[659] Patients were randomized to 1 of 5 treatment arms: placebo plus methotrexate, golimumab 50 mg or 100 mg every 2 or 4 weeks plus methotrexate through week 48. Patients originally assigned to receive injections every 2 weeks had the interval increased to every 4 weeks starting at week 20. Patients assigned to the placebo group were given infliximab 3 mg/kg at weeks 20, 22 and 28 and then every 8 weeks. Methotrexate doses were stable throughout the study period. Seventy-five percent of patients completed the study. The primary endpoint was the proportion of patients achieving an ACR20 response at week 16. The ACR20 response rates at week 16 were 37.1% for placebo + methotrexate group, 50% for golimumab 50 mg every 2 weeks + methotrexate, 60% for golimumab 50 mg every 4 weeks + methotrexate, 79.4% for golimumab 100 mg every 2 weeks + methotrexate (p<0.001 versus placebo), and 55.9% for golimumab 100 mg every 4 weeks + methotrexate. At week 20, patients who had been receiving golimumab injections every 2 weeks switched to injections every 4 weeks without an appreciable decrease in the proportion of ACR20 responders. The patients on golimumab 100 mg + methotrexate had increased injection site reactions (36.1%) compared to the placebo group (11.8%). Three serious infections were reported in the golimumab groups compared to 2 serious infections reported in those patients who received infliximab after week 20.

golimumab (Simponi Aria) IV + methotrexate versus placebo + methotrexate

GO FURTHER was a 24-week randomized, double-blind, placebo-controlled, multicenter, phase 3 trial.[660] Patients (n=592) 18 years of age and older with moderately to severely active RA despite concurrent methotrexate therapy and had not previously been treated with a biological TNF antagonist. Patients were diagnosed by the ACR criteria and had at least 6 swollen and 6 tender joints. Patients were randomized 2:1 to receive golimumab 2 mg/kg IV at weeks 0, 4, and every 8 weeks thereafter (n=395) in addition to methotrexate (15 to 25 mg/kg) or placebo (n=197) in addition to methotrexate (15 to 25

mg/kg). Both groups had similar baseline demographics and 81% were women and 80% were Caucasian. The primary endpoint of the trial was the percentage of patients achieving a 20% ACR improvement by week 14. At week 14, 231 of 395 (58.5%) patients in the golimumab + methotrexate group and 49 of 197 (24.9%) patients in the placebo + methotrexate group achieved a 20% ACR improvement (95% CI, 25.9 to 41.4; p<0.001). The most common adverse effects at week 14 were infections and infestations with 24.3% in the golimumab and 20.8% in the placebo group. In an open-label expansion study, clinical response with golimumab + methotrexate was maintained through week 100.[661]

infliximab (Remicade)

The BeST study compared clinical and radiographic outcomes of 4 different treatment strategies in a multicenter, randomized clinical trial.[662] Treatment strategies were DMARD monotherapy, step-up combination therapy, initial combination therapy with tapered high-dose prednisone, and initial combination therapy with infliximab. Treatment adjustments were done every 3 months. For patients with early RA, initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after 1 year than did sequential monotherapy or step-up combination therapy. After 5 years, initial combination therapy resulted in significantly less joint damage progression, reflecting the earlier clinical response.[663]

infliximab (Remicade) with methotrexate versus placebo + methotrexate

One thousand forty-nine RA patients with active disease and no prior treatment with methotrexate or TNF antagonist were randomized to 1 of 3 treatment groups: methotrexate + placebo, methotrexate + infliximab 3 mg/kg, and methotrexate + infliximab 6 mg/kg.[664] Methotrexate dosages were rapidly escalated to 20 mg/week and infliximab or placebo infusions were given at weeks 0, 2, 6, and every 8 weeks thereafter through week 46. At week 54, the median percentage of improvement in ACR scores was higher for the methotrexate + infliximab 3 mg/kg (38.9%) and methotrexate + infliximab 6 mg/kg (46.7%) groups than for the methotrexate + placebo group (26.4%; p<0.001 for both comparisons). Patients in the methotrexate + infliximab 3 mg/kg and methotrexate + infliximab 6 mg/kg groups also showed less radiographic progression at week 54, as measured by modified TSS, than those receiving methotrexate alone (p<0.001 for each comparison). Methotrexate + placebo halted radiographic progression only if patients achieved remission within 3 months, whereas methotrexate + infliximab halted or minimized progression in patients with low or moderate activity, respectively.[665] Physical function improved significantly more in the methotrexate + infliximab 3 mg/kg and methotrexate + infliximab 6 mg/kg groups than in the methotrexate + placebo group. Infliximab therapy was associated with a significantly higher incidence of serious infections, especially pneumonia.

In ATTRACT (Anti-Tumor Necrosis Factor Trial in RA with Concomitant Therapy), a double-blind trial, 428 patients with active RA and who had received methotrexate for at least 3 months at a stable dose for at least 4 weeks were randomized to placebo or 1 of 4 regimens of infliximab at weeks 0, 2, and 6, then every 4 or 8 weeks thereafter.[666] At 30 weeks, ACR20 was achieved in 50% to 60% of patients receiving infliximab compare with 20% of patients receiving placebo (p<0.001 for each of the infliximab dosage regimens compared to placebo). ACR50 was achieved in 26 to 31% of infliximab patients compared to 5% of patients on placebo (p<0.001). Infliximab was well tolerated with no more withdrawals for adverse events or serious adverse events or infections than in the placebo group.

To evaluate the efficacy and safety of repeated administration of infliximab plus methotrexate over a 2-year period in patients with RA who previously experienced an incomplete response to methotrexate, 428 such patients were randomly assigned to receive methotrexate plus infliximab 3 or 10 mg/kg or

placebo for 54 weeks with an additional year of follow-up.[667] The protocol was later amended to allow for continued treatment during the second year. Of 259 patients who entered the second year of treatment, 216 continued to receive infliximab plus methotrexate for 102 weeks. Ninety-four of these 259 patients experienced a gap in therapy of more than 8 weeks before continuing therapy. Infusions were administered at weeks 0, 2, and 6 followed by treatment every 4 weeks or every 8 weeks at a dose of 3 or 10 mg/kg for a total of 102 weeks (including the gap in therapy). The infliximab plus methotrexate regimens resulted in significantly greater improvement in physical function and quality-of-life physical component scores compared with the methotrexate-only group. There also was stability in the quality-of-life mental component summary score among patients who received the infliximab plus methotrexate regimens. The proportion of patients achieving an ACR20 response at week 102 varied from 40% to 48% for the infliximab plus methotrexate groups compared with 16% for the methotrexate-only group.

infliximab-abda (Renflexis)

The safety and efficacy of infliximab-abda were established in a phase 3, randomized, double-blind, multinational, multicenter, parallel-group study.[668,669] Patients with moderate to severe RA despite methotrexate therapy were randomized in a 1:1 ratio to receive either infliximab-abda or infliximab 3 mg/kg. The primary endpoint was the ACR20 response at week 30. To demonstrated biosimilarity, an ACR20 response difference within ±15% was required. A total of 584 subjects were randomized to infliximab-abda (n=291; 290 analyzed) or infliximab (n=293). The ACR20 response at week 30 in the per-protocol set was 64.1% for infliximab-abda versus 66% for infliximab. The adjusted rate difference was -1.88% (95% CI, -10.26 to 6.51), which was within the predefined equivalence margin. Other efficacy outcomes such as ACR50/70, DAS28, and EULAR response were similar between infliximab-abda and infliximab. The incidence of treatment-emergent adverse events and antidrug antibodies were comparable. Efficacy, safety, and pharmacokinetics by subgroup were all comparable between infliximab-abda and infliximab.

infliximab-dyyb (Inflectra)

A 54-week, randomized, double-blind, parallel-group study compared European infliximab to infliximab-dyyb in 606 patients with active RA despite methotrexate use.[670] Patients were randomized 1:1 to either product at various sites in Europe, Asia, and Latin America; there were no sites in the US. The primary endpoint was ACR20 after 30 weeks of treatment with a 90% CI margin of ± 12%. At week 30, the estimated difference in ACR20 was 2% (90% CI, -5 to 9) in the ITT population. Key secondary endpoints included ACR50, ACR70, DAS28, ACR components, and radiographic score, which were similar as well. Notably, approximately 15% of patients withdrew from the study prior to the week 30 evaluations which may have affected outcome measures; however, there were no differences in withdrawals between groups. Overall safety findings on both products were comparable.

sarilumab (Kevzara)

Safety and efficacy were evaluated in 2 pivotal randomized, double-blind, placebo-controlled trials in adult patients with moderately to severely active RA.[671,672] In MOBILITY, patients (n=1,197) with an inadequate response to methotrexate were enrolled and received sarilumab 150 mg or 200 mg or placebo administered SC every 2 weeks in addition to methotrexate. In Study 2, patients (n=546) who had an inadequate response to at least 1 TNFα inhibitor were randomized to sarilumab 150 mg, sarilumab 200 mg, or placebo administered SC every 2 weeks with concurrent conventional DMARD (methotrexate, sulfasalazine, leflunomide, hydroxychloroquine). The primary endpoint in both trials was the proportion

of patients who achieved ACR20 at week 24. A significantly greater proportion of patients that received sarilumab 150 mg and 200 mg achieved ACR20 compared to those who received placebo at week 24 (MOBILITY: 58% and 66.4% versus 33.4%, respectively; Study 2: 55.8% and 60.9% versus 33.7%, respectively). Similar proportions were seen at week 12 in both studies. Durability of ACR20 was reported at week 52 in MOBILITY; this was not evaluated in Study 2. In addition, at week 24 the secondary endpoints of ACR50 and ACR70 were significantly greater with sarilumab 150 mg and 200 mg than with placebo (ACR50 MOBILITY: 37% and 45.6% versus 16.6%, respectively; ACR50 Study 2: 37% and 40.8% versus 18.2%; ACR70 MOBILITY: 19.8% and 24.8% versus 7.3%, ACR70 Study 2: 19.9% and 16.3% versus 7.2%, respectively). In addition, in MOBILITY radiographs of hands and feet were obtained at baseline, and at weeks 24 and 52. Both doses of sarilumab were reported as being superior to placebo when given with methotrexate, according to the independently reviewed radiographs; least mean difference from placebo in mTSS at week 52 was -1.88 (95% CI, -2.75 to -1.01) for the 150 mg group and -2.52 (95% CI, -3.38 to -1.66) for the 200 mg group. Both doses of sarilumab were associated with greater improvement from baseline in physical function, as assessed by HAQ-DI, compared to placebo at week 16 and week 12 in Studies 1 and 2, respectively; difference from placebo was -0.24 and -0.26, respectively in MOBILITY and -0.2 and -0.21, respectively in Study 2. An open-label, 2-year extension study of the MOBILITY trial found continued efficacy and reported treatment-emergent adverse events and serious adverse events rates of 279.6 events per 100 patient-years and 16.6 events per 100 patient-years, respectively.[673]

sarilumab (Kevzara) versus adalimumab (Humira)

The MONARCH trial was a randomized, active-controlled, double-blind, double-dummy, phase 3 superiority trial that compared monotherapy with sarilumab (200 mg every 2 weeks) and adalimumab (40 mg every 2 weeks) in 369 patients with RA who had an inadequate response or were intolerant to methotrexate.[674] After week 16, dose escalation of adalimumab was allowed in patients who did not achieve 20% improvement in tender and swollen joint counts. The primary endpoint was DAS28 (ESR) at week 24, at which time the mean change from baseline in DAS28 (ESR) was -3.28 for sarilumab versus -2.2 for adalimumab (difference, -1.08; 95% CI, -1.36 to -0.79; p<0.0001); sarilumab was found to be superior. Superiority was defined by at least 0.6 units improvement of sarilumab over adalimumab using a standard deviation of 1.7. Remission, defined as DAS28 (ESR) < 2.6 was reported in 26.6% of patients who received sarilumab compared to 7% who received adalimumab (p<0.0001). In addition, sarilumab was associated with significantly higher ACR20/50/70 response rates (sarilumab: 71.7%/45.7%/23.4%; adalimumab: 58.4%/29.7%/11.9%; all p≤0.0074), significantly greater improvement in HAQ-DI (p=0.0037), and higher rates of Clinical Disease Activity Index remission (7.1% versus 2.7%; nominal p=0.0468). Rates of injection site reactions reported were 9.2% for sarilumab and 4.3% for adalimumab. Despite a higher incidence of neutropenia seen with sarilumab (13.6% versus 0.5%), the incidence of infection (sarilumab, 28.8%; adalimumab, 27.7%) was similar in both groups. In an open-label extension, continued positive benefits were seen at week 48.[675]

tocilizumab (Actemra) IV

The double-blind, parallel-group AMBITION study evaluated the efficacy and safety of tocilizumab monotherapy compared to methotrexate monotherapy in patients with active RA for 24 weeks.[676] Patients had previously not failed on methotrexate or biological agents. Patients (n=673) were randomized to tocilizumab 8 mg/kg IV every 4 weeks or methotrexate starting at 7.5 mg per week and titrated to 20 mg per week within 8 weeks or placebo for 8 weeks followed by tocilizumab 8 mg/kg. ACR20 response rate was the primary endpoint; ACR20 response rate was higher in the tocilizumab group

compared to methotrexate (69.9% versus 52.5%; p<0.001). The DAS28 rate of less than 2.6 was better with tocilizumab (33.6% versus 12.1%). Serious adverse events were reported in 3.8% of patients receiving tocilizumab and 2.8% of patients receiving methotrexate (p=0.5). Serious infections were reported in 1.4% and 0.7% of patients receiving tocilizumab and methotrexate, respectively. Neutropenia (3.1% versus 0.4%) and elevated total cholesterol (≥ 240 mg/dL; 13.2% versus 0.4%) were reported more frequently with tocilizumab than methotrexate, respectively.

In a double-blind, randomized, placebo-controlled study, the efficacy in achieving ACR20 response with tocilizumab 623 patients with moderate to severe RA was evaluated over 24 weeks in the OPTION study.[677] Patients were randomized to IV tocilizumab 8 mg/kg (n=205), tocilizumab 4 mg/kg (n=214), or placebo every 4 weeks. Patients remained on the stable pre-study dose of methotrexate of 10 to 25 mg/week. At 24 weeks, ACR20 response rates were 59% in the high-dose group, 48% in the low-dose group, and 26% in the placebo group (OR, 4; 95% CI, 2.6 to 6.1; p<0.0001 for 8 mg/kg versus placebo; OR, 2.6; 95% CI, 1.7 to 3.9; p<0.0001 for 4 mg/kg versus placebo). Serious infections or infestations were reported in 6 patients in the 8 mg/kg group, 3 patients in the 4 mg/kg group, and 2 patients in the placebo group.

In the double-blind, multicenter, randomized, controlled SATORI study, the efficacy and safety of tocilizumab monotherapy in 125 patients with active RA with an inadequate response to low-dose methotrexate were evaluated over 24 weeks.[678] Patients were randomized to IV tocilizumab 8 mg/kg every 4 weeks plus placebo or placebo plus methotrexate 8 mg/week for 24 weeks. The primary outcome measure was the ACR20 response and the Disease Activity Score in 28 joints. After 24 weeks, 25% of the placebo plus methotrexate group and 80.3% in the tocilizumab group achieved ACR20 response. The tocilizumab group showed superior ACR response criteria over control at all time points. Serious adverse events were reported in 4.7% and 6.6% of the methotrexate group and tocilizumab groups, respectively. Serious infections were reported in 1.6% and 3.3% of the methotrexate group and tocilizumab groups, respectively.

In a phase 3, double-blind, randomized, multicenter study, tocilizumab was compared to placebo in 499 patients with RA who had inadequate response to 1 or more TNF antagonists (RADIATE trial).[679] Patients were randomized to IV tocilizumab 8 mg/kg or 4 mg/kg or placebo given IV every 4 weeks with stable methotrexate for 24 weeks. ACR20 response was achieved by 50%, 30.4%, and 10.1% of patients receiving tocilizumab 8 mg/kg, 4 mg/kg, or placebo, respectively (less than p<0.001 both tocilizumab groups versus placebo). At week 4, more patients in the high-dose tocilizumab group achieved ACR20 compared to the placebo group (p<0.001). Patients responded regardless of the most recently failed TNF antagonist or the number of failed treatments. DAS28 remission rates at week 24 were dose-related with 30.1% (p<0.001), 7.6% (p=0.053), and 1.6% of the tocilizumab 8 mg/kg, 4 mg/kg, or placebo groups, respectively. The incidence of serious adverse events was higher in the placebo group (11.3%) compared to the tocilizumab high-dose group (6.3%) and low-dose group (7.4%).

In TOWARD, the efficacy and safety of tocilizumab in combination with other DMARDS were investigated in 1,220 patients with active RA.[680] In the phase 3, double-blind, placebo-controlled, multicenter study, patients remained on stable doses of DMARDs and received IV tocilizumab 8 mg/kg or placebo (control group) every 4 weeks for 24 weeks. At week 24, the proportion of patients achieving an ACR20 was significantly greater in the tocilizumab plus DMARD group (61%) than in the control group (25%; p<0.0001). Tocilizumab also provided greater improvement in the secondary endpoints including ACR50 or ACR70 responses, the DAS28, and DAS28 remission responses (DAS28<2.6). More adverse effects were reported in the tocilizumab group. Serious adverse effects were reported in 6.7% and 4.3% of patients in

the tocilizumab and placebo groups, respectively. Elevated liver enzymes were observed in 4% and 1% of the tocilizumab and placebo groups, respectively. Elevated total cholesterol levels were reported in 23% and 6% of the tocilizumab and placebo groups, respectively.

The ROSE trial evaluated efficacy of tocilizumab in patients with moderate to severe active RA and inadequate clinical response to DMARDs.[681] Safety-related outcomes were also analyzed. In a 24-week, double-blind trial, patients with moderate to severe active RA and inadequate clinical response to DMARD therapy were randomized 2:1 to IV tocilizumab 8 mg/kg (n=412) or placebo (n=207) every 4 weeks while continuing background DMARD in both groups. The primary endpoint of ACR50 response at week 24, was higher with tocilizumab versus placebo (30.1% versus 11.2%; p<0.0001). Percentages of ACR20 and ACR50 responders were significantly higher with tocilizumab versus placebo as early as week-4 and continued to week 24; more patients in the tocilizumab arm also achieved ACR70 responses beginning at week-8 compared to the placebo group (p<0.01). A substudy examining early response to therapy showed improved patient global assessment of disease activity (p=0.005) and pain (p=0.01) and DAS28 (p=0.007) with tocilizumab versus placebo at day-7. Safety findings were consistent with the known tocilizumab safety profile; rates of serious infections (per 100 patient-years) were 7.87 (95% CI, 4.3 to 13.2) and 1.2 (95% CI, 0.03 to 6.66) in the tocilizumab and placebo groups, respectively.

ADACTA was a randomized, double-blind, multicenter controlled phase 4 trial that compared IV tocilizumab monotherapy versus SC adalimumab monotherapy for adults with rheumatoid arthritis (diagnosed for at least 6 months) who were intolerant to methotrexate or for whom continuation of methotrexate was deemed inappropriate.[682] The study enrolled 326 patients who were randomized 1:1 (163 assigned to tocilizumab and 162 assigned to adalimumab). Patients previously treated with a biologic DMARD were excluded. Patients received either tocilizumab 8 mg/kg IV every 4 weeks plus placebo SC every 2 weeks or adalimumab 40 mg SC every 2 weeks plus placebo IV every four weeks for 24 weeks. The primary efficacy endpoint was change in disease activity score using 28 joints (DAS28; using erythrocyte sedimentation rate) from baseline to week 24. Key secondary efficacy endpoints were proportion of patients achieving a DAS28 of 3.2 or lower, a DAS28 of less than 2.6, ACR20, 50, 70 responses, EULAR good response at week 24, and EULAR good or moderate response at week 24. A total of 24 of 163 (15%) of patients in the tocilizumab group and 28 of 163 (17%) of patients in the adalimumab group withdrew early from the study. Safety reasons for withdrawal included adverse events (9 with tocilizumab and 10 with adalimumab) and death (2 for tocilizumab: 1 death was deemed unrelated to tocilizumab and 1 death was ruled possibly related to tocilizumab although the cause of death was not known, and the patient had multiple cardiac comorbidities). Other reasons for withdrawal included insufficient treatment response (7 for tocilizumab, 14 for adalimumab), treatment refusal (3 for tocilizumab, 6 for adalimumab), and failure to return (3 for tocilizumab). The primary endpoint, mean change of DAS28 from baseline to week 24, was significantly greater with tocilizumab (-3.3) than with adalimumab (-1.8; difference -1.5; 95% CI, -1.8 to -1.1; p<0.001). Secondary endpoints at week 24 demonstrated significantly more patients in the tocilizumab group than in the adalimumab group had a DAS28 of 3.2 or less (p<0.001), a DAS28 of less than 2.6 (p<0.001), and ACR20 (p=0.0038), 50 (p=0.002), 70 (p=0.0023) responses. EULAR responses were also more common in the tocilizumab group compared with the adalimumab group (EULAR good p<0.001; EULAR good or moderate p<0.001). The rates of adverse events were similar in each group, 82.1% for tocilizumab versus 82.7% for adalimumab. The most commonly reported adverse events were upper respiratory tract infections (11.1% for tocilizumab and 10.5% for adalimumab), nasopharyngitis (10.5% for tocilizumab versus 8% for adalimumab), and worsening of rheumatoid arthritis symptoms (6.8% for tocilizumab versus 9.9% with adalimumab). Incidence of serious adverse events was also similar between the groups; serious infections were the

most common and were reported at similar proportions in both groups (23 in the tocilizumab group and 21 in the adalimumab group) with no specific type of infection predominating. More patients treated with tocilizumab than adalimumab needed dose modification or interruption because of adverse events, these were most commonly related to infections or laboratory abnormalities. The study sponsor, Hoffman-LA Roche, parent company of Genentech, designed the study, collected, analyzed, and interpreted the data, and wrote the report; the lead authors had full access to all the data.

tocilizumab (Actemra) SC

SUMMACTA: Study SC-1 was a randomized, double-blind, active-controlled, multicenter, non-inferiority study comparing tocilizumab 162 mg SC administered every week to tocilizumab 8 mg/ kg IV every 4 weeks in patients > 18 years of age with moderate to severe active RA.[683,684] A total of 1,262 patients with moderate to severe active RA diagnosed according to ACR criteria who had at least 4 tender and 4 swollen joints at baseline were randomized 1:1 to receive tocilizumab SC or IV in combination with non-biologic DMARD(s). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. The pre-specified non-inferiority margin was a treatment difference of 12% or less. At week 24, 69% of the per protocol population who received tocilizumab SC had an ACR20 compared to 73.4% of the patients who received tocilizumab IV. The weighted difference was -4% (95% CI, -9.2 to 1.2), demonstrating non-inferiority of tocilizumab SC administration to IV administration. Results of the SUMMACTA study at week 97 indicate that SC and IV tocilizumab have comparable long-term efficacy and safety, with the exception of injection site reactions being more common with the SC formulation.[685]

MUSASHI: This was a double-blind, double-dummy, parallel-group, comparative study of tocilizumab SC 162 mg every 2 weeks to tocilizumab IV 8 mg/kg every 4 weeks in Japanese patients.[686] Patients were 20 to 75 years of age and had RA for ≥ 6 months, diagnosed 1987 ACR criteria. Inclusion criteria included: an inadequate response of ≥ 12 weeks to any synthetic DMARD (methotrexate, salazosulfapyridine, bucillamine and leflunomide), biologic DMARD (infliximab, etanercept and adalimumab) or immunosuppressant (e.g., tacrolimus); ≥ 8 tender joints; ≥ 6 swollen joints; and an erythrocyte sedimentation rate (ESR) of ≥ 30 mm/hour or a CRP level of ≥ 1 mg/dL. Patients (n=346) were randomized 1:1 into each treatment group and received drugs. No DMARDs or immunosuppressants were allowed during the study, although low dose corticosteroids and an NSAID were permitted. The primary endpoint was the ACR20 response rate at week 24, with a prespecified tocilizumab SC to tocilizumab IV noninferiority margin of 18%. At week 24, the per protocol ACR20 response was achieved in 79.2% (95% CI, 72.9 to 85.5) of the tocilizumab SC group and in 88.5% (95% CI, 83.4 to 93.5) of the tocilizumab IV group; and the weighted difference was −9.4% (95% CI, −17.6 to −1.2).

Study (SC-II) was a randomized, double-blind, placebo controlled, multicenter study in patients with active RA comparing tocilizumab 162 mg SC administered every other week to placebo.[687] Subjects were > 18 years of age with moderate to severe active RA, diagnosed according to ACR criteria, who had at least 8 tender joints and 6 swollen joints at baseline, and an inadequate response to their existing DMARD therapy. Patients (n=656) were randomized 2:1 to tocilizumab 162 mg SC every other week or placebo, in combination with non-biologic DMARD(s). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. In SC-II, 61% of patients treated with tocilizumab 162 mg SC every other week achieved an ACR20 response compared to 32% of placebo-treated patients in the intent to treat population with a weighted difference of 30% (95% CI, 22 to 37). A benefit was also found in SF-36.

tofacitinib (Xeljanz, Xeljanz XR)

Solo Study: A 6-month, randomized, double-blind, monotherapy study in 610 patients with moderate to severe active RA who had an inadequate response to a DMARD (non-biologic or biologic).[688] Patients were randomized to receive tofacitinib 5 or 10 mg twice daily or placebo. At the month 3 visit, all patients on placebo were switched to tofacitinib 5 or 10 mg twice daily. Primary efficacy endpoints were ACR20, Health Assessment Questionnaire-Disability Index (HAQ-DI), and DAS28 < 2.6 at month 3. A greater proportion of patients on tofacitinib 5mg or 10 mg had ACR20 responses compared to placebo (59.8% and 65.7% versus 26.7%, respectively; p≤0.05 for both). ACR50 and ACR70 responses were consistent with the ACR20 results. ACR20, ACR50, and ACR70 responses were numerically higher for tofacitinib 10 mg compared 5 mg at all time points; the differences between the dosages were most pronounced for ACR70. The differences in HAQ-DI from placebo were similar between the 5 mg and 10 mg dose groups (0.5 and 0.57, versus 0.19, respectively; p<0.0001 for both). ACR20 and HAQ-DI efficacy responses were observed starting at week 2 and were maintained throughout the study. The proportion of patients achieving DAS28-4(ESR) < 2.6 at month 3 was numerically but not statistically significantly greater for both tofacitinib dosages (5.6% and 8.7% versus 4.4%, respectively).

Scan, Sync, and Standard Studies: Three 12-month double-blind phase 3 studies included patients with moderate to severe active RA who had an inadequate response to a non-biologic DMARD, including methotrexate.[689] In the Scan study, patients (n=797) received tofacitinib 5 or 10 mg twice daily or placebo added to background methotrexate treatment; Sync study patients (n=792) received tofacitinib 5 or 10 mg twice daily or placebo added to background DMARDs; Standard study patients (n=717) received tofacitinib 5 or 10 mg twice daily, adalimumab 40 mg SC every other week, or placebo added to background methotrexate. The co-primary endpoints for all 3 studies were the proportion of patients who achieved an ACR20 response at month 6, changes in HAQ-DI at month 3, and rates of DAS28-4(ESR) < 2.6 at month 6. In the studies 45 to 49% of placebo patients were considered nonresponders (e.g., those not reaching ACR20) and were switched to tofacitinib 5 mg or 10 mg twice daily at month 3. At the end of month 6, all placebo patients were switched to tofacitinib 5 mg or 10 mg twice daily. ACR20 response rate was greater in patients treated with tofacitinib 5 mg or 10 mg compared with placebo (47.3% to 61.8% and 51.5% to 52.7% versus 25.3% to 31.2%, respectively). Placebo patients rapidly responded after advancing to tofacitinib. The proportion of patients who achieved ACR20 response was similar in the tofacitinib treatment groups and the adalimumab treatment group (51.5% and 52.6%, versus 47.3%, respectively). ACR50 response rates were greater in the tofacitinib 5 mg treatment group than in the adalimumab treatment group at month 3 (p≤0.05); although at month 6 neither dose of tofacitinib was statistically significantly different to adalimumab. ACR70 response rates were better in both tofacitinib dose groups than in the adalimumab group at month 6 (p≤0.0019). The changes from baseline in HAQ-DI were similar or better for tofacitinib 5 mg or 10 mg than that seen for adalimumab group during the entire treatment period (0.56 and 0.64 versus 0.51, respectively). The proportion of patients achieving DAS28-4(ESR) < 2.6 at the primary time point was statistically significantly different from the placebo group for both tofacitinib dose groups across the phase 3 background DMARD studies (p<0.05). The proportions for the tofacitinib 10 mg dose group were notably greater than for the 5 mg dose group.

The Scan study also assessed progression of structural damage using modified Total Sharp Score (mTSS) at month 6; no progression in mTSS was defined as ≤ 0.5 unit increase from baseline. At baseline treatment groups were similar in degree of damage as shown on x-ray and their estimated annual rate of progression. Changes in mean mTSS at month 6 for tofacitinib 5mg and 10 mg and placebo were 0.12, 0.06, and 0.47, respectively; this represented approximately 74% and 87% reductions relative to placebo,

respectively. The difference compared to placebo was statistically significant for the 10 mg dose (p=0.0376) at month 6; but not for the 5 mg dose (p=0.0792). Reductions continued through month 12. The proportion of patients with no progression of mTSS for both tofacitinib doses (88.8% for 5 mg, 86.9% for 10 mg) was statistically greater than placebo (77.7%) at month 6. Effect of tofacitinib on inhibition of the progression of structural damage was maintained for up to 12 months.

Step Study: The Step Study was a 6-month phase 3 trial in 399 patients with moderate to severe active RA who had an inadequate response to at least 1 TNF-inhibitor biologic agent.[690] These patients received tofacitinib 5 mg or 10 mg twice daily or placebo added to background methotrexate treatment. At month 3, all patients on placebo treatment were switched to tofacitinib 5 mg or 10 mg twice daily. The primary endpoints were the proportion of patients who achieved an ACR20 response, HAQ-DI, and DAS28-4(ESR) < 2.6 at month-3. ACR20 response rate for tofacitinib 5 mg and 10 mg and placebo were 41.7, 48.01, and 24.4%, respectively. Changes from baseline in HAQ-DI were 0.43, 0.46, and 0.18, respectively. Proportion of patients with DAS28 < 2.6 were 8.8%, 6.7%, and 1.7%, respectively. The authors noted that the magnitudes of these improvements tended to be lower in this trial than in the other background DMARD studies, which was expected for patients with biologic DMARD refractory RA.

ORAL-Strategy, a 12 month, double-blind, non-inferiority, randomized controlled trial, compared the efficacy of oral tofacitinib (with or without methotrexate) to SC adalimumab in patients ≥ 18 years of age with active RA despite methotrexate treatment (n=1,146).[691] Patients were randomized 1:1:1 to tofacitinib 5 mg twice daily, tofacitinib 5 mg twice daily in combination with methotrexate, or adalimumab 40 mg every other week in combination with methotrexate. The primary endpoint was the proportion of patients who attained ACR50 at 6 months. This occurred in 38% of patients treated with tofacitinib monotherapy, 46% treated with tofacitinib plus methotrexate, and 44% treated with adalimumab plus methotrexate. Noninferiority was demonstrated for tofacitinib plus methotrexate versus adalimumab plus methotrexate (treatment difference, 2%; 98.34% CI, -6 to 11) but not for tofacitinib monotherapy.

Approval of extended-release tofacitinib (Xeljanz XR) was based on efficacy and safety data established with immediate-release tofacitinib.

upadacitinib (Rinvoq)

The SELECT program, consisting of 5 multicenter, randomized (1:1), double-blind studies, supported the approval of upadacitinib.[692] All trials assessed safety and efficacy of upadacitinib in patients with moderately to severely active RA. Study eligibility criteria included the following: age ≥ 18 years, presence of ≥ 6 tender and swollen joints, and systemic inflammation (as determined by elevated hsCRP ≥ 3 mg/L). Among exclusion criteria was prior exposure to any JAK inhibitor. In SELECT-MONOTHERAPY, patients were also excluded if they had prior exposure to a biologic DMARD. Most studies assessed upadacitinib doses of 15 mg and 30 mg once daily. The higher dose provided minimal clinically meaningful added benefit but was associated with an increased safety risk; the 30 mg daily dose was not proposed for marketing.

SELECT-EARLY (n=947; RA-I), a 24-week study, compared upadacitinib to methotrexate in patients methotrexate-naïve.[693] The mean difference in change from baseline in the proportion of patients that achieved ACR20 at week 12 (primary endpoint) was 22% (95% CI, 14 to 29), favoring upadacitinib. The mean difference in change from baseline to 12 weeks in the proportion of patients that achieved ACR50, ACR70, and DAS28-CRP were 24% (95% CI, 16 to 31), 18% (95% CI, 12 to 25), and 22% (95% CI, 15 to 28), respectively, all favoring upadacitinib.

SELECT-MONOTHERAPY (n=648; RA-II), a 14-week study, compared upadacitinib to methotrexate monotherapy in patients with an inadequate response to methotrexate.[694,695] The mean difference in change from baseline in the proportion of patients that achieved ACR20 at week 14 (primary endpoint) was 26% (95% CI, 17 to 36), favoring upadacitinib. The mean difference in change from baseline to 14 weeks in the proportion of patients that achieved ACR50, ACR70, and DAS28-CRP were 27% (95% CI, 18 to 35), 20% (95% CI, 14 to 26), and 20% (95% CI, 13 to 27), respectively, all favoring upadacitinib.

SELECT-NEXT (n=661; RA-III), a 12-week study, compared upadacitinib to placebo in patients with an inadequate response to a conventional DMARD.[696,697] Each group also received background conventional DMARD therapy. The mean difference in change from baseline in the proportion of patients that achieved ACR20 at week 12 (primary endpoint) was 28% (95% CI, 19 to 37), favoring upadacitinib. The mean difference in change from baseline to 12 weeks in the proportion of patients that achieved ACR50, ACR70, and DAS28-CRP were 23% (95% CI, 15 to 31), 15% (95% CI, 19 to 21), and 21% (95% CI, 14 to 28), respectively, all favoring upadacitinib.

SELECT-COMPARE (n=1,629; RA-IV), a 48-week study, compared upadacitinib and active comparator (SC adalimumab 40 mg every other week) to placebo in patients with an inadequate response to methotrexate.[698] Each group also received background methotrexate. The mean difference in change from baseline in the proportion of patients that achieved ACR20 at week 12 for upadacitinib versus placebo (primary endpoint) was 34% (95% CI, 29 to 39), favoring upadacitinib. The mean difference in change from baseline to 12 weeks in the proportion of patients that achieved ACR50, ACR70, and DAS28-CRP for upadacitinib versus placebo were 30% (95% CI, 26 to 35), 20% (95% CI, 16 to 24), and 23% (95% CI, 19 to 27), respectively, favoring upadacitinib.

SELECT-BEYOND (n=499; RA-V), a 12-week study, compared upadacitinib to placebo in patients with an inadequate response or intolerance to a biologic DMARD.[699,700] Each group also received background conventional DMARD therapy. The mean difference in change from baseline in the proportion of patients that achieved ACR20 at week 12 (primary endpoint) was 36% (95% CI, 26 to 46), favoring upadacitinib. The mean difference in change from baseline to 12 weeks in the proportion of patients that achieved ACR50, ACR70, and DAS28-CRP were 22% (95% CI, 14 to 31), 5% (95% CI, -1 to 11), and 19% (95% CI, 11 to 27), respectively, favoring upadacitinib when statistically significant.

SELECT-CHOICE (n=612), a 24-week, double-blind, randomized, controlled noninferiority trial, compared the efficacy of upadacitinib with IV abatacept for the treatment of rheumatoid arthritis in 303 patients who were refractory to treatment with a biologic DMARD.[701] Included patients were randomized 1:1 to oral upadacitinib (15 mg once daily) or IV abatacept, both in combination with stable doses of conventional DMARDs. The primary endpoint was the change in DAS28-CRP at week 12, which were -2.52 and -2 in the upadacitinib and abatacept groups, respectively (difference, -0.52; 95% CI, -0.69 to -0.35; $p<0.001$ noninferiority and superiority; noninferiority set at a margin of 0.6 in DAS28-CRP). Thirty percent of patients achieved clinical remission with upadacitinib compared to 13.3% of those treated with abatacept (treatment difference, 16.8%; 95% CI, 10.4 to 23.2; $p<0.001$ for superiority). Regarding safety, a greater number of patients treated with upadacitinib experienced elevated hepatic aminotransferase levels. Other reported notable adverse effects in upadacitinib-treated patients during the treatment period included 1 death, 1 nonfatal stroke, and 2 venous thromboembolisms.

Still's Disease (Adult-Onset)

canakinumab (Ilaris)

Approval of canakinumab (Ilaris) for AOSD is based on pharmacokinetic data and extrapolation of clinical data of established efficacy in JIA patients.[702] In addition, a randomized, double-blind, placebo-controlled study of 36 AOSD patients ages 22 to 70 years found similar data when compared to pooled results in patients with JIA.

Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

tocilizumab (Actemra)

A phase 3, multinational, randomized, double-blind, placebo-controlled trial, focuSSced, assessed the efficacy and safety of tocilizumab for the treatment of SSC-ILD in 212 adults as defined by the 2013 ACR/EULAR classification criteria.[703,704] Enrolled patients were required to have diffuse cutaneous systemic sclerosis for ≤ 60 months and a modified Rodnan skin score (mRSS) of 10 to 35 at screening, elevated inflammatory markers or platelets, and active disease. Included patients were randomized 1:1 to SC tocilizumab 162 mg weekly or placebo for 48 weeks. Rescue treatment was allowed at 16 weeks in patients with a > 10% predicted forced vital capacity (FVC) decline or if there was worsening skin fibrosis at 24 weeks. Of those randomized, 65% of tocilizumab-treated patients and 64% of placebo-treated patients had SSc-ILD at baseline (confirmed by a visual read of high-resolution computed tomograph [HRCT] by blinded radiologists). The primary efficacy endpoint was the change from baseline in mRSS at week 48. The change from baseline in FVC at week 48 was a secondary endpoint. At week 48, no difference was found in mRSS (difference, -1.73; 95% CI, -3.78 to 0.32); however, statistical differences were found in tocilizumab-treated patients in FVC outcomes at 48 weeks and *post hoc* assessments were used to evaluate subgroups. Noted differences were primarily impacted by the subgroup with SSc-ILD at baseline. In this subgroup, the difference between the groups in change from baseline in mRSS at week 48 was -2.11 (95% CI, -4.89 to 0.67), which was not statistically significant, but statistically significant differences from placebo were found in this subgroup at week 48 in the percent predicted FVC (difference, 6.47; 95% CI, 3.43 to 9.5) and observed FVC (difference, 241; 95% CI, 124 to 358). FVC results (but not mRSS results) were supported with another phase 2/3 multicenter, randomized, double-blind, placebo-controlled trial. Due to the analytical methods and limited data, these results should be interpreted cautiously.

Ulcerative Colitis (UC)

adalimumab (Humira)

Study UC-I, was a randomized, double-blind, placebo-controlled study in 390 TNF antagonist naive adults with moderate to severe active UC (Mayo score 6 to 12 on a 12-point scale, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants including corticosteroids, azathioprine, or 6-mercaptopurine (6-MP).[705] Patients were randomized to 1 of 3 treatment groups, which included placebo or 1 of 2 different regimens of adalimumab. Concomitant stable doses of aminosalicylates and immunosuppressants, including corticosteroids, azathioprine, and 6-MP were permitted. The placebo group received doses at weeks 0, 2, 4, and 6. The first treatment group, (160/80), received adalimumab 160 mg adalimumab at week 0 and 80 mg at week 2, and the second treatment group, (80/40), received adalimumab 80 mg at week 0 and 40 mg at week 2. After week 2, patients in both treatment groups received 40 mg every other week. Induction of clinical remission was

defined as a Mayo score ≤ 2 with no individual subscores > 1) at week 8. A total of 18.5% of subjects receiving adalimumab 160/80 mg achieved a clinical remission at 8 weeks compared to 9.2% of subjects receiving placebo (treatment difference, 9.3%; 95% CI, 0.9 to 17.6; p<0.05 using a pairwise comparison of proportions). In the adalimumab 80/40 mg group and the placebo group at week 8, there was no statistically significant difference in clinical remission. Study UC-II, was a randomized, double-blind, placebo-controlled study in 518 TNF antagonist naive adult patients with moderate to severe active UC (Mayo score 6 to 12 on a 12 point scale, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP or who had lost response or were intolerant to TNF antagonists.[706] Forty percent of patients had previously used another TNF antagonist. Patients were randomized to either placebo or adalimumab. Concomitant stable doses of aminosalicylates and immunosuppressants, including corticosteroids, azathioprine, and 6-MP were permitted. Subjects received either placebo at weeks 0, 2, 4, and 6 or an initial dose of adalimumab 160 mg at week 0 and 80 mg at week 2. After week 2, patients received 40 mg every other week. Induction of clinical remission was defined as a Mayo score ≤ 2 with no individual subscores > 1 at week 8. Clinical remission at week 52 and sustained clinical remission (defined as clinical remission at both weeks 8 and 52) were evaluated. A total of 16.5% of subjects receiving adalimumab 160/80 mg achieved a clinical remission at 8 weeks compared to 9.3% of subject receiving placebo (treatment difference, 7.2%; 95% CI, 1.2 to 12.9). The rate of sustained clinical remission was 8.5% for adalimumab 160/80 mg and 4.1% for placebo for a treatment difference of 4.4% (95% CI, 0.1 to 8.6). Both the rate of induction of clinical remission at 8 weeks and the rate of sustained clinical remission for adalimumab 160/80 mg were statistically significant (p<0.05 using a pairwise comparison of proportions). Rates of clinical remission at week 52, were 17.3% for adalimumab compared to 8.5% for placebo (treatment difference, 8.8%; 95% CI, 2.8 to 14.5; p<0.05).The safety profile with adalimumab in patients with ulcerative colitis was reported as similar to the profile seen in patients with rheumatoid arthritis.

Efficacy and safety of adalimumab in pediatric patients with moderately to severe, active ulcerative colitis was based on data with adalimumab in adults and a multicenter, randomized, double-blind, 52-week trial (ENVISION, NCT02065557).[707,708] Patients 5 to 17 years of age (n=93) with a Mayo score of 6 to 12 and endoscopy subscore of 2 to 3 points and an inadequate response or intolerance to corticosteroids and/or an immunomodulator (e.g., azathioprine, 6-mercaptopurine, or methotrexate) were eligible for enrollment. A total of 16% of those enrolled had previously received a TNF antagonist. Initially, 77 patients were randomized 3:2 to receive 1 of 2 dosing regimens. All patients received 2.4 mg/kg of adalimumab (maximum of 160 mg) at week 0, 1.2 mg/kg (maximum of 80 mg) at week 2, and 0.6 mg/kg (maximum of 40 mg) at weeks 4 and 6. At week 1, those randomized to the higher dosage group were given an additional dose of 2.4 mg/kg (maximum of 160 mg). Following the initial randomization of these 77 patients into the double-blinded treatment regimens previously described, the protocol was amended to enroll another 16 patients in the higher arm dosage group without blinding. The coprimary endpoints were clinical remission per Partial Mayo Score (PMS; defined as PMS ≤ 2 and no individual subscore > 1) at week 8 and clinical remission per the Mayo Score (defined as Mayo Score ≤ 2 and no individual subscore > 1) at week 52 in those who reached clinical response per PMS at week 8. At week 8, 62 patients with a clinical response were randomized 1:1 to 0.6 mg/kg (maximum of 40 mg) every other week (lower dosage group) or 0.6 mg/kg (maximum of 40 mg) every week (higher dosage group), and an additional 12 patients with clinical response were randomized to placebo. Those who met criteria for disease flare ≥ week 12 were randomized to receive a reinduction dose of 2.4 mg/kg (maximum of 160 mg) or a dose of 0.6 mg/kg (maximum of 40 mg) with continuation of the dose to which they were randomized at week 8. The primary endpoint of week 8 PMS remission was reached in 60% of patients (28/47) in the higher dosage

group (excluding the 16 open-label higher dose patients) and 43% (13/30) of those in the lower dosage group. Study findings from the higher dose group are expected to be similar to results from the approved dosage. Week 52 data were evaluated in the 12 patients randomized to placebo following a clinical response at week 8 and those who received 0.6 mg/kg (maximum of 40 mg) every other week (lower dosage) or 0.6 mg/kg (maximum of 40 mg) every week (higher dosage) from week 8 to week 52. The placebo data were limited by small sample size, but at week 52, 33% of placebo-treated patients were in clinical remission, 33% had a clinical response, and 33% had endoscopic improvement. The primary endpoint, clinical remission evaluated at week 52, was observed in 29% of patients (9/31) in the low dose group compared with 45% (14/31) in the high dose group. Clinical response at week 52 was similar in the low dose (61%) and high dose (68%) groups, whereas the high dose group (52%) exhibited greater endoscopic improvement at week 52 compared to the low dose group (39%). A secondary endpoint evaluated clinical remission at week 52 in those who were remitters at week 8 and found 43% of patients (9/21) in the low dose group and 45% of patients (10/22) in the high dose group achieved remission. Although the low dose group evaluated a lower dosage than the recommended FDA-approved dose, clinically meaningful differences in efficacy are not expected between the higher dose group and the recommended FDA-approved adalimumab dosing in pediatric ulcerative colitis patients. Adverse events were comparable to those seen in adults.

golimumab (Simponi)

The phase 3 portion of the PURSUIT-SC trial was a randomized, double-blind, placebo-controlled, 6-week induction trial in 771 patients ≥ 18 years of age with moderately to severely active ulcerative colitis (Mayo score 6 to 12).[709] Subjects also had an endoscopy subscore of 2 or 3 on a 3-point scale, and were corticosteroid dependent, or had an inadequate response or failed to tolerate at least 1 of the following: aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine (6-MP). Subjects were randomized to the following SC treatments at week 0 and week 2: placebo at both time points, 200 mg followed by 100 mg, or 400 mg followed by 200 mg. The primary endpoint was the percent of responders at week 6, defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 (no blood seen) or 1 (streaks of blood with stool less than half the time). Stable doses of oral aminosalicylates, oral corticosteroids (less than 40 mg/day), azathioprine, 6-MP, and/or methotrexate were permitted. Patients who received TNF inhibitors previously were excluded. Fifty-two percent of patients receiving golimumab 200 mg/100 mg had a response at week 6 compared to 30% of patients on placebo for a treatment difference of 22% (95% CI, 14 to 30%; p<0.0001). There was no additional benefit in the 400 mg/200 mg group and the 100 mg 50 mg group did not show a response.

PURSUIT-M was a randomized, double-blind, placebo-controlled, 54-week maintenance trial in 463 patients ≥ 18 years of age with moderate to severely active ulcerative colitis who achieved a clinical response with golimumab induction at 6 weeks and who tolerated therapy.[710] Subjects were randomized to placebo, golimumab 50 mg or 100 mg SC every 4 weeks. Concomitant oral aminosalicylates, azathioprine, 6-MP, and/or methotrexate were permitted if doses were stable. Corticosteroid dosage was tapered at the start of treatment. The clinical response was assessed every 4 weeks and the primary endpoint was the percent of patients maintaining a clinical response through week 54. Fifty-one percent of patients receiving golimumab 100 mg (n=154) maintained a clinical response through week 54 as compared to 31% of placebo patients (n=156) for a treatment difference of 19% (95% CI, 8 to 30; p<0.001).

infliximab (Remicade)

The efficacy of infliximab for induction and maintenance therapy in adults with moderate to severe active ulcerative colitis was evaluated in 2 randomized, double-blind, placebo-controlled studies (ACT1 and ACT2).[711] Each study had 364 patients who received either placebo or infliximab 5 or 10 mg/kg of body weight IV at weeks 0, 2, and 6 and then every 8 weeks through week 46 (ACT1) or week 22 (ACT2). Patients were followed for 54 weeks in ACT1 and 30 weeks in ACT2. By week 8 in ACT1, clinical response (defined as a decrease in Mayo score of at least 3 points and decrease of 30% with a decrease in rectal bleeding measured by 2 scales) was seen in 69%, 61%, and 37% of patients receiving infliximab 5 mg, infliximab 10 mg, and placebo, respectively ($p<0.001$ for both comparisons to placebo). In ACT2, the clinical response rates were 64%, 69%, and 29% ($p<0.001$ for both comparisons to placebo). At week 30, patients receiving infliximab were more likely to have a clinical response ($p\leq0.002$ for all comparisons). At week 52 in ACT1, the clinical response rates were 45% and 44% for infliximab 5 and 10 mg, respectively, compared to 20% in the placebo group ($p<0.001$ for both comparisons).

The safety and effectiveness of infliximab in pediatric patients ages 6 and older with moderately to severely active UC to reduce the signs and symptoms and inducing and maintaining clinical remission were established in an open-label trial of 60 children.[712]

tofacitinib (Xeljanz)

Two replicate phase 3, randomized, double-blind, placebo-controlled trials assessed the efficacy of tofacitinib IR for induction in patients with moderately to severely active UC (OCTAVE Induction I, n=598; OCTAVE Induction II, n=541).[713,714] Patients who had failed ≥ 1 prior treatment with corticosteroids (oral or IV), other select conventional therapies (azathioprine or 6-MP), or a TNF antagonist and with a total Mayo score of 6 to 12, an endoscopy subscore ≥ 2, and a rectal bleeding subscore ≥ 1 were included. These patients were randomized 4:1 to either oral tofacitinib 10 mg twice daily or placebo for 8 weeks. Patients were able to continue stable doses of oral aminosalicylates and corticosteroids (prednisone ≤ 25 mg/day or equivalent). The primary endpoint in both trials was remission at 8 weeks, defined as a total Mayo score of ≤ 2, with no subscore > 1, and a rectal bleeding subscore of 0. In OCTAVE Induction I, 18.5% of the tofacitinib-treated patients achieved remission compared to 8.2% in the placebo group (treatment difference, 10.3%; 95% CI, 4.3 to 16.3; $p=0.007$). In OCTAVE Induction II, 16.6% of the tofacitinib-treated patients achieved remission compared to 3.6% in the placebo group (treatment difference, 13%; 95% CI, 8.1 to 17.9; $p<0.001$). Mucosal healing, defined as a Mayo endoscopic subscore ≤ 1 at 8 weeks, occurred in 31.3% of tofacitinib-treated patients compared to 15.6% of placebo-treated patients in OCTAVE Induction I (treatment difference, 15.7%; 95% CI, 8.1 to 23.4; $p<0.001$) and 28.4% of tofacitinib-treated patients compared to 11.6% of placebo-treated patients in OCTAVE Induction I (treatment difference, 16.8%; 95% CI, 9.5 to 24.1; $p<0.001$).

Patients who achieved clinical response to induction therapy in the OCTAVE Induction I and II trials were then randomized 1:1:1 in the OCTAVE Sustain trial, a phase 3, double-blind, placebo-controlled, maintenance therapy trial, to tofacitinib 5 mg or 10 mg twice daily or placebo for 52 week (n=593).[715,716] In OCTAVE Sustain, 34.3% of the tofacitinib-treated patients achieved remission at 52 weeks compared to 11.1% in the placebo group (treatment difference, 23.2%; 95% CI, 15.3 to 31.2; $p<0.001$). Mucosal healing at 52 weeks occurred in 37.4% of tofacitinib-treated patients compared to 13.1% of placebo-treated patients (treatment difference, 24.2%; 95% CI, 16 to 32.5; $p<0.001$).

Approval of extended-release tofacitinib (Xeljanz XR) was based on efficacy and safety data established with immediate-release tofacitinib.

upadacitinib (Rinvoq)

Two replicate multinational, randomized, double-blind, placebo-controlled trials, UC-1 (NCT02819635) and UC-2 (NCT03653026), assessed the effectiveness and safety of upadacitinib for the induction treatment of adults with UC (total n=988).[717] In both trials, adults with moderately to severely active UC (based on modified Mayo score [mMS] between 5 to 9 with an endoscopy score of 2 or 3) who had an inadequate response, loss of response, or intolerance to oral aminosalicylates, corticosteroids, immunosuppressants, and/or biologic therapy were randomized 2:1 to oral upadacitinib 45 mg once daily or placebo for 8 weeks. Patients were also able to continue stable doses of select conventional therapies, including corticosteroids (maximum of 30 mg/day prednisone equivalent; 38%) and oral aminosalicylates (68%). Notably, 51% had failed treatment to ≥ 1 biologic. The investigators defined initial response as a decrease of ≥ 1 point and ≥ 30% from baseline in partial mMS and a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore ≤ 1. The primary endpoint was clinical remission, defined as stool frequency ≤ 1 and not greater than baseline, rectal bleeding of 0, and endoscopy subscore of ≤ 1 without friability on the mMS at week 8. Clinical response, also based on mMS, was defined as a decrease ≥ 2 points and ≥ 30% from baseline mMS and a decrease in rectal bleeding ≥ 1 from baseline or an absolute rectal bleeding ≤ 1. At baseline, the median mMS was 7, and over one-third received corticosteroids and approximately two-thirds received aminosalicylates in both trials. After 8 weeks, a greater proportion of patients treated with upadacitinib achieved endoscopic remission compared to placebo (UC-1: 14% versus 1%, respectively; UC-2: 18% versus 2%, respectively). Also at 8 weeks, a greater proportion of patients treated with upadacitinib achieved clinical remission, the primary endpoint, compared to placebo (UC-1: 26% versus 5%, respectively [treatment difference; 22%; 95% CI, 16 to 27], p<0.001; UC-2: 33% versus 4%, respectively [treatment difference; 29%; 95% CI, 23 to 35], p<0.001). Clinical response occurred in 73% of upadacitinib-treated patients compared to 27% of those treated with placebo (treatment difference, 46%; 95% CI, 38 to 54; p<0.001) in UC-1 and 74% of upadacitinib-treated patients compared to 25% of those treated with placebo (treatment difference, 49%; 95% CI, 42 to 57; p<0.001) in UC-2. Significant differences were also seen in endoscopic improvement and histologic endoscopic mucosal improvement.

A multinational, randomized, double-blind, placebo-controlled trial, UC-3 (NCT02819635), assessed the effectiveness and safety of upadacitinib for the maintenance treatment of adults with UC (n=451).[718] Eligible patients were those who had received the 45 mg induction dose in prior clinical trials for induction who had achieved clinical response. These individuals were re-randomized to oral upadacitinib 15 mg or 30 mg once daily or to placebo for up to 52 weeks. The primary endpoint for was clinical remission, defined based on mMS scores and corticosteroid-free period, at week 52. Secondary endpoints included corticosteroid-free clinical remission, endoscopic improvement, and histologic endoscopic mucosal improvement. The primary endpoint was achieved by 12%, 42%, and 52% of those treated with placebo, upadacitinib 15 mg, and upadacitinib 30 mg, respectively (treatment difference 15 mg versus placebo, 31% [95% CI, 22 to 40]; treatment difference 30 mg versus placebo, 39% [95% CI, 30 to 48]; p<0.001 for both). A greater percentage of patients also achieved each of the secondary endpoints in each active treatment group compared to placebo.

ustekinumab (Stelara)

UNIFI: Two randomized, double-blind, placebo-controlled studies established the efficacy of ustekinumab for the treatment of moderate to severe active UC who had an inadequate response to or failure or intolerance of ≥ 1 biologic (e.g., TNF antagonist, vedolizumab), corticosteroids, or a thiopurine (e.g., azathioprine or mercaptopurine).[719,720] The first study consisted of an 8-week IV induction study in 961

patients followed by a 44-week SC maintenance study that was a treatment-withdrawal design. Included patients had a Mayo score of 6 to 12 and a Mayo endoscopy subscore ≥ 2. Patients were eligible to receive select other UC treatments, including aminosalicylates, azathioprine, mercaptopurine, methotrexate, and oral corticosteroids. In the induction study, patients were randomized 1:1:1 to placebo or ustekinumab 6 mg/kg or 130 mg. The primary endpoint was clinical remission at week 8. At baseline, 51% had failed ≥ 1 biologic, and 52% patients were receiving oral corticosteroids, 28% patients were receiving azathioprine, mercaptopurine, or methotrexate, and 69% patients were receiving aminosalicylates. At 8 weeks, 15.5% of those treated with 6 mg/kg of ustekinumab compared to 5.3% of those treated with placebo achieved clinical remission (treatment difference, 12.2%; p<0.001), which was defined as Mayo stool frequency and endoscopy subscores of 0 or 1 and a Mayo rectal bleeding subscore of 0. Endoscopic improvement (Mayo endoscopy subscore of 0 or 1) occurred in 27% of those treated with ustekinumab 6 mg/kg compared to 13.8% of those treated with placebo (treatment difference, 13.2%; p<0.001). Clinical response (≥ 2 points and ≥ 30% decrease in mMS [3-component Mayo score without the PGA]) occurred in 61.8% of those treated with ustekinumab 6 mg/kg compared to 31.3% of those treated with placebo (treatment difference, 30.5%; p<0.001). In addition, combined histologic-endoscopic mucosal improvement occurred in 18.4% of those treated with ustekinumab 6 mg/kg compared to 8.9% of those treated with placebo (treatment difference, 9.5%; p<0.001). An extension study through 2 years of maintenance therapy found sustained improvement and no new safety signals.[721]

In the second study, 523 patients who achieved clinical response during the induction study were randomized 1:1:1 to receive SC ustekinumab 90 mg every 8 or 12 weeks or placebo.[722,723] The primary endpoint assessed was the proportion of patients with clinical remission (as defined in the previous study) after 44 weeks in the treatment phase. At 44 weeks, 43.8% of those treated with ustekinumab 90 mg SC every 8 weeks achieved clinical remission compared to 24% treated with placebo (treatment difference, 19.8%; p<0.001), and 71% of those treated with ustekinumab 90 mg SC every 8 weeks had maintained clinical response at week 44 compared to 44.6% treated with placebo (treatment difference, 26.4%; p<0.001). Endoscopic improvement occurred in 51.1% of those treated with ustekinumab every 8 weeks compared to 28.6% of those treated with placebo (treatment difference, 22.5%; p<0.001). Corticosteroid-free clinical remission occurred in 42% of those treated with ustekinumab every 8 weeks compared to 23.4% of those treated with placebo (treatment difference, 18.6%; p<0.001). In addition, maintenance of clinical remission at week 44 in patients who achieved clinical remission 8 weeks following induction occurred in 58% of those treated with ustekinumab every 8 weeks compared to 38% of those treated with placebo (treatment difference, 20%; p<0.001).

vedolizumab (Entyvio)

Two randomized, double-blind, placebo-controlled trials (UC Trials I and II) were conducted to evaluate the safety and efficacy of vedolizumab in adult patients with moderately to severely active UC.[724] Severely active UC was defined in both trials as a Mayo score of 6 to 12 with endoscopy subscore of 2 or 3. Enrolled patients in the US had over the previous 5-year period an inadequate response or intolerance to immunomodulator therapy (e.g., thiopurines [azathioprine or mercaptopurine]) and/or an inadequate response, loss of response, or intolerance to a TNF antagonist. Outside the US, prior treatment with corticosteroids was sufficient for entry if over the previous 5-year period the patients were corticosteroid dependent or had an inadequate response or intolerance to corticosteroids. Patients that had ever received natalizumab and patients that had received a TNF antagonist in the past 60 days were excluded from enrollment.

In UC Trial I, patients (n=374) were randomized in a double-blind fashion (3:2) to receive vedolizumab 300 mg or placebo by IV infusion at week 0 and week 2. Concomitant stable dosages of aminosalicylates, corticosteroids, and immunomodulators were permitted through week 6 and efficacy assessments were conducted at week 6. A total of 39% of patients had an inadequate response, loss of response, or intolerance to TNF antagonist therapy and 18% only had an inadequate response, inability to taper or intolerance to prior corticosteroid treatment. The median baseline Mayo score was 9 in the vedolizumab group and 8 in the placebo group. In UC Trial I, a greater percentage of patients treated with vedolizumab compared to patients treated with placebo (47% versus 26%, p<0.001) achieved clinical response at week 6. A greater percentage of patients treated with vedolizumab compared to patients treated with placebo (17% versus 5%, p=0.001) also achieved clinical remission and improvement of endoscopic appearance of the mucosa (25% versus 41%, p=0.001) at week 6.

In UC Trial II, 373 patients who had a clinical response to vedolizumab at week 6 were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at week 6: vedolizumab 300 mg every 8 weeks, vedolizumab 300 mg every 4 weeks, or placebo every 4 weeks. Concomitant aminosalicylates and corticosteroids were permitted through week 52 and efficacy assessments occurred at week 52. Concomitant immunomodulators were permitted outside the US but were not permitted beyond week 6 in the US. At week 6, patients were receiving corticosteroids (61%), immunomodulators (32%) and aminosalicylates (75%). A total of 32% of patients had an inadequate response, loss of response or intolerance to a TNF antagonist therapy. At week 6, the median Mayo score was 8 in all 3 groups. Patients who had achieved clinical response at week 6 and were receiving corticosteroids were required to begin a corticosteroid tapering regimen at week 6. In the trial, a greater percentage of patients in groups treated with vedolizumab as compared to placebo (42% versus 16%, p<0.001) achieved clinical remission at week 52 and maintained clinical response (57% versus 24 %, p <0.001). In addition, a greater percentage of patients in groups treated with vedolizumab as compared to placebo were in clinical remission at both weeks 6 and 52 (21% versus 9%, p <0.001), and had improvement of endoscopic appearance of the mucosa at week 52 (52% versus 20%, p<0.001). The vedolizumab every 4-week dosing regimen did not demonstrate additional clinical benefit over the every-8-week dosing regimen and is not the recommended dosing regimen.

vedolizumab (Entyvio) versus adalimumab (Humira)

VARSITY, a multinational, phase 3b, double-blind, double-dummy, randomized trial, compared the efficacy of vedolizumab with adalimumab in adults with moderately to severely active ulcerative colitis (n=769).[725] Notably, included patients were not allowed to have been previously treated with adalimumab, but 25% of those included had received prior treatment with another TNF antagonist. Included patients were randomized to either vedolizumab 300 mg as an infusion on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 or SC adalimumab 160 mg at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter until week 50. The primary outcome was clinical remission at week 52, which was defined as a total Mayo scale score of ≤ 2 and no individual subscore exceeding 1 on any of the components. This was achieved in 31.3% of those treated with vedolizumab compared to 22.5% of those treated with adalimumab (difference, 8.8%; 95% CI, 2.5 to 15; p=0.006). Endoscopic improvement was also higher in those treated with vedolizumab compared to adalimumab (39.7% versus 27.7%, respectively; difference, 11.9% [95% CI, 5.3 to 18.5; p<0.001]). Notably, however, corticosteroid-free remission occurred in 12.6% of those treated with vedolizumab compared to 21.8% of those treated with adalimumab (difference, -9.3%; 95% CI, -18.9 to 0.4), although this did not reach statistical significance.

Uveitis

adalimumab (Humira)

The efficacy of adalimumab for the treatment of non-infectious intermediate, posterior, and panuveitis in adults was established in 2 double-masked, placebo-controlled, randomized clinical trials (VISUAL I, n=217; VISUAL II, n=226). In each trial, patients were randomized 1:1 to either placebo or adalimumab SC 80 mg for 1 dose then 40 mg every other week beginning 1 week following the initial dose. VISUAL I included patients with active uveitis treated with oral prednisone 10 to 60 mg/day and underwent a steroid tapering schedule (discontinued by week 15).[726,727,728] VISUAL II included patients with inactive uveitis treated with oral corticosteroids 10 to 35 mg/day who also underwent a steroid tapering schedule (discontinued by week 19). Patients with anterior uveitis were excluded in both trials. In both studies, the primary endpoint was time to treatment failure, defined as the development of inflammatory chorioretinal and/or vascular lesions, increased anterior chamber (AC) cell grade or vitreous haze (VH) grade, or a decrease in best corrected visual acuity (BCVA). In VISUAL I, treatment with adalimumab resulted in a lower percentage of patient treatment failures (78.5% versus 54.5% for placebo and adalimumab, respectively; HR, 0.5; 95% CI, 0.36 to 0.7; p<0.001). The median time to failure was 3 months (95% CI, 2.7 to 3.7) with placebo compared to 5.6 months (95% CI, 3.9 to 9.2) with adalimumab. In VISUAL II, treatment with adalimumab also resulted in a lower percentage of patient treatment failures (55% versus 39.1% for placebo and adalimumab, respectively). The median time to failure was 8.3 months (95% CI, 4.8 to 12) with placebo and was not estimable (> 18 months) with adalimumab due to limited failure events (HR, 0.57; 95% CI, 0.39 to 0.84; p=0.004). VISUAL III, a long-term, open-label extension study of those who had completed VISUAL I and II, demonstrated maintenance of quiescence.[729]

The efficacy of adalimumab for the treatment of non-infectious intermediate, posterior, and panuveitis in adults was established in a randomized, double-masked, placebo-controlled study that included 90 pediatric patients (ages 2 to < 18 years) with active JIA-associated non-infectious uveitis.[730] Patients were randomized to either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) every other week in combination with a dose of methotrexate. Use of corticosteroids was permitted at study entry but was followed by a mandatory reduction in topical corticosteroids within 3 months. The primary endpoint was time to treatment failure, defined as worsening or sustained non-improvement in ocular inflammation or worsening of ocular co-morbidities, and was found to be 24.1 weeks (95% CI, 12.4 to 81) in those treated with placebo and was not estimable in those treated with adalimumab as fewer than half had an event. Failure occurred less often in those treated with adalimumab versus placebo (26.7% versus 60%, respectively; HR, 0.25 [9% CI, 0.12 to 0.49]).

META-ANALYSES

Ankylosing Spondylitis (AS)

Several meta-analyses have assessed the role of TNF antagonists in the treatment of AS. A meta-analysis of 18 randomized controlled trials involving anti-TNF agents (4 adalimumab versus placebo, 8 etanercept versus placebo, 2 golimumab versus placebo, 3 infliximab versus placebo, and 1 etanercept versus infliximab) for the treatment of AS.[731] Most included trials allowed for the use of concomitant stable traditional DMARDs, NSAIDs, or corticosteroids. The anti-TNF agents were more likely than placebo to achieve an ASAS40 response before 6 months (adalimumab: risk ratio [RR], 3.53 [95% credible interval (CrI), 2.49 to 4.91]; etanercept: RR 3.31 [95% CrI, 2.38 to 4.53]; golimumab: RR 2.9 [95% CrI, 1.9 to 4.23]; and infliximab: RR 4.07 [95% CrI, 2.8 to 5.74]). The number needed to treat (NNT) ranged from 3 to 11 to

achieve an ASAS partial. Withdrawals due to adverse events in the anti-TNF group were higher than with placebo, but the absolute increase in harm was small. Trials were of a short duration (24 weeks or less) and most were funded by the manufacturer of the product.

A second meta-analysis on the use of anti-TNF agents also included patients with axial spondyloarthritis (20 double-blind, randomized controlled trials: 15 AS, 4 axial spondyloarthritis, and 1 with both).[732] In AS patients, anti-TNF agents showed better efficacy than placebo for BASDAI (effect size, 1; 95% CI, 0.87 to 1.13), BASFI (effect size, 0.67; 95% CI, 0.58 to 0.76) and ASAS40 response (OR, 4.7; 95% CI, 3.8 to 6). A similar network meta-analysis of 25 trials (n=2,989), which also included non-US clinical trials, evaluated the 5 TNF antagonists (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab).[733] All were found to be superior to placebo in various ASAS measures, but few differences were found between agents in indirect comparisons. Certolizumab pegol appeared to have a more favorable adverse effect profile (OR, 0.22; 95% CI, 0.05 to 0.93). Etanercept achieved the best ASAS20 response, infliximab achieved the best ASAS40 and ASAS-partial response, and adalimumab achieved the highest ASAS5/6 response. However, consistent superiority was not found among any agent.

A more recent network meta-analysis of 14 randomized controlled trials (n=2,672) compared the efficacy of biologic regimens in the treatment of AS based on week 12 or 14 ASAS20 improvement.[734] Most trials were compared to placebo, and the meta-analysis included non-US clinical trials. Biologics included in the meta-analysis were adalimumab, etanercept, infliximab, golimumab, secukinumab, and tocilizumab. The authors found no overall differences in efficacy for AS, but noted infliximab was superior to tocilizumab (OR, 4.81; 95% CrI, 1.43 to 17.4), although tocilizumab is not indicated for AS. However, the relatively small number and size of studies may limit these results. Another indirect comparison meta-analysis also found no significant difference in achievement of ASAS20.[735]

Atopic Dermatitis

A systematic review and meta-analysis that searched studies from the Cochrane Central Register of Controlled Trials and other sources through June 15, 2021.[736] A total of 60 trials (n=16,579) were identified that were of ≥ 8 weeks in duration for the treatment of adults with moderate to severe atopic dermatitis. Abrocitinib 200 mg (mean difference [MD], 2.2; 95% CrI, 0.2 to 4) and upadacitinib 30 mg daily (MD, 2.7; 95% CrI, 0.6 to 4.7) were associated with slightly better improvements in EASI scores compared to dupilumab (600 mg then 300 mg every 2 weeks). Upadacitinib 15 mg daily produced similar EASI scores to dupilumab. Abrocitinib 100 mg daily (MD, −2.1; 95% CrI, −4.1 to −0.3), baricitinib 4 mg (MD, −3.2; 95% CrI, −5.7 to −0.8), baricitinib 2 mg daily (MD, −5.2; 95% CrI, −7.5 to −2.9), and tralokinumab 600 mg then 300 mg every 2 weeks (MD, −3.5; 95% CrI, −5.8 to −1.3) reduced EASI scores slightly less that dupilumab. Tralokinumab (Adbry), an IL-13 antagonist, is not included in this class review.

Crohn's Disease (CD) and Ulcerative Colitis (UC)

A systematic review evaluated infliximab (Remicade), adalimumab (Humira), and certolizumab (Cimzia) in the maintenance of remission in Crohn's disease.[737] Literature from 1966 to 2007 was reviewed and nine studies met inclusion criteria. Studies considered included randomized controlled trials involving patients > 18 years with Crohn's disease who had a clinical response or clinical remission with a TNF-blocking agent, or patients with Crohn's disease in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF-blocking agent or placebo. Infliximab maintains clinical remission, maintains clinical response, has corticosteroid-sparing effects, and maintains fistula healing in patients with Crohn's disease having a response to infliximab induction therapy. There

were no significant differences in remission rates between infliximab doses of 5 mg/kg or 10 mg/kg. Adalimumab maintains clinical remission, maintains clinical response, and has corticosteroid-sparing effects in patients with Crohn's disease who have responded or entered remission with adalimumab induction therapy. There were no significant differences in remission rates between adalimumab 40 mg weekly and adalimumab every other week. There is evidence from one randomized controlled trial that certolizumab maintains clinical remission and maintains clinical response in patients who have responded to certolizumab induction therapy.

Another meta-analysis included 14 trials with 3,995 patients with Crohn's disease who were treated with infliximab, adalimumab, or certolizumab.[738] The primary endpoints were clinical remission for luminal Crohn's disease and fistula closure at ≥ 2 consecutive visits. In overall analysis, TNF antagonists were effective for induction of remission at week 4 (mean difference, 11%; 95% CI, 6 to 16; p<0.001) and maintenance of remission at weeks 20 to 30 in patients who responded to induction therapy and in patients randomized before induction (mean difference, 23%; 95% CI, 18 to 28; and mean difference, 8%; 95% CI, 3 to 12%, respectively; p<0.001 for all comparisons). In the 10 studies evaluating TNF antagonists for fistulizing Crohn's disease (n=776 patients), TNF antagonists were effective for fistula closure only in maintenance trials following open-label induction (mean difference, 16%; 95% CI, 8 to 25%; p<0.001). In the 21 studies evaluated for safety, TNF antagonists did not increase the risk of death, malignancy, or serious infection.

A network meta-analysis evaluated the efficacy and safety of biologic therapies for the treatment of moderate to severe Crohn's disease (31 randomized controlled studies).[739] Using data from 15 studies, the following agents were associated with a higher odds of inducing remission in in biologic-naïve patients compared to certolizumab pegol: infliximab (OR, 4.53; 95% CI, 1.49 to 13.79), infliximab combined with azathioprine (OR, 7.49; 95% CI, 2.04 to 27.49), adalimumab (OR, 3.01; 95% CI, 1.25 to 7.27), and ustekinumab (OR, 2.63; 95% CI, 1.1 to 6.28). Compared to vedolizumab, infliximab combined with azathioprine was also associated with significantly higher odds of inducing remission (OR, 3.76; 95% CI, 1.01 to 14.03). Using data from 10 studies of patients with prior biologic exposure, adalimumab following loss of response to infliximab (OR, 2.82; 95% CI, 1.2 to 6.62) and risankizumab (OR, 2.1; 95% CI, 1.12 to 3.92) were associated with higher odds of inducing remission than vedolizumab.

A systematic review with meta-analysis compared the efficacy of biologics (e.g., infliximab, adalimumab, certolizumab, golimumab, natalizumab, vedolizumab) for induction and maintenance of mucosal healing in patients with either Crohn's disease (CD) or ulcerative colitis (UC).[740] Twelve randomized controlled trials were included: 2 and 8 examining induction for CD and UC, respectively, and 4 and 5 examining maintenance therapy for CD and UC, respectively. Biologics were found to be superior to placebo for both induction and maintenance. A network meta-analysis was not possible for induction trials in CD due to limited data. Notable statistically significant differences between agents in the network meta-analysis revealed that adalimumab therapy was inferior to infliximab (OR, 0.45; 95% CrI, 0.25 to 0.82) and combination infliximab-azathioprine (OR, 0.32; 95% CrI, 0.12 to 0.84) for inducing mucosal healing in UC (but not for CD). No statistically significant pairwise differences were found between vedolizumab and anti-TNF agents in UC.

A systematic review found that infliximab, based on literature available through 2005, was effective in inducing clinical remission and response in patients with moderate to severe ulcerative colitis with refractory disease.[741] The need for colectomy was reduced in short-term trials with infliximab.

A systematic review and network meta-analysis on the first-line treatment of moderate to severe ulcerative colitis assessed the efficacy and safety of both small molecule (tofacitinib and ozanimod) and biologic agents (infliximab, adalimumab, golimumab, vedolizumab, and etrolizumab [not available in US]).[742] The authors assessed clinical remission, clinical response, mucosal healing, and sustained remission. For induction, most agents were more effective than placebo at induction of a clinical response, with infliximab identified as the best drug for induction of clinical response (5 mg/kg: OR, 4.15 [95% CI, 2.96 to 5.84]). Other agents were identified as having similar efficacy, excluding etrolizumab, which was not statistically superior to placebo. For clinical remission at 6 to 8 weeks, most agents (excluding etrolizumab and ozanimod) were more effective than placebo (OR range: 1.9 to 4.6) with infliximab again being ranked best and with statistical superiority over adalimumab (OR, 2.35; 95% CI, 1.35 to 4.14). For the maintenance of clinical remission at 48 to 52 weeks, all treatments were superior to placebo, with vedolizumab (OR, 3.84; 95% CI, 2.13 to 7.15) and tofacitinib (OR, 5.51; 95% CI, 3.31 to 9.56) ranked highest and tofacitinib superior to adalimumab and golimumab. All options were better than placebo in inducing and maintaining mucosal healing, with infliximab, tofacitinib, and vedolizumab with the highest success. Sustained clinical remission (remission or response at both induction and maintenance) was superior to placebo for all agents, with the exception of golimumab. Tofacitinib also had the best success in sustained clinical remission, with superiority over adalimumab and golimumab. All treatments were found to have a similar rate of serious adverse effects; however, golimumab, tofacitinib, and vedolizumab had the statistically highest rates compared to placebo of infections, while adalimumab and infliximab showed no difference in infection rate compared to placebo.

A systematic review and network meta-analysis that searched data from January 1, 1990 to July 1, 2021 included 29 studies evaluating biologics and small molecule drugs for the treatment of moderate to severe UC, of which 23 studies assessed induction therapy.[743] The analysis reported that upadacitinib demonstrated significantly greater benefit compared to all other interventions for the induction of clinical remission (infliximab [OR, 2.7; 95% CI, 1.18 to 6.2], adalimumab [OR, 4.64; 95% CI, 2.47 to 8.71], golimumab [OR, 3; 95% CI, 1.32 to 6.82], vedolizumab [OR, 3.56; 95% CI, 1.84 to 6.91], ustekinumab [OR, 2.92; 95% CI, 1.31 to 6.51], etrolizumab [OR, 4.91; 95% CI, 2.59 to 9.31], tofacitinib [OR, 2.84; 95% CI, 1.28 to 6.31], filgotinib 100 mg [OR, 6.15; 95% CI, 2.98 to 12.72], filgotinib 200 mg [OR, 4.49; 95% CI, 2.18 to 9.24], and ozanimod (OR, 2.7; 95% CI, 1.18 to 6.2). No differences were seen between the agents regarding adverse events and serious adverse events. Vedolizumab ranked lowest for both adverse events (surface under the cumulative ranking [SUCRA], 0.184) and serious adverse events (SUCRA, 0.139), upadacitinib ranked highest for adverse events (SUCRA, 0.843), and ozanimod ranked highest for serious adverse events (SUCRA, 0.831). Etrolizumab and filgotinib are not available in the US.

Juvenile Idiopathic Arthritis

A small (5 studies; n=286) network meta-analysis of agents (anakinra, canakinumab, rilonacept, and tocilizumab) for sJIA found that canakinumab appeared to be the most effective for the treatment of sJIA in achieving ACR30 in a pediatric population (OR, 55.04; 95% CrI 15.52 to 253.29).[744] Efficacy (greatest to least) was then followed by anakinra, tocilizumab, rilonacept, and then placebo; however, the results should be interpreted with extreme caution due to the very limited data and overlapping credible intervals.

Plaque Psoriasis

A systematic review evaluated the efficacy and safety of biologic agents in the treatment of plaque psoriasis.[745] Randomized, controlled, double-blind, monotherapy trials of alefacept (n=3), efalizumab

(n=5), etanercept (n=4) and infliximab (n=4) with a total of 7,931 patients met inclusion criteria. Efficacy was measured by PASI 75 achievement after 10 to 14 weeks of treatment, using intention-to-treat analysis. All biological agents for psoriasis were efficacious (p<0.001); however, there was a graded response for achievement of PASI 75: infliximab (pooled relative risk [RR], 17.4; NNT=2), etanercept (RR, 11.73; NNT=3), and alefacept (RR, 0.7; NNT=8). The risk of 1 or more adverse events was evaluated by RR and number needed to harm (NNH). This was increased in the alefacept (RR, 1.09; p=0.03; NNH=15) and infliximab (RR, 1.18; p<0.001; NNH=9) groups compared with placebo. Alefacept and efalizumab are not available currently in the US.

Another systematic review evaluated 24 clinical trials with 9,384 patients with moderate to severe psoriasis.[746] Sixteen double-blind trials were included. Based on PASI 75 at weeks 8 to 16 in the trials, infliximab was significantly superior to all other interventions (risk difference [RD], 77%; 95% CI, 72 to 81). Adalimumab (RD, 64%; 95% CI, 61 to 68) was superior to cyclosporine (RD, 33%; 95% CI, 13 to 52), etanercept 50 mg twice weekly (RD, 44%; 95% CI, 40 to 48) and etanercept 25 mg twice weekly (RD, 30%; 95% CI, 25 to 35).

A systematic literature review and meta-analysis compared the efficacy of psoriasis treatments.[747] Randomized controlled trials evaluating PASI were identified and evaluated for quality. PASI responses were modeled using a mixed-treatment comparison, which enabled the estimation of the relative effectiveness of several treatments. A total of 22 trials were included. TNF inhibitors were most likely to achieve PASI 75, with a mean relative risk (RR) of 15.57 (95% CI, 12.46 to 19.25) versus mean RRs of 9.24 (95% CI, 5.33 to 13.91) for systemic and 5.65 (95% CI, 3.74 to 7.97) for T cell therapies. Infliximab (81%) and adalimumab (71%) had greater probabilities of achieving PASI 75 than etanercept (50%), although dosage was an important determinant of outcome.

A more recent systematic review and meta-analysis of 38 randomized, double-blind, placebo-controlled trials assessed the efficacy of immunobiologic and small molecule inhibitor drugs for psoriasis as measured by PASI 75.[748] Overall, these agents were found to be superior to placebo (risk difference, 0.59; 95% CI, 0.58 to 0.6).

A Cochrane review and meta-analysis assessed the role of 20 systemic pharmacologic treatments for chronic plaque psoriasis in patients with moderate to severe disease (158 studies; n=57,831).[749] All interventions were superior to placebo in achieving PASI 90. In general, the biologic DMARDs were superior to small molecule and traditional DMARDs in reaching PASI 90, specifically brodalumab, guselkumab, infliximab, ixekizumab, risankizumab, and secukinumab were significantly more effective in reaching PASI 90 than adalimumab, certolizumab pegol, etanercept, and ustekinumab. In addition, adalimumab and ustekinumab were more effective than etanercept, ustekinumab was more effective than certolizumab pegol, and adalimumab and ustekinumab had similar efficacy. No significant difference was found between apremilast and tofacitinib. Compared to placebo of those with the greatest benefit, the clinical effectiveness (defined as risk ratio [RR] in PASI 90) were infliximab RR 50.29 (95% CI, 20.96 to 120.67), ixekizumab RR 32.48 (95% CI, 27.13 to 38.87), and risankizumab RR 28.76 (95% CI, 23.96 to 34.54), secukinumab RR 25.79 (95% CI, 21.61 to 30.78), guselkumab RR 25.52 (95% CI, 21.25 to 30.64), and brodalumab RR 23.55 (95% CI, 19.48 to 28.48). In general, no statistical differences were seen in treatment-emergent adverse effects.

Another systematic review and network meta-analysis of biologics for psoriasis determined that all included biologics (adalimumab, etanercept, infliximab, secukinumab, ustekinumab, and ixekizumab) were superior to placebo or methotrexate at 12 to 16 weeks (41 randomized controlled trials,

n=20,561).[750] Notable differences among agents included poorer tolerability, despite high efficacy, of ixekizumab and infliximab and that adalimumab, secukinumab, and ustekinumab were comparable in efficacy and safety based on limited data. Long-term data were limited for evaluation.

Another systemic review and meta-analysis analyzed the efficacy and safety of IL-12/23, IL-17, and selective IL-23 inhibitors in moderate to severe plaque psoriasis (24 randomized, controlled trials) versus placebo.[751] The risk ratio versus placebo of achieving PASI 75 and PASI 90 were similar between agents, with overlapping confidence intervals. Safety was also similar, but the authors found a slightly increased risk of withdrawal due to toxicity with ixekizumab compared to placebo. A similar network meta-analysis of IL-12/23, IL-17, and IL-23 inhibitors included brodalumab, guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab for the treatment of in moderate to severe plaque psoriasis (28 studies; n=19,840).[752] All interventions were superior to placebo in PASI 75, PASI 100, and sPGA 0/1, IGA 0/1, or PGA 0/1. Notably, the effect size of PASI 75 was strongest with ixekizumab 80 mg every 2 weeks (RR, 18.64; 95% CI, 13.46 to 25.8) and secukinumab 300 mg (RR, 18.17; 95% CI, 12.79 to 25.81), the effect size of PASI 100 was strongest with ixekizumab 80 mg every 2 weeks (RR, 81.67; 95% CI, 27.65 to 241.26) and brodalumab 210 mg (RR, 75.5; 95% CI, 38.76 to 147.04), and the effect sizes of sPGA 0/1, IGA 0/1, or PGA 0/1 were highest with secukinumab 300 mg (RR, 26.51; 95% CI, 16.51 to 42.54) and secukinumab 150 mg (RR, 21.05; 95% CI, 13.1 to 33.85). Another similar network meta-analysis of all biologics using phase 3 data assessing PASI response at 12 to 16 weeks of treatment found a greater clinical benefit with ixekizumab and brodalumab compared to secukinumab, followed by secukinumab, guselkumab, infliximab, adalimumab, ustekinumab, and etanercept.[753] Like all network meta-analyses, these results should be interpreted cautiously.

Psoriatic Arthritis (PsA)

A meta-analysis evaluated the efficacy and safety of TNF antagonists in the management of PsA.[754] Six randomized controlled trials with 982 patients investigated adalimumab, etanercept, and infliximab. All 3 TNF antagonists were significantly more effective than placebo on Psoriatic Arthritis Response Criteria (PsARC) and ACR20, ACR50, and ACR70 ratings. There were no significant differences between TNF-alpha inhibitors and placebo in the proportions of patients experiencing withdrawal for any reason (RR, 0.48; 95% CI, 0.2 to 1.18), or withdrawal due to adverse events (RR, 2.14; 95% CI, 0.73 to 6.27), serious adverse events (RR, 0.98; 95% CI, 0.55 to 1.77), or upper respiratory tract infections (RR, 0.91; 95% CI, 0.65 to 1.28). Pooled injection site reactions were significantly higher for adalimumab and etanercept than for placebo (RR, 2.48; 95% CI, 1.16 to 5.29), but there was no significant difference in the proportion of patients experiencing infusion reactions with infliximab (RR, 1.03; 95% CI, 0.48 to 2.2) compared against placebo.

Another meta-analysis of 5 randomized controlled trials of 4 non-TNF antagonist biologics and small molecules (abatacept, secukinumab, ustekinumab, and apremilast) found no difference in efficacy to achieve ACR20 between agents using an indirect comparison methodology (n=625; range p-values, 0.14 to 0.98).[755] Notably, this sample size is small and the methodology limits the application of these results.

A network meta-analysis assessed the comparative efficacy, safety and tolerability of IL-6, IL-12/23 and IL-17 inhibitors for patients with active PsA (6 trials; n=2,411).[756] The results demonstrated a similar efficacy over placebo of the agents. The most notable safety findings were that ixekizumab had a higher rate of adverse effects, while ustekinumab appeared to have higher tolerability when compared to placebo. Regarding efficacy, secukinumab appeared to have the highest efficacy, and may offer an

optimal balance of safety and efficacy; however, the style of study and the limited included data significantly warrant caution in the result interpretation.

A network meta-analysis assessed the comparative efficacy and safety or biologics and small molecules for the treatment of PsA (30 studies; n=10,191).[757] Regarding notable differences found, etanercept and infliximab were reported to be more effective than golimumab in ACR20 (OR, 3.33 [95% CI, 1.17 to 9.48; and 1.24 [95% CI, 0.61 to 2.52], respectively). Infliximab was also superior to certolizumab pegol in PASI 75 response (OR, 10.08; 95% CI, 1.54 to 75.48). When considering safety and efficacy, etanercept, infliximab, and golimumab were found to be the best choice. Like all network meta-analyses, results should be interpreted cautiously.

Rheumatoid Arthritis (RA)

A meta-analysis of 13 clinical trials with etanercept (Enbrel), adalimumab (Humira), infliximab (Remicade), or anakinra (Kineret) were included in a systematic review of the literature in the management of RA.[758] Efficacy was based on ACR20 or ACR50 response after 6 months of therapy. In all trials, active treatment was efficacious in comparison to placebo or methotrexate. For each treatment, the inclusion of methotrexate in combination improved the response. After adjustment for study-level variables, the authors found TNF antagonists to be more efficacious compared with anakinra ($p<0.05$). Indirect comparisons between the 3 TNF antagonists indicated no difference in efficacy. Author findings included treatment with anakinra is better than placebo; for each treatment, the use of combination methotrexate improves the probability of response; treatment with any of the TNF antagonists is better than with anakinra; and all drugs in the TNF antagonist class are no different from each other. Findings from another systematic review from 2006 were similar.[759]

A systematic review analyzed the efficacy and safety of anti-TNF drugs (infliximab, etanercept, and adalimumab) for treating RA.[760] A total of 13 articles with 7,087 patients met inclusion criteria. All studies were at least 6 months in duration and evaluated response to treatment using ACR20, ACR50, and ACR70. The combined relative risk to achieve a therapeutic response to treatment with recommended doses of any TNF antagonist was 1.81 (95% CI, 1.43 to 2.29) with a number-needed-to-treat (NNT) of 5 for ACR20, 5 for ACR50, and 7 for ACR70. Overall therapeutic effects were also similar regardless of the specific TNF antagonist used, as well as when higher-than-recommended doses were administered. However, lower-than-recommended doses elicited low ACR70 responses (NNT=15). For patients with an insufficient prior response to methotrexate, the TNF antagonists plus methotrexate had NNT values of 3 for ACR20, 4 for ACR50, and 8 for ACR70. Comparisons of anti-TNF drugs plus methotrexate versus methotrexate alone in patients with no previous resistance to methotrexate showed somewhat lower effects. Adverse effects were more likely with TNF antagonists than controls (overall combined NNH=27). Patients receiving infliximab were more likely to withdraw because of adverse effects (NNH=24) and to suffer severe adverse effects (NNH=31), infections (NNH=10), and infusion reactions (NNH=9). Patients receiving adalimumab were also more likely to drop out because of side effects (NNH=47) and to suffer injection site reactions (NNH=22). Patients receiving etanercept were less likely to drop out because of side effects (NNH for control versus etanercept, 26) but more likely to experience injection site reactions (NNH=5).

A meta-analysis compared the benefits and safety of abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab in patients with RA.[761] ACR50 response rates were the major outcomes evaluated. A mixed-effects logistic regression was used to provide an indirect comparison of the treatment effects between the biologics. The biologics reported higher ACR50 rates compared to placebo (OR, 3.35; 95% CI, 2.62 to 4.29) and a NNT for benefit of 4 (95% CI, 4 to 6). Discontinuations due to adverse

events were higher with the biologics (OR, 1.39; 95% CI, 1.13 to 1.71), with a NNH of 52 (95% CI, 29 to 152). Anakinra was less effective than all of the other biologics, although this difference was statistically significant only for the comparison with adalimumab (OR, 0.45; 95% CI, 0.21 to 0.99) and etanercept (OR, 0.34; 95% CI, 0.14 to 0.81). Adalimumab, anakinra, and infliximab were more likely than etanercept to lead to withdrawals related to adverse events (adalimumab OR, 1.89 [95% CI, 1.18 to 3.04]; anakinra OR, 2.05 [95% CI, 1.27 to 3.29]; and infliximab OR 2.7 [95% CI, 1.43 to 5.26]).

A meta-analysis evaluated the efficacy and safety of using the TNF antagonists including adalimumab, etanercept, and infliximab in the treatment of adults with RA.[762] A total of 21 randomized, placebo-controlled trials were included. A total of 1,524 patients with adalimumab, 1,116 patients received infliximab, and 1,029 patients received etanercept, and 2,834 patients received placebo with or without methotrexate in all groups. Efficacy was compared using ACR20, ACR50, and ACR70 criteria. In the short term trials (12 to 30 weeks), etanercept had the highest risk ratios for reaching ACR20 and ACR50: 2.94 (95% CI, 2.27 to 3.81) and 5.28 (95% CI, 3.12 to 8.92), respectively. ACR70 achievement was highest with adalimumab (5.36; 95% CI, 3.76 to 7.64). Over long-term treatment (1 to 3 years), adalimumab demonstrated the highest risk ratios for ACR20 (1.85; 95% CI, 1.07 to 3.19), ACR50 (2.8; 95% CI, 1.16 to 6.77), and ACR70 (3.23; 95% CI, 1.37 to 7.61). No significant differences were observed between the active treatments and placebo.

A systematic review of 16 randomized controlled trials comparing the efficacy of anti-TNF agents with placebo at 24 weeks in patients who have had an inadequate response to methotrexate was performed.[763] Relative efficacy was estimated using Bayesian mixed treatment comparison (MTC) models. Three different outcome measures were used: ACR20 and ACR50 response and the percentage improvement in Health Assessment Questionnaire (HAQ) score. All anti-TNF agents showed significantly improved efficacy over placebo. The results also provide evidence of some differences in efficacy among the agents. Etanercept was favored over infliximab and golimumab, and certolizumab was favored over infliximab and adalimumab. ACR results indicate improved efficacy of certolizumab over golimumab. On HAQ analysis, adalimumab, certolizumab, etanercept and golimumab appear superior to infliximab, and etanercept shows improved efficacy compared with adalimumab.

A total of 18 published trials and 1 abstract were included in a meta-analysis examining the efficacy of a biological agent in RA at 6 months in patients with an incomplete response to methotrexate or an anti-TNF biologic.[764] In patients with incomplete response to methotrexate, anti-TNF agents had the same probability of reaching an ACR50 compared to non-anti-TNF biologicals taken together (OR, 1.3; 95 % CI, 0.91 to 1.86). However, when compared to specific biological agents, anti-TNFs demonstrated a higher probability of reaching an ACR50 than abatacept (OR, 1.52; 95 % CI, 1 to 2.28), but not in comparison to rituximab and tocilizumab. In patients with prior incomplete response to anti-TNF agents, rituximab demonstrated a higher probability of achieving an ACR50 than tocilizumab (OR, 2.61; 95% CI, 1.1 to 6.37), but no significant differences existed between golimumab and other biologicals.

A meta-analysis including similarly designed double-blind, randomized, placebo-controlled trials over an 18-year period compared the response of tocilizumab and other biologic agents in patients with RA who had inadequate response to DMARD therapy.[765] Biologic agents included abatacept, rituximab, etanercept, infliximab, adalimumab, and tocilizumab. The endpoint of interest was ACR20/50/70 response criteria at 24 to 30 weeks. The effectiveness of tocilizumab appeared to be comparable to that of other biologic agents for ACR20 and ACR50 responses but greater for ACR70. Specifically, tocilizumab had greater ACR70 responses than both TNF-alpha inhibitors (RR, 1.8; CrI, 1.2 to 2.6) and abatacept (RR, 2; CrI, 1.3 to 3.1). A network meta-analysis also compared the efficacy of biologics for RA using tocilizumab

as a comparator (versus abatacept, adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, and rituximab; 68 randomized clinical trials).[766] While findings suggest superiority of tocilizumab over conventional DMARDs, such as methotrexate, minimal significant differences were seen between tocilizumab and other biologics.

A network meta-analysis of 28 randomized controlled trials compared the efficacy of novel DMARDs (abatacept, anakinra, adalimumab, certolizumab, etanercept, golimumab, infliximab, tocilizumab, or tofacitinib) as monotherapy or with methotrexate on ACR response at 24 weeks.[767] Most novel DMARDS with methotrexate demonstrated comparable efficacy with the exception of anakinra with methotrexate. When compared as monotherapy, greater response was seen with tocilizumab compared to other anti-TNF agents or tofacitinib, and efficacy of tocilizumab with methotrexate was similar to tocilizumab monotherapy (OR, 1.08 [95% CrI, 0.4 to 2.84]; OR , 1.24 [95% CrI, 0.44 to 3.61]; and OR, 0.95 [95% CrI, 0.33 to 2.72] for ACR20, ACR50, and ACR70, respectively; however, the efficacy of anti-TNF agents with methotrexate appears superior to the anti-TNF agents used as monotherapy (OR, 2.41 [95% CrI, 0.51 to 11.61]; OR , 2.85 [95% CrI, 0.51 to 17.67]; and OR, 1.28 [95% CrI, 0.21 to 8.42] for ACR20, ACR50, and ACR70, respectively. Overall, the number of studies available for inclusion limited the results and, in most cases, the credible intervals were broad.

A Cochrane review assessed the benefits of abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib in patients with RA who have failed to respond to methotrexate or DMARDs (79 randomized controlled trials; n=32,874).[768] Data demonstrated that the addition of a biologic to traditional therapy (methotrexate or other traditional DMARDs) improved remission rates and ACR50; however, differences between biologic treatments were not described. A similar Cochrane review, a network meta-analysis of 158 clinical trials (n=37,000), compared methotrexate monotherapy and methotrexate combination therapy (traditional DMARDS, biologics, tofacitinib). It found that the addition of other agents to methotrexate (e.g., traditional triple therapy or methotrexate plus biologics or tofacitinib) were similarly effective.[769] Again, this meta-analysis did not distinguish the efficacy of agents within this class.

Other Cochrane network meta-analyses have assessed the role of biologics and tofacitinib for RA. The first assessed the role of these agents in patients naïve to methotrexate (19 randomized, controlled trials; n=6,485; included adalimumab, etanercept, golimumab, infliximab, abatacept, and tofacitinib).[770] While the findings suggest that combination therapy (biologics with methotrexate) was associated with benefits in 3 of the efficacy outcomes (ACR50, HAQ scores, and RA remission rates) compared to methotrexate monotherapy, data were too limited to provide insight into differences between biologics or tofacitinib. A second Cochrane review assessed the role of biologics or tofacitinib for people with RA who have been unsuccessfully treated with biologics (12 randomized, controlled trials; n=3,364; included certolizumab pegol, etanercept, golimumab, infliximab, abatacept, tocilizumab, and tofacitinib).[771] Compared to placebo or traditional DMARDs, biologics and tofacitinib were considered statistically superior; however, again, data were too few to distinguish differences between agents in this class.

A network meta-analysis compared the efficacy of tofacitinib and biologic agents for the treatment of moderate to severe RA (27 randomized controlled trials). ACR50 results at week 24 in the included trials, the majority of which compared an active agent to placebo, were used to compare efficacy.[772] Agents included were abatacept, adalimumab, anakinra, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab, and tofacitinib. Monotherapy of biologics alone or in combination with methotrexate were superior (based on 95% CI) to placebo with methotrexate for all comparisons, with the exceptions of the following agents as monotherapy: etanercept, certolizumab, tofacitinib, and

adalimumab. Other statistical differences were also found. Certolizumab demonstrated superiority in efficacy than anakinra and adalimumab. In addition, tocilizumab (monotherapy or in combination with methotrexate) was superior to adalimumab. Statistically, etanercept with methotrexate appeared to have the greatest efficacy and adalimumab and anakinra appeared to have the weakest efficacy; however, limitations in power resulted in very wide confidence intervals, so the results of this network meta-analysis should be interpreted cautiously.

Another network meta-analysis aimed to compare the efficacy of small molecule and biologic agents for the treatment of early-stage RA, which was defined as disease duration for < 1 year (14 randomized controlled trials).[773] The authors aimed to determine which agent is most likely to achieve a 1-year good clinical response. ACR50 and ACR70 results at 1 year in the included trials. Agents included were abatacept, adalimumab, certolizumab pegol, etanercept, infliximab, rituximab, tocilizumab, and tofacitinib. The agents found to have the highest probability in achieving ACR50 at 1 year were tofacitinib (64.83%) and etanercept (23.26%). The agents found to have the highest probability in achieving ACR70 at 1 year were rituximab (52.81%) and etanercept (26.85%).

Safety

A meta-analysis of 9 clinical trials (3 to 12 months duration involving nearly 3,500 patients) of adalimumab (Humira) and infliximab (Remicade) identified a dose-related increase in the incidence of malignancies (OR, 3.3; 95% CI, 1.2 to 9.1) compared with placebo.[774] Infections requiring antimicrobial therapy also occurred at a higher rate in the active treatment groups compared to placebo (OR, 2; 95% CI, 1.3 to 3.1).

A meta-analysis of 9 trials of longer than 12 weeks durations involving 3,316 patients of which 2,244 received etanercept for the treatment of RA evaluated the risk of malignancies.[775] A total of 26 patients in the etanercept group (incidence rate 10.47/1,000 person-years) were diagnosed with a malignancy. In the control group, 7 patients had a diagnosis of malignancy (incidence rate of 6.66/1,000 person-years); the results were not statistically significant. A Cox's proportional hazards, fixed-effect model stratified by trial yielded a hazard ratio of 1.84 (95% CI, 0.79 to 4.28) for the etanercept group compared with the control group.

A systematic review of the TNF antagonists to evaluate the risk of infection and malignancy in patients with plaque psoriasis and psoriatic arthritis included randomized, placebo-controlled trials of etanercept, infliximab, adalimumab, golimumab, and certolizumab.[776] A total of 20 studies with 6,810 patients were included. The odds ratios for overall infection and serious infection over a mean of 17.8 weeks were 1.18 (95% CI, 1.05 to 1.33) and 0.7 (95% CI, 0.4 to 1.21), respectively. The odds ratio for malignancy was 1.48 (95% CI, 0.71 to 3.09) and 1.26 (95% CI, 0.39 to 4.15) when nonmelanoma skin cancer was excluded. In the short term, the authors concluded that there is a small risk of overall infection with the TNF antagonists. No evidence of an increased risk of serious infection or malignancy was observed in the short-term trials.

A meta-analysis assessed the risk of serious adverse effects associated with biological and targeted drugs in patients with RA (117 trials; n=47,615).[777] Based on the limited data, serious adverse effects occurred more commonly with certolizumab pegol compared with abatacept (rate ratio, 1.58; 95% CI, 1.18 to 2.14), adalimumab (rate ratio, 1.36; 95% CI, 1.02 to 1.81), etanercept (rate ratio, 1.6, 95% CI, 1.18 to 2.17), golimumab (rate ratio, 1.45; 95% CI, 1 to 2.08), rituximab (rate ratio, 1.63; 95% CI, 1.16 to 2.3), and tofacitinib (rate ratio, 1.44; 95% CI, 1.03 to 2.02). Serious adverse effects also occurred more commonly with tocilizumab compared with abatacept (rate ratio, 1.3; 95% CI, 1.03 to 1.65), etanercept (rate ratio, 1.31; 95% CI, 1.04 to 1.67) and rituximab (rate ratio, 1.34; 95% CI, 1.01 to 1.78).

A meta-analysis of pregnancy outcomes in women using anti-TNF agents for inflammatory bowel disease (CD or UC) demonstrated no increase in occurrence of adverse pregnancy outcomes compared to controls, with the exception of a decrease in gestational age of newborns in exposed mothers in 1 trial.[778]

A meta-analysis evaluated the risk of venous thromboembolism (including pulmonary embolism and deep vein thrombosis) with JAK inhibitors (42 studies) in clinical trials using approved dosing regimens.[779] The investigators evaluated 6,542 JAK inhibitor patient exposure years compared to 1,578 placebo patient exposure years. Fifteen events occurred in the JAK inhibitor group compared to 4 in the placebo group. The rate ratios found for venous thromboembolism, pulmonary embolism, and deep vein thrombosis were 0.68 (95% CI, 0.36 to 1.29), 0.44 (95% CI, 0.28 to 0.7), and 0.59 (95% CI, 0.31 to 1.15), respectively.

SUMMARY

Cytokines and CAMs have been implicated in RA, plaque psoriasis, psoriatic arthritis, Crohn's disease, and ankylosing spondylitis. The development of antagonists to these mediators has yielded significant clinical benefits in those patients for whom less sophisticated treatments provide little relief.

Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

Axial spondyloarthritis (axSpA) is an inflammatory condition generally affecting the spine and can be furthered subdivided into ankylosing spondylitis (AS; radiographic axSpA) and nonradiographic axSpA (nr-axSpA). Adalimumab and its biosimilar (Humira, Amjevita), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi, Simponi Aria), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), ixekizumab (Taltz), secukinumab (Cosentyx), tofacitinib (Xeljanz, Xeljanz XR), and upadacitinib (Rinvoq) are indicated for ankylosing spondylitis. Although it has been established that TNF antagonist therapies are effective for symptoms of ankylosing spondylitis, it is still unclear whether they prevent structural damage. In addition to their indications for ankylosing spondylitis, certolizumab pegol (Cimzia), ixekizumab (Taltz)secukinumab (Cosentyx), and upadacitinib (Rinvoq) carry an indication for the treatment of adults with active nonradiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation; upadacitinib is indicated for patients who have had an inadequate response or intolerance to TNF blocker therapy. Current guidelines, updated in 2019, do not recommend one anti-TNF agent over another, but do recommend monoclonal antibodies over etanercept in cases of recurrent iritis or inflammatory bowel disease.

Crohn's Disease

Adalimumab and its biosimilar (Humira, Amjevita), certolizumab pegol (Cimzia), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), risankizumab-rzaa (Skyrizi), ustekinumab (Stelara), and vedolizumab (Entyvio) are indicated in patients with Crohn's disease. Infliximab and its biosimilars also are indicated in reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease, as well as the treatment of children ages 6 years and older. Adalimumab and its biosimilar are also indicated in children ages ≥ 6 years who have had an inadequate response to conventional therapy. Comparative data are lacking; however, adalimumab is specifically indicated for adult patients who are intolerant to or have a diminished response to infliximab or, therefore, biosimilar agents. Certolizumab pegol and vedolizumab (Entyvio) are indicated for patients who have had an inadequate response to conventional therapy.

Both the American Gastroenterology Association (AGA) and the American College of Gastroenterology (ACG) have provided detailed guidance on the treatment of Crohn's disease with agents in this class.

Juvenile Idiopathic Arthritis and Adult Onset Still's Disease

Abatacept (Orencia), adalimumab and its biosimilar (Humira, Amjevita), etanercept (Enbrel), and IV golimumab (Simponi Aria) are indicated for polyarticular juvenile idiopathic arthritis (JIA) in children ≥ 2 years of age. Tocilizumab (Actemra) is indicated for polyarticular and systemic JIA in children 2 years of age and older. Canakinumab (Ilaris) is indicated for systemic JIA in children 2 years of age and older. Abatacept (Orencia) and golimumab (Simponi Aria) for JIA must be administered intravenously (IV). Tofacitinib (Xeljanz), a non-biologic, is approved for polyarticular course JIA in children who are at least 2 years old. Current treatment guidelines recommend initial therapy with anakinra, glucocorticoid monotherapy, or nonsteroidal anti-inflammatory drugs (NSAIDs) for patients with active systemic disease. Continued disease activity may be treated with canakinumab, tocilizumab, methotrexate, leflunomide, or an anti-TNF agent based on response and initial treatment agent. While agents in this review are not recommended as initial therapy in patients without systemic disease, they may be appropriate as continued therapy based on initial treatment response. Detailed guidelines on nonsystemic disease are available and updated systemic disease guidelines are in the pipeline.

Adult onset Still's disease (AOSD) is a rare inflammatory disorder that is an adult-onset counterpart to systemic JIA. It is most commonly treated with NSAIDs for inflammation and antipyretics; methotrexate or corticosteroids also may also be used for systemic symptoms. Currently, only canakinumab is FDA-approved for the treatment of AOSD in the US.

Plaque Psoriasis

Adalimumab and its biosimilar (Humira, Amjevita), apremilast (Otezla), brodalumab (Siliq), certolizumab pegol (Cimzia), etanercept (Enbrel), guselkumab (Tremfya), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), ixekizumab (Taltz), risankizumab-rzaa (Skyrizi), secukinumab (Cosentyx), tildrakizumab-asmn (Ilumya), and ustekinumab (Stelara) are approved for the treatment of plaque psoriasis. Cytokine and CAM antagonists indicated for the treatment of psoriasis have similar efficacy. Notably, apremilast is approved for all patients who are candidates for phototherapy or systemic therapy, regardless of severity.

Adalimumab and its biosimilar (Humira, Amjevita), brodalumab (Siliq), certolizumab pegol (Cimzia), etanercept (Enbrel), guselkumab (Tremfya), ixekizumab (Taltz), risankizumab-rzaa (Skyrizi), secukinumab (Cosentyx), tildrakizumab-asmn (Ilumya), and ustekinumab (Stelara) are administered subcutaneously (SC). Infliximab and its biosimilars are given by IV infusion. Apremilast (Otezla) is an oral tablet given twice daily.

Ustekinumab (Stelara) is an interleukin (IL)-12 and IL-23 antagonist, and guselkumab (Tremfya) and tildrakizumab-asmn (Ilumya) are IL-23 antagonists. Brodalumab (Siliq), ixekizumab (Taltz), and secukinumab (Cosentyx) are IL-17A antagonists. Ustekinumab and ixekizumab shown effectiveness against etanercept (Enbrel) in adults with moderate to severe plaque psoriasis. The 2019 evidence-based clinical practice guidelines regarding biologics for plaque psoriasis by the American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) recommend adalimumab, etanercept, and infliximab for moderate to severe psoriasis. Due to limited evidence, certolizumab does not have a recommendation, but they state that it is likely to have class characteristics similar to other TNF antagonists. Apremilast, brodalumab, guselkumab, ixekizumab, secukinumab, tildrakizumab, and ustekinumab are also recommended for moderate to severe psoriasis. Risankizumab is recommended for

moderate to severe psoriasis; however, they assigned this a lower strength of recommendation as this was not FDA-approved at the time of guideline publication.

Psoriatic Arthritis

Abatacept (Orencia), adalimumab and its biosimilar (Humira, Amjevita), apremilast (Otezla), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi, Simponi Aria), guselkumab (Tremfya), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), ixekizumab (Taltz), risankizumab-rzaa (Skyrizi), secukinumab (Cosentyx), tofacitinib (Xeljanz, Xeljanz XR), upadacitinib (Rinvoq), and ustekinumab (Stelara) are approved for the treatment of psoriatic arthritis.

Patients with mild to moderate psoriatic arthritis may be treated with NSAIDs and/or intra-articular steroid injections. The clinical trial proportion of patients achieving at least 20% improvement in American College of Rheumatology response criteria (ACR20) efficacy data at the primary endpoint with all 6 FDA-approved TNF antagonists (data on biosimilars extrapolated from reference product) for the treatment of PsA are roughly equivalent; the choice of which TNF agent to use is an individual one with the degree and severity of cutaneous involvement an important consideration. In 2018, the American College of Rheumatology (ACR) and the National Psoriasis Foundation published a guideline on the treatment of PsA, emphasizing a treat-to-target approach. In general, the group recommends treatments in the following order: TNF antagonist, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, and tofacitinib, with a varying role of oral small molecules depending on the patient population and treatment history.

Rheumatoid Arthritis

The agents in this class approved for treatment of RA are abatacept (Orencia), adalimumab and its biosimilar (Humira, Amjevita), anakinra (Kineret), baricitinib (Olumiant), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi, Simponi Aria), infliximab (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), sarilumab (Kevzara), tocilizumab (Actemra), tofacitinib (Xeljanz, Xeljanz XR), and upadacitinib (Rinvoq).

Anakinra (Kineret), an IL-1 receptor antagonist, is associated with inferior efficacy and higher toxicity compared with the TNF antagonist therapies. Anakinra is given as monotherapy or in combination with methotrexate or other non-TNF-targeting DMARDs. Infliximab (Remicade) and its biosimilars are administered at an outpatient facility as an IV infusion. Abatacept (Orencia) and tocilizumab (Actemra) may be administered either IV in an outpatient facility for RA or may be administered as a SC injection for RA. Baricitinib (Olumiant) and tofacitinib (Xeljanz, Xeljanz XR), Janus kinase (JAK) inhibitors, are approved for patients with an inadequate response or intolerance to ≥ 1 TNF antagonist.

The ACR updated the guidelines for the management of RA in 2021. The guidelines address treatment with DMARDs, including both conventional and targeted small molecule DMARDs and biologics. The 2021 guidelines continue to focus on a treat-to-target approach based on mutual determination of a target between the patient and clinician. In general, select conventional small molecule DMARDs are preferred by ACR in low disease activity, and monotherapy with methotrexate is conditionally recommended over its use in combination with a biologic or targeted small molecule DMARD in patients with prior conventional DMARD treatment with moderate to high disease activity who are methotrexate-naïve. ACR conditionally recommends switching to a biologic or targeted small molecule DMARD of a different class over to one of the same class in patients not at clinical target.

The 2012 consensus statement on the biologic agents for the treatment of rheumatic diseases from the international Annual Workshop on Advances in Targeted Therapies states that anti-TNF agents used in combination with methotrexate yield better results in the treatment of RA than monotherapy. There is no evidence that any one TNF antagonist should be used before another one can be tried for the treatment of RA or JIA (except with systemic-onset JIA, when anakinra may be effective). There is no evidence that any one TNF antagonist is more effective than any other for the treatment of RA or AS. These guidelines have not addressed the role of infliximab biosimilars.

Ulcerative Colitis

Adalimumab and its biosimilar (Humira, Amjevita), golimumab (Simponi), infliximab, (Remicade), infliximab-abda (Renflexis), infliximab-axxq (Avsola), infliximab-dyyb (Inflectra), tofacitinib (Xeljanz, Xeljanz XR), upadacitinib (Rinvoq), ustekinumab (Stelara), and vedolizumab (Entyvio) are indicated for treating ulcerative colitis (UC). Infliximab, infliximab-abda, and infliximab-dyyb are effective in inducing clinical remission and response in patients with moderate to severe UC with refractory disease. Infliximab and its biosimilars are also indicated in children ≥ 6 years old. Adalimumab is indicated for the treatment of moderately to severely active UC in adults and pediatric patients ≥ 5 years old. Adalimumab-atto (Amjevita) is indicated only for adults with UC. Golimumab is approved for inducing and sustaining clinical remission in adult patients with moderate to severe active UC who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine, or 6-mercaptopurine. Golimumab is also approved in patients who have failed to respond to oral aminosalicylates and who cannot tolerate immunosuppressants or aminosalicylates. Tofacitinib is indicated for patients with moderate to severely active disease. Vedolizumab (Entyvio) is approved for moderate to severe disease after trial or intolerance to a TNF antagonist, immunomodulator, or corticosteroid.

Both the American College of Gastroenterology (ACG) and the American Gastroenterology Association (AGA) have provided detailed guidance on the treatment of UC with agents in this class.

Other Indications

Abatacept (Orencia) is also approved for the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients ≥ 2 years old undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor.

Adalimumab (Humira) is also indicated for the treatment of moderate to severe hidradenitis suppurativa (HS), a chronic skin condition that features small lumps under the skin, most commonly where skin rubs together, and can be painful. Adalimumab (Humira) is also approved for the treatment of non-infectious intermediate, posterior, and panuveitis in adults. It is the only biologic agent approved for this use. The adalimumab biosimilar (Amjevita) does not carry these indications.

Apremilast (Otezla) is approved for oral ulcers associated with Behçet's disease.

Baricitinib (Olumiant) is also indicated in adults with severe alopecia areata.

Canakinumab (Ilaris) and rilonacept (Arcalyst) are both indicated for cryopyrin-associated periodic syndromes (CAPS) associated with familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), while anakinra (Kineret) is indicated for CAPS associated with Neonatal-Onset Multisystem Inflammatory Disease (NOMID). Anakinra and rilonacept are also approved for the

treatment of and maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA), respectively. In addition, rilonacept is approved for the treatment of recurrent pericarditis.

Secukinumab (Cosentyx) is also approved for the treatment of enthesitis-related arthritis (ERA) in patients ≥ 4 years of age.

Both IV inebilizumab-cdon (Uplizna) and SC satralizumab-mwge (Enspryng) are approved for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

Tocilizumab (Actemra) is approved for the treatment of giant cell arteritis (GCA) in adults, treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and pediatric patients ≥ 2 years of age, and for slowing the rate of decline in pulmonary function in adults with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

Abrocitinib (Cibinqo) and upadacitinib (Rinvoq) are also approved for the treatment of adults with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable; upadacitinib is indicated in pediatric patients ≥ 12 years of age for this indication.

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