South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

September 8, 2023

South Dakota Department of Social Services

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South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

September 8, 2023
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Meeting Link:

https://teams.microsoft.com/l/meetup-join/19%3ameeting_MDYwMGNmZGMtZDY4ZC00MTQyLTgxNzItYzUyY2MwN2FkYjc0%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%22b6efd724-b34e-4a86-b34c-e34f07dd4ceb%22%7d

Join with a video conferencing device
425899727@t.plcm.vc
Video Conference ID: 111 568 862 35

Join by phone
+1 952-222-7450
Phone Conference ID: 587 125 638#

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Opioid edits**
- **Opioid update**

New business
- **Vyvanse dose limit**
- **Qelbree**
- **Adalimumab**
- **Growth Hormones**
- **Rukobia**
- **Sotyktu**

Public input accepted after individual topic discussion
Next meeting date December 8, 2023 & adjournment

South Dakota Department of Social Services, Division of Medicaid Services
Pharmacy & Therapeutics (P&T) Committee Meeting Minutes

Friday, June 9, 2023
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	X	Matthew Stanley, DO	X
Dana Darger, RPh, Chair	X	Deidre Van Gilder, PharmD	X
Bill Ladwig, RPh	X	Taylor Koerner, DSS Staff	X
Kelley Oehlke, PharmD	X	Mike Jockheck, DSS Staff	X
Lenny Petrik, PharmD	-	Matthew Ballard, DSS Staff	X
Heather Preuss, MD	X	Sarah Aker, DSS Staff	X

Administrative Business

Darger called the meeting to order at 1:02 pm. The minutes of the March meeting were presented. Baack made a motion to approve. Van Gilder seconded the motion. The motion was unanimously approved.

Jockheck introduced a new pharmacist on the DSS staff, Taylor Koerner, 2020 SDSU graduate.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from January 1, 2023, to March 31, 2023. A total of 2,459 PAs were reviewed of which 147 requests (6%) were received via telephone, 156 requests (6.3%) were received via fax, 940 (38.2%) were reviewed electronically, and 49.5% PAs were received via ePA. There was a 25% increase of PAs received compared to the previous quarter which was the result of the ePA implementation effective 1/1/2023. Faxed PAs decreased 88% due to the ePA option provided to prescribers.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from January 1, 2023, to March 31, 2023. The top five therapeutic classes based on paid amount were atypical antipsychotics, skin and mucous membrane agents, disease-modifying anti-rheumatic agents, amphetamines, and cystic fibrosis correctors. These top 15 therapeutic classes comprise 25.82 % of total claims. The committee also reviewed the top 50 drugs based on amount paid and number of claims. The top 50 drugs by amount paid make up 9.3% of total claims. Darger commented on Skyrizi utilization increasing.

Old Business

Eucrisa review

The committee reviewed Eucrisa utilization. Darger stated implementing a PA on Eucrisa would be appropriate and Baack concurred. After reviewing the other states' PA criteria, Baack recommending PA criteria similar to State A with some minor tweaks; adding age criteria of 3 months and shorter trial period of 30 days. Baack made the motion to add PA to Eucrisa with the minor changes and Ladwig seconded the motion. Darger inquired if there was any public testimony. There were none. The motion was approved unanimously.

Winlevi PA
The committee reviewed the proposed PA criteria for Winlevi. Van Gilder made the motion to accept the proposed criteria and Baack seconded the motion. Darger inquired if there was any public testimony. There were none. The motion was approved unanimously.

Vtama PA
The committee reviewed the proposed PA criteria for Vtama. Van Gilder and Baack recommending removing the dermatology consult requirement. Baack made the motion to proposed PA criteria without the dermatology consult. Van Gilder seconded the motion. Darger inquired if there was any public testimony. There were none. The motion was approved unanimously.

Opioid update
The committee reviewed 1Q2023 opioid outcomes compared to previous quarters from the opioid initiatives. There was a slight increase in opioid utilization and utilizers during 1Q2023 in addition to an increase in total eligibility. Darger commented that the initiatives are continuing to work. Ladwig concurred. Jockheck commented on changing the DUR edits from message to a soft edit for opioid utilization with concomitant utilization with skeletal muscle relaxants, benzodiazepines, anticonvulsants, medication assisted therapy, or prenatal. Baack was concerned regarding the prenatal edit. Stanley supported the soft edit for skeletal muscle and benzodiazepines but express his concerns of abrupt benzodiazepine cessation. Jockheck will provide more information and what other states are doing.

New Business
Antidepressant PA review
The committee reviewed the antidepressant PA reviews. After reviewing the sertraline PA requests for quantity limits, Ladwig made the motion to remove quantity limits on sertraline. Stanley seconded the motion. Darger inquired if there was any public testimony. There were none. The motion was approved unanimously.

Asthma guidelines
Dr. James Wallace, MD, pediatric pulmonology specialist, provided a presentation on the new asthma guidelines especially the updates focused on children.

Aker announced her resignation as the Medicaid Director. She expressed her thanks to the committee. The committee wished her well.

Adjournment
The next meeting is scheduled on September 8, 2023. The December and March meetings are tentatively scheduled for December 8, 2023, and March 1, 2024, respectively. The motion to adjourn the meeting was unanimous, and the meeting adjourned at 2:58 pm CT.

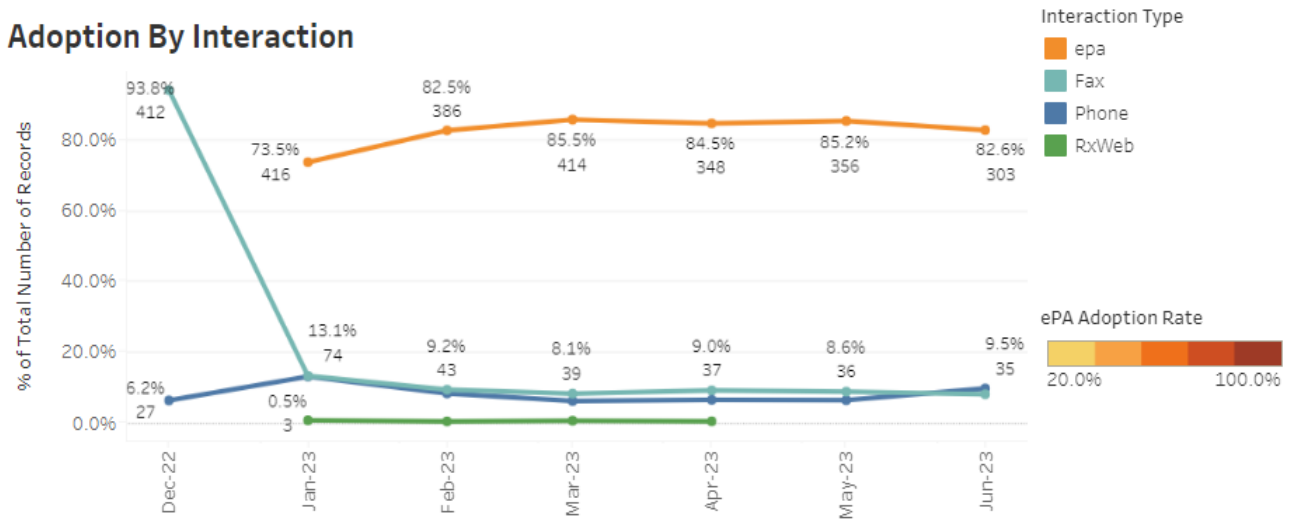
PA Report
4/1/2023 – 6/30/2023

Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	1,657	1,657	0	100.00%	0.00%
Urgent	191	191	0	100.00%	0.00%
Grand Total	**1,848**	**1,848**	**0**		

Priority	Standard	Urgent
ePA	844	163
Fax	97	5
Phone	67	22
Real-Time	649	

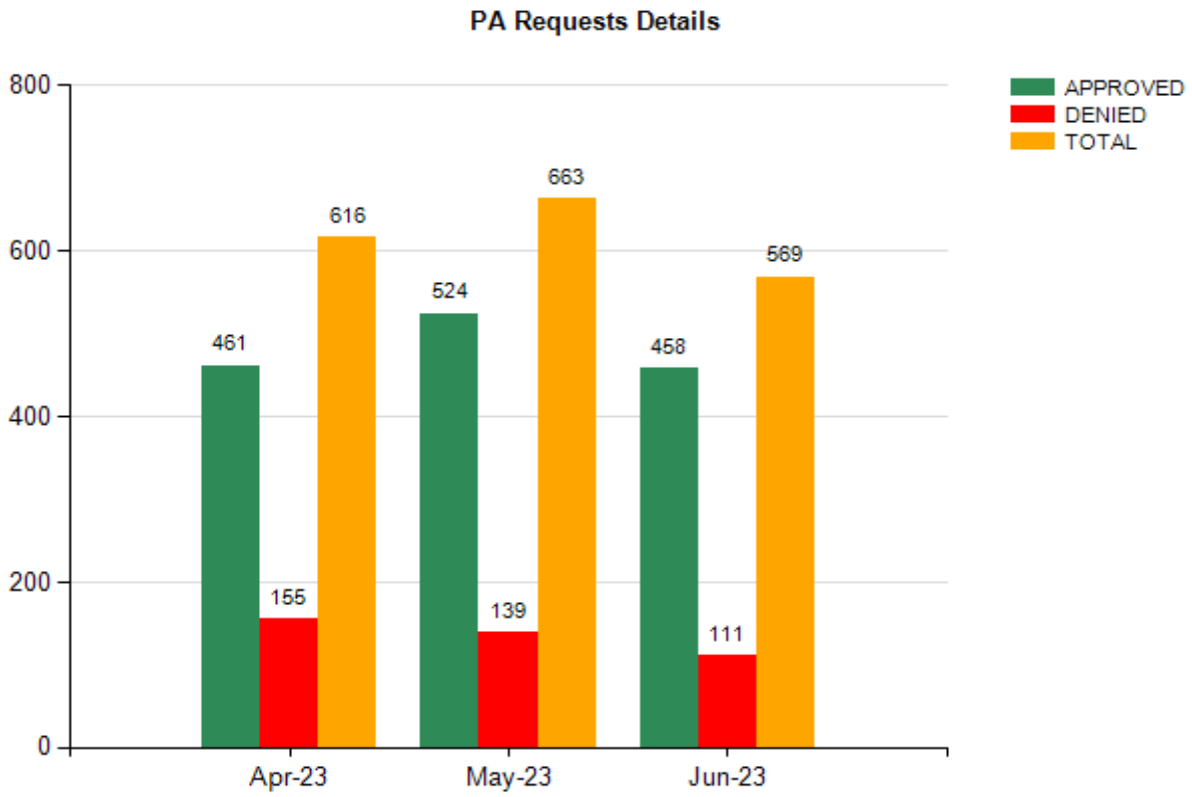
Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**1,848**	**89**	**4.8%**	**102**	**5.5%**	**649**	**35.2%**	**1,007**	**54.5%**



This graph shows the adoption of Interaction Types in percentage. This graph considers all resolved cases (Approved + Denied).

PA Initial Requests Summary

Month	Approved	Denied	Total
Apr-23	461	155	616
May-23	524	139	663
Jun-23	458	111	569
2Q23	**1,443**	**405**	**1848**
Percent of Total	**78.08%**	**21.92%**	



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIDIABETICS	297	70	367	80.93%	19.86%	, OZEMPIC
ANTIPSYCHOTICS/ANTIMANIC	300	16	316	94.94%	17.10%	, INVEGA SUSTENNA
DERMATOLOGICALS	125	60	185	67.57%	10.01%	DUPIXENT, STELARA
ANALGESICS - OPIOID	143	37	180	79.44%	9.74%	, HYDROCODONE/APAP, TRAMADOL
ANTIDEPRESSANTS	113	13	126	89.68%	6.82%	, SERTRALINE
OTHERS -	465	209	674	68.99%	36.47%	
2Q23	**1,443**	**405**	**1,848**	**78.08%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
27 - ANTIDIABETICS*	297	70	367	80.93%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	300	16	316	94.94%
90 - DERMATOLOGICALS*	125	60	185	67.57%
65 - ANALGESICS - OPIOID*	143	37	180	79.44%
58 - ANTIDEPRESSANTS*	113	13	126	89.68%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	55	45	100	55.00%
67 - MIGRAINE PRODUCTS*	59	34	93	63.44%
52 - GASTROINTESTINAL AGENTS - MISC.*	63	20	83	75.90%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	52	14	66	78.79%
66 - ANALGESICS - ANTI-INFLAMMATORY*	44	12	56	78.57%
41 - ANTIHISTAMINES*	23	7	30	76.67%
12 - ANTIVIRALS*	24	5	29	82.76%
16 - ANTI-INFECTIVE AGENTS - MISC.*	19	6	25	76.00%
54 - URINARY ANTISPASMODICS*	16	7	23	69.57%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	7	12	19	36.84%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	10	8	18	55.56%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	15	2	17	88.24%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	12	4	16	75.00%
72 - ANTICONVULSANTS*	13	2	15	86.67%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	14	0	14	100.00%
50 - ANTIEMETICS*	6	4	10	60.00%
75 - MUSCULOSKELETAL THERAPY AGENTS*	4	6	10	40.00%
34 - CALCIUM CHANNEL BLOCKERS*	5	3	8	62.50%
83 - ANTICOAGULANTS*	5	3	8	62.50%
33 - BETA BLOCKERS*	4	3	7	57.14%
39 - ANTIHYPERLIPIDEMICS*	6	1	7	85.71%
74 - NEUROMUSCULAR AGENTS*	1	2	3	33.33%
02 - CEPHALOSPORINS*	2	0	2	100.00%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS*	1	1	2	50.00%
20 - ALLERGENIC EXTRACTS/BIOLOGICALS MISC*	0	2	2	0.00%
36 - ANTIHYPERTENSIVES*	1	1	2	50.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	1	2	50.00%
86 - OPHTHALMIC AGENTS*	0	2	2	0.00%
82 - HEMATOPOIETIC AGENTS*	1	0	1	100.00%
84 - HEMOSTATICS*	0	1	1	0.00%
85 - HEMATOLOGICAL AGENTS - MISC.*	1	0	1	100.00%
87 - OTIC AGENTS*	1	0	1	100.00%
97 - MEDICAL DEVICES AND SUPPLIES*	0	1	1	0.00%
2Q23	**1,443**	**405**	**1,848**	
Percent of Total	**78.08%**	**21.92%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Apr-23	20	71.43%	8	28.57%	28
May-23	19	86.36%	3	13.64%	22
Jun-23	11	84.62%	2	15.38%	13
2Q23	**50**	**79.37%**	**13**	**20.63%**	**63**

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
LUBIPROSTONE	4	4	8	50.00%
AIMOVIG	5	1	6	83.33%
EMGALITY	2	2	4	50.00%
AJOVY	3	0	3	100.00%
LINZESS	3	0	3	100.00%
NORDITROPIN FLEXPRO	3	0	3	100.00%
OZEMPIC	1	2	3	33.33%
EPCLUSA	2	0	2	100.00%
GENOTROPIN	2	0	2	100.00%
MAVYRET	2	0	2	100.00%
XELJANZ	0	2	2	0.00%
AMICAR	1	0	1	100.00%
AMPHETAMINE/DEXTROAMPHETAMINE	1	0	1	100.00%
BELSOMRA	1	0	1	100.00%
DAYVIGO	1	0	1	100.00%
DEXLANSOPRAZOLE	1	0	1	100.00%
DEXMETHYLPHENIDATE ER	1	0	1	100.00%
ENBREL	1	0	1	100.00%
ENOXAPARIN	1	0	1	100.00%
GATTEX	1	0	1	100.00%
GEMTESA	0	1	1	0.00%
HUMATROPE	1	0	1	100.00%
HUMIRA	1	0	1	100.00%
HUMIRA PEN	1	0	1	100.00%
HYDROCODONE/APAP	1	0	1	100.00%
HYDROMORPHONE HCL	1	0	1	100.00%
MOUNJARO	1	0	1	100.00%
MYRBETRIQ	0	1	1	0.00%
NUCALA	1	0	1	100.00%
OLANZAPINE	1	0	1	100.00%
OXYCODONE	1	0	1	100.00%
OXYCODONE/APAP	1	0	1	100.00%
STELARA	1	0	1	100.00%
TETRABENAZINE	1	0	1	100.00%
XIFAXAN	1	0	1	100.00%
XOLAIR	1	0	1	100.00%
2Q23	**50**	**13**	**63**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 4/1/2023 – 6/30/2023					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	13,994	$183,659.90	$13.12	6.63%
2	ANTICONVULSANTS, MISCELLANEOUS	11,707	$1,025,035.68	$87.56	5.54%
3	ATYPICAL ANTIPSYCHOTICS	9,085	$2,585,320.52	$284.57	4.30%
4	SECOND GENERATION ANTIHISTAMINES	7,859	$87,737.38	$11.16	3.72%
5	AMINOPENICILLIN ANTIBIOTICS	7,499	$111,175.20	$14.83	3.55%
6	RESPIRATORY AND CNS STIMULANTS	7,281	$724,103.89	$99.45	3.45%
7	SELECTIVE BETA-2-ADRENERGIC AGONISTS	7,189	$402,720.47	$56.02	3.40%
8	AMPHETAMINES	6,805	$1,383,327.43	$203.28	3.22%
9	PROTON-PUMP INHIBITORS	6,242	$169,453.54	$27.15	2.96%
10	ADRENALS	6,009	$644,551.68	$107.26	2.85%
11	OPIATE AGONISTS	5,196	$166,171.95	$31.98	2.46%
12	ANXIOLYTICS, SEDATIVES, AND HYPNOTICS, MISC	4,802	$63,906.03	$13.31	2.27%
13	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	4,130	$269,896.40	$65.35	1.96%
14	CENTRAL ALPHA-AGONISTS	3,723	$66,073.29	$17.75	1.76%
15	ANTIDEPRESSANTS, MISCELLANEOUS	3,565	$83,353.39	$23.38	1.69%
Total		**105,086**	**$7,966,486.75**	**$75.81**	**49.76%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 4/1/2023 – 6/30/2023					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	386	$2,653,411.34	$6,874.12	0.18%
2	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	813	$2,599,379.24	$3,197.27	0.38%
3	ATYPICAL ANTIPSYCHOTICS	9,085	$2,585,320.52	$284.57	4.30%
4	CYSTIC FIBROSIS (CFTR) CORRECTORS	65	$1,400,784.02	$21,550.52	0.03%
5	AMPHETAMINES	6,805	$1,383,327.43	$203.28	3.22%
6	INCRETIN MIMETICS	1,389	$1,261,109.37	$907.93	0.66%
7	ANTINEOPLASTIC AGENTS	302	$1,207,930.99	$3,999.77	0.14%
8	ANTICONVULSANTS, MISCELLANEOUS	11,707	$1,025,035.68	$87.56	5.54%
9	HEMOSTATICS	45	$826,827.36	$18,373.94	0.02%
10	RESPIRATORY AND CNS STIMULANTS	7,281	$724,103.89	$99.45	3.45%
11	ADRENALS	6,009	$644,551.68	$107.26	2.85%
12	LONG-ACTING INSULINS	1,254	$526,385.18	$419.76	0.59%
13	GI DRUGS, MISCELLANEOUS	421	$501,689.66	$1,191.66	0.20%
14	RAPID-ACTING INSULINS	1,171	$478,465.35	$408.60	0.55%
15	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	864	$469,855.28	$543.81	0.41%
Total		**47,597**	**$18,288,176.99**	**$384.23**	**22.54%**

Total Rx Claims from 4/1/2023 – 6/30/2023	**211,200**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 4/1/2023 – 6/30/2023						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	5,666	$181,628.09	$32.06	2.68%
2	Penicillins	AMOXICILLIN	5,623	$74,000.82	$13.16	2.66%
3	Antidepressants	*FLUOXETINE HCL*	5,065	$60,518.92	$11.95	2.40%
4	ADHD & Narcolepsy Medications	METHYLPHENIDATE HCL	4,570	$283,397.15	$62.01	2.16%
5	Antidepressants	*SERTRALINE HCL*	4,486	$58,151.58	$12.96	2.12%
6	Antihistamines	CETIRIZINE HCL	4,086	$42,401.63	$10.38	1.93%
7	ADHD & Narcolepsy Medications	VYVANSE	3,761	$1,257,257.08	$334.29	1.78%
8	Proton Pump Inhibitors	*OMEPRAZOLE*	3,758	$43,262.69	$11.51	1.78%
9	Anticonvulsants - 2nd Generation	GABAPENTIN	3,240	$53,420.13	$16.49	1.53%
10	Antidepressants	TRAZODONE HCL	3,227	$34,147.24	$10.58	1.53%
11	Antidepressants	ESCITALOPRAM OXALATE	3,154	$40,093.85	$12.71	1.49%
12	Thyroid Hormones	LEVOTHYROXINE SODIUM	2,982	$38,647.71	$12.96	1.41%
13	Leukotriene Modulators	MONTELUKAST SODIUM	2,963	$38,630.63	$13.04	1.40%
14	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAMP	2,736	$75,613.78	$27.64	1.30%
15	Biguanides & Combos	*METFORMIN HCL*	2,427	$29,543.91	$12.17	1.15%
16	Antiadrenergic Antihypertensives	CLONIDINE HCL	2,362	$21,680.19	$9.18	1.12%
17	Antidepressants	*BUPROPION HCL*	2,358	$41,834.06	$17.74	1.12%
18	Atypical Antipsychotics	ARIPIPRAZOLE	2,116	$32,976.34	$15.58	1.00%
19	ADHD & Narcolepsy Medications	GUANFACINE ER	2,108	$33,934.03	$16.10	1.00%
20	Opioid Agonists & Combos	HYDROCODONE BIT/AC	2,082	$31,361.44	$15.06	0.99%
21	Statins & Combos	ATORVASTATIN CALCIUM	1,980	$22,969.98	$11.60	0.94%
22	ACE Inhibitors & Combos	LISINOPRIL	1,929	$18,580.87	$9.63	0.91%
23	Penicillins	AMOXICILLIN/CLAVULANATE	1,871	$36,567.73	$19.54	0.89%
24	Antidepressants	*DULOXETINE HCL*	1,863	$29,810.38	$16.00	0.88%
25	Antianxiety Agents	*HYDROXYZINE HCL*	1,820	$22,604.20	$12.42	0.86%
26	Cephalosporins	CEPHALEXIN	1,778	$31,051.38	$17.46	0.84%
27	Atypical Antipsychotics	RISPERIDONE	1,765	$21,843.21	$12.38	0.84%
28	Antiemetics	ONDANSETRON ODT	1,684	$23,248.52	$13.81	0.80%
29	Anticonvulsants - 2nd Generation	LAMOTRIGINE	1,673	$22,733.50	$13.59	0.79%
30	Glucocorticosteroids	PREDNISONE	1,635	$15,902.16	$9.73	0.77%
31	Antihistamines	LORATADINE	1,608	$17,188.64	$10.69	0.76%
32	Macrolides	AZITHROMYCIN	1,604	$25,625.05	$15.98	0.76%
33	Nasal Steroids	FLUTICASONE PROPIONATE	1,529	$22,777.09	$14.90	0.72%
34	Antianxiety Agents	*BUSPIRONE HCL*	1,519	$18,703.44	$12.31	0.72%
35	Cephalosporins	CEFDINIR	1,483	$33,588.71	$22.65	0.70%
36	Corticosteroids - Topical	TRIAMCINOLONE ACETONIDE	1,433	$23,308.65	$16.27	0.68%
37	Atypical Antipsychotics	QUETIAPINE FUMARATE	1,426	$18,036.23	$12.65	0.68%
38	Anticonvulsants - 2nd Generation	CLONAZEPAM	1,331	$14,906.99	$11.20	0.63%
39	Compounds	-	1,315	$27,558.35	$20.96	0.62%
40	Anticonvulsants - 2nd Generation	LEVETIRACETAM	1,281	$26,452.67	$20.65	0.61%
41	Anticonvulsants - 2nd Generation	TOPIRAMATE	1,262	$16,678.14	$13.22	0.60%
42	Proton Pump Inhibitors	PANTOPRAZOLE SODIUM	1,209	$17,341.15	$14.34	0.57%
43	Calcium Channel Blockers	AMLODIPINE BESYLATE	1,186	$11,784.87	$9.94	0.56%
44	Muscle Relaxants & Combos	CYCLOBENZAPRINE HCL	1,184	$11,751.28	$9.93	0.56%
45	H-2 Antagonists	FAMOTIDINE	1,158	$25,968.96	$22.43	0.55%
46	Vitamins & Supplements	FOLIC ACID	1,121	$10,100.20	$9.01	0.53%
47	ADHD & Narcolepsy Medications	DEXMETHYLPHENIDATE HCL	1,114	$47,932.07	$43.03	0.53%
48	Vitamins & Supplements	VITAMIN D	1,110	$11,352.53	$10.23	0.53%
49	Angiotensin II Receptor Antagonists & Combo	LOSARTAN POTASSIUM	1,106	$12,572.50	$11.37	0.52%
50	Antidepressants	MIRTAZAPINE	1,093	$16,086.33	$14.72	0.52%
	Total Top 50 Drugs		**112,840**	**$3,127,527.05**	**$27.72**	**53.43%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 4/1/2023 – 6/30/2023						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Chronic Inflammatory Disease	***HUMIRA, PEN, STARTER***	160	$1,500,907.66	$9,380.67	0.08%
2	Cystic Fibrosis	TRIKAFTA	60	$1,291,009.92	$21,516.83	0.03%
3	ADHD & Narcolepsy Medications	VYVANSE	3,761	$1,257,257.08	$334.29	1.78%
4	Chronic Inflammatory Disease	STELARA	49	$1,068,712.66	$21,810.46	0.02%
5	Chronic Inflammatory Disease	DUPIXENT	292	$1,015,783.43	$3,478.71	0.14%
6	Atypical Antipsychotics	**INVEGA SUSTENNA, TRINZA**	294	$907,498.98	$3,086.73	0.14%
7	GLP-1 Receptor Agonists	OZEMPIC	797	$722,696.87	$906.77	0.38%
8	Atypical Antipsychotics	VRAYLAR	371	$450,485.15	$1,214.25	0.18%
9	Atypical Antipsychotics	***ARISTADA, INITIO***	133	$368,422.92	$2,770.10	0.06%
10	Anticonvulsants - 2nd Generation	EPIDIOLEX	134	$363,163.06	$2,710.17	0.06%
11↑	Movement Disorder Drug Therapy	INGREZZA	43	$319,966.05	$7,441.07	0.02%
12	Chronic Inflammatory Disease	COSENTYX SENSOREADY PEN	39	$312,311.22	$8,007.98	0.02%
13	Chronic Inflammatory Disease	***ENBREL, MINI, SURECLICK***	45	$299,549.40	$6,656.65	0.02%
14	SGLT-2 Inhibitors & Combos	JARDIANCE	544	$292,475.46	$537.64	0.26%
15	Atypical Antipsychotics	REXULTI	219	$284,951.41	$1,301.15	0.10%
16	ADHD & Narcolepsy Medications	METHYLPHENIDATE HCL	4,570	$283,397.15	$62.01	2.16%
17	Chronic Inflammatory Disease	TALTZ	32	$276,893.80	$8,652.93	0.02%
18	Chronic Inflammatory Disease	***SKYRIZI, PEN***	14	$269,063.68	$19,218.83	0.01%
19	Cystic Fibrosis	PULMOZYME	52	$213,848.60	$4,112.47	0.02%
20↑	GLP-1 Receptor Agonists	MOUNJARO	219	$211,800.97	$967.13	0.10%
21	HIV-Multiclass Combo	BIKTARVY	55	$202,820.75	$3,687.65	0.03%
22	GLP-1 Receptor Agonists	TRULICITY	221	$196,404.88	$888.71	0.10%
23	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	5,666	$181,628.09	$32.06	2.68%
24	Antihemophilic Products	ADVATE	6	$180,832.26	$30,138.71	0.00%
25	Glucagon-Like Peptide-2 (GLP-2) Analogs	GATTEX	4	$176,845.60	$44,211.40	0.00%
26↑	Hepatitis C	SOFOSBUVIR/VELPATASVIR	22	$176,205.70	$8,009.35	0.01%
27	Anti-Infective Agents - Misc.	XIFAXAN	64	$174,182.81	$2,721.61	0.03%
28	Spinal Muscular Atrophy (SMA) Agent	EVRYSDI	7	$172,587.87	$24,655.41	0.00%
29↑	Antihemophilic Products	ALPROLIX	11	$160,128.85	$14,557.17	0.01%
30↑	Oncology	KOSELUGO	10	$155,157.84	$15,515.78	0.00%
31	Antihemophilic Products	NOVOSEVEN RT	2	$154,221.10	$77,110.55	0.00%
32	Oral Anticoagulants	***ELIQUIS, STARTER PACK***	317	$151,366.56	$477.50	0.15%
33↑	Hepatitis C	EPCLUSA	6	$149,573.40	$24,928.90	0.00%
34	Antihemophilic Products	RECOMBINATE	3	$146,080.95	$48,693.65	0.00%
35	Growth Hormones	NORDITROPIN FLEXPRO	46	$141,684.43	$3,080.10	0.02%
36	Insulin	LANTUS SOLOSTAR	340	$139,891.98	$411.45	0.16%
37	Antihemophilic Products	XYNTHA SOLOFUSE	3	$137,287.65	$45,762.55	0.00%
38↑	HIV-Multiclass Combo	GENVOYA	37	$136,981.24	$3,702.20	0.02%
39↑	ADHD & Narcolepsy Medications	JORNAY PM	325	$129,297.31	$397.84	0.15%
40	Atypical Antipsychotics	ABILIFY MAINTENA	53	$128,635.17	$2,427.08	0.03%
41↑	Hepatitis C	MAVYRET	10	$128,432.60	$12,843.26	0.00%
42↑	Atypical Antipsychotics	CAPLYTA	94	$128,150.99	$1,363.31	0.04%
43	Bile Acid Synthesis Disorder Agents	CHOLBAM	6	$124,413.30	$20,735.55	0.00%
44	ADHD & Narcolepsy Medications	QELBREE	297	$124,097.58	$417.84	0.14%
45	Hereditary Angioedema	ORLADEYO	3	$121,067.55	$40,355.85	0.00%
46↓	Pulmonary Arterial Hypertension	OPSUMIT	10	$120,888.80	$12,088.88	0.00%
47	Inhaled Steroids	FLUTICASONE PROPIONATE HF	663	$116,507.78	$175.73	0.31%
48	Insulin	INSULIN ASPART FLEXPEN	328	$116,041.45	$353.78	0.16%
49	Chronic Inflammatory Disease	TREMFYA	9	$115,735.35	$12,859.48	0.00%
50	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	191	$115,330.55	$603.82	0.09%
	Total Top 50 Drugs		**20,637**	**$16,112,675.86**	**$780.77**	**9.77%**

Old Business

Opioid CDUR edits

Medicaid States	Opioid + Anticonvulsant	Opioid + Benzodiazepine	Opioid + MAT	Opioid + Prenatal	Opioid + Skeletal Muscle
South Dakota	-	message	soft edit	message	-
State A	-	soft edit	hard edit	extract	-
State B	-	message	hard edit	soft edit	-
State C	-	message	soft edit	message	-
State D	-	>7ds of concurrent BZD + opiates require PA review for medical necessity	PA	extract	-

CDUR Response Type:

Hard edit

- Deny the claim and does not allow pharmacy to override with DUR conflict
- Provides alert message of potentially unsafe or inappropriate prescriptions
- To override requires PA

Soft edit

- Promote specific behaviors without disruption of member services; can be informational and result in an initial deny at POS that can be overridden with DUR PPS codes
- Deny the claim but allows the pharmacy to override a DUR conflict by submitting appropriate conflict, intervention, and outcome codes

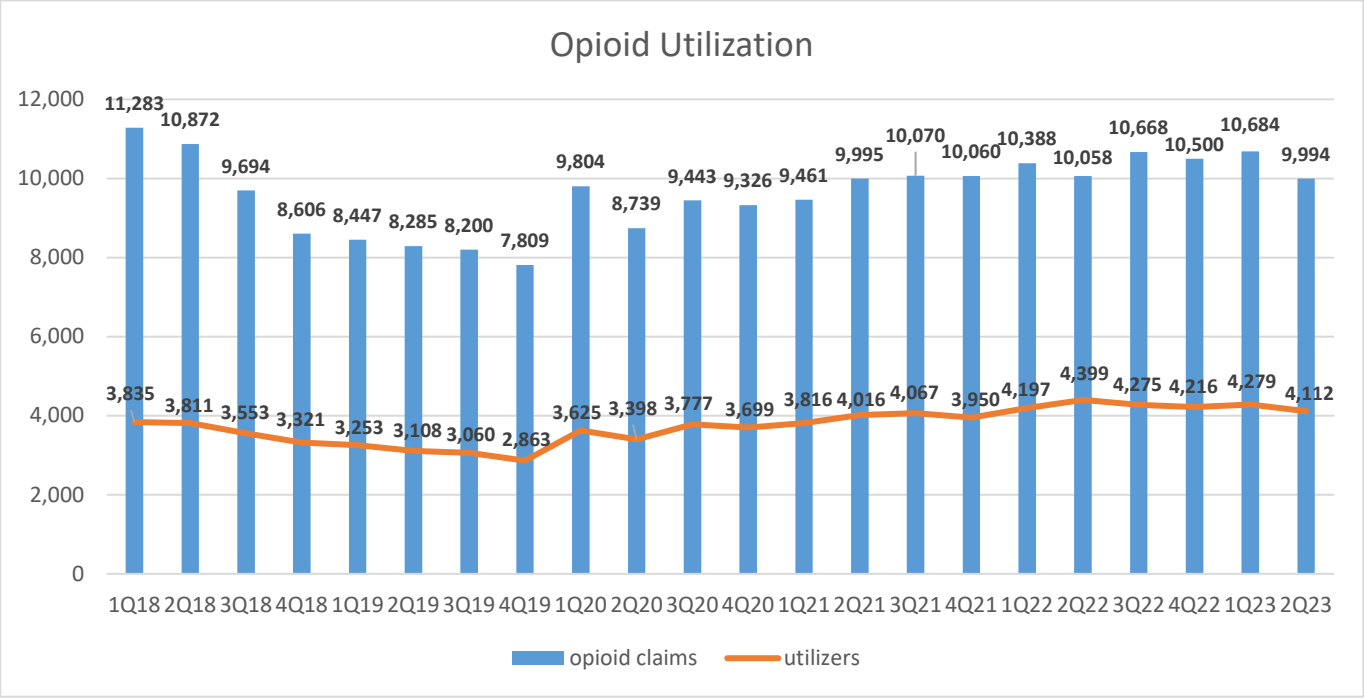
Message

- Pays the claim but sends a conflict alert message back to the pharmacy

Extract

- Pays the claim with no message sent to the pharmacy

Opioid Summary



- 1Q2018 to 4Q2019 excludes IHS
- 1Q2020 to current includes IHS
- March 13, 2020 – Pandemic Closure

Opioid Initiatives:

1. June 1, 2018 – early refill threshold for controlled substance changed from 75% to 85%
2. July 1, 2028 – PA for more than one LAO and one SAO
3. August 1, 2018 – opioid Naïve PA (initial 7-day supply and 60 MED limit)
4. October 1, 2018 to October 1, 2019 – decrease from 300 MED to 90 MED (cancer diagnosis excluded)

Other Initiatives:

- Buprenorphine PA (Bunavail/Suboxone/Zubsolv/Subutex) and ST (Belbuca/Butrans) removed 10/14/2019
- Lidoderm PA removed 8/1/2020

Total Eligibility and Utilizers

Quarter	Avg eligible members	Avg utilizing members of all drugs	% utilizing members of all drugs
1Q2020	123,573	27,090	21.9%
2Q2020	126,777	20,746	16.4%
3Q2020	132,373	23,417	17.7%
4Q2020	136,262	23,489	17.2%
1Q2021	139,748	24,407	17.5%
2Q2021	142,872	26,206	18.3%
3Q2021	146,023	27,933	19.1%
4Q2021	149,034	29,317	19.7%
1Q2022	151,735	29,092	19.2%
2Q2022	154,608	28,370	18.3%
3Q2022	157,627	29,167	18.5%
4Q2022	160,060	32,124	20.1%
1Q2023	162,684	31,612	19.4%
2Q2023	142,001	27,296	19.2%

Opioid Utilization Snapshot

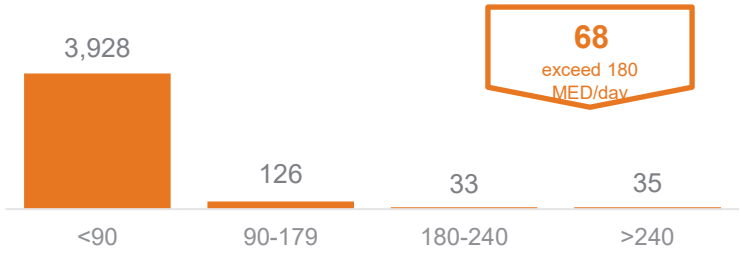
SDM 2Q2023
Mar 23 to Jun 23

Opioid Claims **9,994**
2.9% prescription claims filled for an opioid
0.9% higher than Medicaid FFS benchmark

Utilizers **4,122**
29% are high utilizers [1]
1.6% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy
55 opioid utilizing members with 3+ pharmacies

343 Shoppers: Poly Prescriber
opioid utilizing members with 3+ prescribers

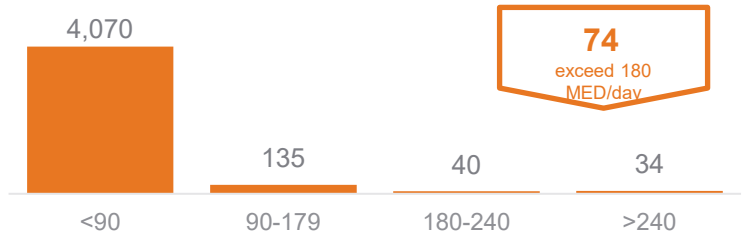
1Q2023
Dec 22 to Mar 23

Opioid Claims **10,684**
2.9% prescription claims filled for an opioid
1.0% higher than Medicaid FFS benchmark

Utilizers **4,279**
30.6% are high utilizers [1]
1.8% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy
66 opioid utilizing members with 3+ pharmacies

349 Shoppers: Poly Prescriber
opioid utilizing members with 3+ prescribers

OPTUMRx®

[1]Defined as 3+ opioid scripts within 120 days period; [4]**MED** – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; [5]JAMA. 2016 Apr 19;315(15):1624-45. [6]MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

Opioid Utilization

SDM 2Q2023
Opportunities date range: Mar - Jun 2023
Benchmark: MEDICAID FEE FOR SERVICE

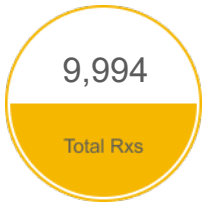
Utilizers: 4,122

2.9% of all Rx claims are filled for an Opioid

Opioid dependence can start in just a few days, and the risk of chronic opioid use increases with each additional day of opioid supplied, starting with the third day. Our Opioid Risk Management program, which includes point of sale, utilization management and retrospective drug utilization edits, are tightly aligned with CDC opioid prescribing guidelines which can help reduce exposure to excessive doses and prevent more members from transitioning from acute to chronic use.

- Opioid prescriptions account for 2.9% of all prescriptions this period, which is 0.9% higher than the benchmark
- 1,197 high opioid utilizers were identified this period, which is 1.6% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
9.4%

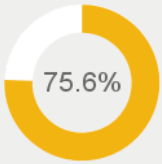
Opioid utilizers

HIGH UTILIZERS
29.0%
1,197 high utilizers

1.6% over benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

75.6% of all opioid Rxs were filled for short acting opioids. **1,798** Rxs were for medication assisted therapy (MAT) and **180** were for rescue therapy. CDC guidelines advise prescribers to manage pain with the lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day.

MAT – view definition
Overdose rescue therapy – view definition
MME – view definition

Utilizers by cumulative MED

68 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	3,928	126	33	35

MED – view definition

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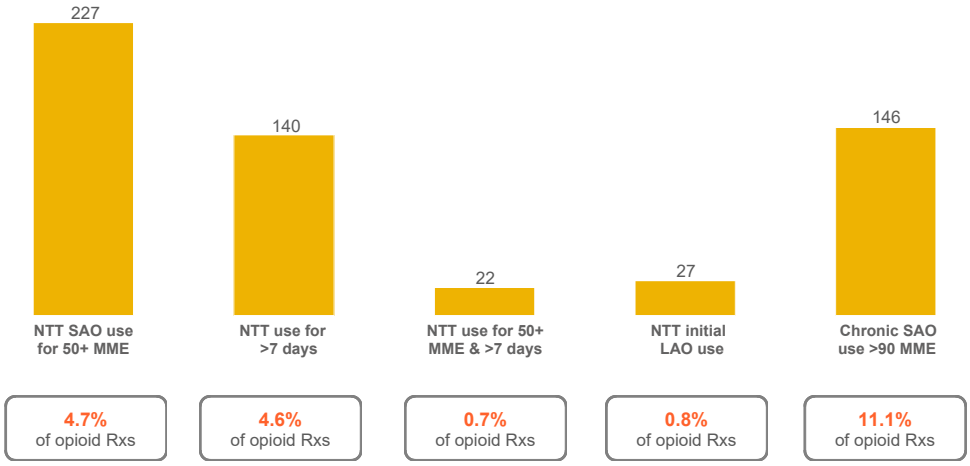
Opioid Opportunity Assessment

SDM 2Q2023
Opportunities date range: Mar - Jun 2023
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 9.4%

Utilizers non-compliant to opioid Rx CDC guidelines

(new to therapy and chronic use)



NTT - view definition | SAO - view definition | LAO - view definition | MME - view definition

DID YOU KNOW?

55 opioid utilizing members use 3 or more pharmacies and 343 opioid utilizing members use 3 or more prescribers.

Identification, management and prevention of fraudulent or potential abuse of opioid medications are monitored and addressed by OptumRx through various means in pharmacy network audit capabilities and high touch clinical programs that include care coordination with opioid prescribers.

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
736	499	723	354	128

Anticonvulsants –view definition

Language Assistance / Non-Discrimination Notice **Asistencia de Idiomas / Aviso de no Discriminación** **語言協助 / 不歧視通知**

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New Business

Vyvanse Dose Limit

Adult Dosing
Attention deficit hyperactivity disorder

- Initial, 30 mg orally once daily in the morning; and may increase dosage in increments of 10 mg or 20 mg per day at approximately weekly intervals to optimal response; **MAX 70 mg/day**.

Binge eating disorder (Moderate to Severe)

- Initial, 30 mg orally once daily in the morning; and titrate in 20-mg increments at approximately weekly intervals to target dose of 50 to 70 mg once daily in the morning; **MAX 70 mg/day**. Discontinue use if binge eating does not improve.

Geriatric Adult Dosing
Attention deficit hyperactivity disorder

- The usual adult initial dose is 30mg PO once daily in the morning. However, in geriatric patients, generally start with lower initial doses. If necessary, dosage increases may be made in increments of 10 to 20 mg per day at weekly intervals. **Do not exceed 70 mg/day PO**.

Pediatric Dosing
Attention deficit hyperactivity disorder

- (6 to 17 years) Initial, 30 mg orally once daily in the morning; and may increase dosage in increments of 10 mg or 20 mg per day at approximately weekly intervals to optimal response; **MAX 70 mg/day**

Quantity Limit: 1 per day for each strength

Time Frame: April – June 2023

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
Vyvanse CAPS	3,617	$1,212,371.78	$333.89	#29.4/29.5 days	1,594	4 – 64
Vyvanse CHEW	173	$59,273.30	$342.62	#29.92/29.4 days	84	6 – 41

Members exceeding 70mg/day

1. Vyvanse 50 mg and 60 mg – 110 mg/day (19 years old, male) – could be switching to higher strength
2. Vyvanse 50 mg and 60 mg – 110 mg/day (15 years old, male) – could be switching to higher strength
3. Vyvanse 20 mg and 70 mg – 90 mg/day (35 years old male)
4. Vyvanse 10 mg and 70 mg – 80 mg/day (38 years old, female)
5. Vyvanse 20 mg and 60 mg – 80 mg/day (14 years old, male)
6. Vyvanse 30 mg and 50 mg – 80 mg/day (17 years old, female)
7. Vyvanse Chew 40 mg #60/30 days – 80 mg/day (12 years old, female)

Members taking 2 different strengths totaling 70mg/day or less: ~29 members

Qelbree

Time Frame: April – July 2023

Non-Stimulants	Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
atomoxetine	atomoxetine cap	860	$31,617.25	$36.76	33.6/29.3 days	379	4 – 60
	Strattera cap	12	$5,104.16	$425.35	29.3/29.3 days	4	13 – 35
clonidine	clonidine ER tab	552	$19,545.61	$35.41	70.5/29.4 days	235	5 – 36
guanfacine	guanfacine ER tab	2,904	$46,895.93	$16.15	31.9/29.8 days	1,151	2 – 60
	Intuniv tab	6	$1,213.28	$202.21	30/30 days	2	14, 15
Viloxazine	**Qelbree cap ER**	**297**	**$124,097.58**	**$417.84**	**39.6/29.3 days**	**132**	5 – 63

*Red font denotes DAW PA

Qelbree proposed step therapy:

- XX-day trial of atomoxetine OR stimulants in the last XXX days

Adalimumab

Time Frame: January – July 2023

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
HUMIRA INJ 20/0.2ML (CF)	13	$90,131.21	$6,131.21	2 per 30.6 days	3	2, 6, 9
HUMIRA INJ 40/0.4ML (CF)	36	$296,711.96	$8,241.99	2.4 per 28 days	7	8 – 57
HUMIRA KIT 40MG/0.8ML	4	$26,510.52	$6,627.63	2 per 28 days	2	16, 56
HUMIRA PEN INJ 40/0.4ML (CF)	219	$1,946,497.27	$8,888.12	2.8 per 27 days	48	11 – 64
HUMIRA PEN INJ 40MG/0.8ML	51	$424,421.34	$8,321.99	2.5 per 28 days	16	17 – 58
HUMIRA PEN INJ 80/0.8ML (CF)	37	$510,193.58	$13,789.02	2 per 28 days	8	19 – 59
HUMIRA PEN INJ CD/UC/HS	3	$45,302.02	~$20,194.06 (1 claim w/other ins)	6 per 28 days	3	23 – 40
HUMIRA PEN INJ PS/UV	1	$13,465.36	$13,465.36	4 per 28 days	1	56
HUMIRA PEN KIT CD/UC/HS	7	$125,829.92	~$20,775.19 (1 claim w/other ins)	3 per 28 days	7	18 – 45
HUMIRA PEN KIT PS/UV	1	$13,85.52	$13,85.52	3 per 28 days	1	39
AMJEVITA, CYLTEZO, HADLIMA, HULIO, HYMIROZ, IDACIO, YUFLYMA, YUSMIRY	0					

*Red font denotes PA

Current step therapy:

- Trial and failure of Humira before Humira CF (citrate-free)

Proposed criteria:

- Trial and failure of Humira before biosimilars
- 90-day trial of Humira in the last 180 days

Growth Hormones

Time Frame: January – July 2023

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range	Net Cost
Genotropin 0.2mg	1	$860.55	$860.55	28 per 28 days	1	2	
Genotropin 0.4mg	4	$1,345.68	$336.42	28 per 28 days	1	5	
Genotropin 0.6mg	0	0					
Genotropin 0.8mg	12	$16,793.07	$1,399.42	15.8 per 16.8 days	3	4 – 13	
Genotropin 1mg	10	$25,608.86	$2,560.87	16.8 per 8.4 days	1	13	
Genotropin 1.2mg	3	$5,132.29	$1,710.76	9.3 per 9.3 days	1	13	
Genotropin 1.4mg	1	$5,961.15	$5,961.15	28 per 28 days	1	10	$
Genotropin 1.6mg	0	0					
Genotropin 1.8mg	0	0					
Genotropin 2mg	4	$17,043.96	$4,260.99	14 per 14 days	1	13	
Genotropin 5mg	9	$42,027.91	$4,669.77	6.7 per 28 days	4	5 – 18	
Genotropin 12mg	1	$1,731.98	$1,731.98	1 per 20 days	1	7	
Total	45	$116,505.45	$2,589.01	14.9 per 18 days	11		
Norditropin 5/1.5ml	33	$44,632.71	$2,589.01	4 per 26 days	12	2 – 35	
Norditropin 10/1.5ml	50	$191,150.66	$3,82301	3.9 per 27.4 days	16	1 – 23	
Norditropin 15/1.5ml	20	$57,911.49	$2,895.57	2.3 per 28.3	9	4 – 41	$
Norditropin 30/3ml	8	$82,320.19	$10,290.02	6.7 per 31.6 days	4	9 – 16	
Total	111	$376,015.05	$3,387.52	3.9 per 27.5 days	35		
Nutropin AQ 5mg	17	$12,124.08	$713.18	2.2 per 22.3 days	3	1 – 22	
Nutropin AQ 10mg	13	$42,947.29	$3,303.64	8 per 28.8 days	8	3 – 18	$$$
Nutropin AQ 20mg	0	0					
Total	30	$55,071.37	$1,835.71	4.7 per 25 days	11		
Humatrope 6mg	11	$21,353.27	$1,941.21	3.1 per 27 days	4	1 – 15	
Humatrope 12mg	1	$4,490.72	$4,490.73	4 per 30 days	1	13	$$$$
Humatrope 24mg	7	$48,835.17	$6,976.45	2.1 per 22 days	2	12 – 13	
Total	19	$74,679.16	$3,930.48	2.8 per 25.4 days	5		
Omnitrope 5/1.5ml	9	$37,608.75	$4,178.75	10 per 27.2 days	3	9 – 11	
Omnitrope 10/1.5ml	6	$30,074.34	$5,012.39	6 per 28 days	1	15	$$
Total	15	$67,683.09	$4,512.21	8.4 per 27.5 days	4		
Saizen 5mg Saizen 8.8mg	0						$$
Zomacton 5mg Zomacton 10mg	0						$
Skytrofa 3mg	1	$2,750.54	$2,750.54			1	
Skytrofa 3.6mg	0	0					
Skytrofa 4.3mg	9	$31,164.66	$3,462.74			4	
Skytrofa 5.2mg	0	0		4 per 28 days	2		$$$
Skytrofa 6.3mg	0	0					
Skytrofa 7.6mg	0	0					
Skytrofa 9.1mg	0	0					
Total	10	$33,915.20	$3,391.52				
Sogroya 5mg	0	0					
Sogroya 10mg	1	$7,928.50	$3,964.25	1.5 per 24.5 days	3	8 – 9	$$$$
Sogroya 15mg	2	$5,282.15	$5,282.15	3 per 34 days			
Total	3	$13,210.65	$4,403.55	2 per 27.7 days			

*Red font denotes drug is on PA

**Sogroya utilization from August 1-22, 2023

Growth Hormone proposed criteria:

A. Trial and failure of all first line drugs (diagnosis dependent) before second line drugs:
    1. First line: Genotropin and Norditropin
    2. Second line: Humatrope, Nutropin AQ, Omnitrope, Saizen, Zomacton, Skytrofa, or Sogroya

Indication	Genotropin	Norditropin	Humatrope	Nutropin AQ	Omnitrope	Saizen	Zomacton	Skytrofa	Sogroya
Growth failure associated with chronic renal insufficiency before renal transplant				✔					
Growth failure associated with Noonan syndrome		✔							
Growth failure associated with Prader-Willi syndrome	✔	✔			✔				
Growth failure associated with short-stature homeobox-containing gene deficiency							✔		
Growth failure associated with Turner syndrome	✔	✔	✔	✔	✔		✔		
Growth failure in children born small for gestational age	✔	✔	✔		✔		✔		
Growth failure due to GH deficiency	✔	✔	✔	✔	✔	✔	✔	✔	
Adults with GH deficiency	✔	✔	✔	✔	✔	✔	✔		✔
Idiopathic short stature	✔	✔	✔	✔	✔		✔		

- Genotropin, Norditropin, Nutropin AQ, Humatrope, Omnitrope, Saizen, Zomactan (somatropin)
- Skytrofa (lonapegsomatropin-tcgd, long-acting prodrug of somatropin; it consists of somatropin conjugated to a methoxyprolyethylene glycol carrier)
- Sogroya (somapacitan-beco; reversibly binds to circulating albumin, thus prolonging the product's half-life; first GH therapy to be administered once weekly instead of once daily for adult GHD)

Rukobia

Rukobia (fostemsavir), a human immunodeficiency virus type 1 (HIV-1) gp 120-directed attachment inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regiment due to resistance, intolerance, or safety considerations.

Coverage criteria:

Health plan A:

1. Rukobia will be approved based on both of the following criteria:
    a. Patient has been diagnosed with multidrug-resistant HIV-1 infection AND
    b. Patient is currently taking or will be prescribed an optimized background antiretroviral regimen

Health plan B:

A. Initial Therapy: Approve for 6 months if the individual meets ALL of the following conditions
    i. The individual is 18 years of age or older; AND
    ii. The individual has HIV-1 infection; AND
    iii. According to the prescriber, the individual is failing a current antiretroviral regimen HIV; and
    iv. According to the prescriber, the individual has exhausted at least FOUR of the following antiretroviral classes, defined as elimination of all antiretrovirals within a given class due to demonstrated or projected resistance to the agents(s) in that class OR due to significant intolerance:
        A. Nucleoside reverse transcriptase inhibitor
        B. Non-nucleoside reverse transcriptase inhibitor
        C. Protease inhibitor
        D. Fusion inhibitor
        E. Integrase strand transfer inhibitor
        F. CCR5-antagonist
    v. The requested agent will be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents: AND
    vi. The requested agent is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection
B. Individual currently on Rukobia: Approve for 1 year if the individual meets ALL of the following conditions:
    i. The individual has HIV-1 infection; AND
    ii. The requested agent will be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents: AND
    iii. The individual has responded to a Rukobia-containing regiment, as determined by the prescriber. Note: examples of a response are HIV RNA < 40 cells/mm^3, HIV-1 RNA $\geq$ 0.5 $\log_{10}$ reduction from baseline in viral load.

Health Plan C:

A. Multi-drug resistant HIV1 infection
    1. Documentation of a diagnosis of HIV and a baseline HIV RNA viral load of greater than ≥ 400 copies/mL [Documented within the past 30 days]
    2. Prescriber attestation of member adherence to highly active antiretroviral therapy for at least 6 months AND is failing, or has recently failed therapy within the past 8 weeks
    3. Documentation of current member's DC4 count [within past 30 days]
    4. Confirmation that the member has been prescribed and will continue to take an optimized background antiretroviral regiment (OBR), containing at least one antiretroviral agent that demonstrates full viral sensitivity/susceptibility must be submitted]
    5. Viral resistance to at least ONE agent from EACH of the FOUR classes of HIV antiretroviral medications (as single agent products or combination products), unless contraindicated or clinically significant adverse effects are experienced. Documented resistance as measured by resistance testing, completed while member is currently on therapy or within 4 weeks if possible.
        i. Protease inhibitor
        ii. Nucleoside reverse transcriptase inhibitor (NRTI)
        iii. Non-nucleoside reverse transcriptase inhibitor (NNRTI)

iv. Integrase inhibitors
v. CCR5 antagonists
vi. Entry inhibitors

6. Prescriber attestation that member is not concurrently taking any strong cytchromeP450 (CYP) 3Q inducers

Duration of approval – Initial authorization: 6 months, Continuation of Therapy: 12 months

Quantity 600mg – 60 tabs per 30 days

Prescriber requirements: prescribed by, or in consultation with, a board-certified infectious disease or HIV specialist. Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

Age restrictions – 18 years of age and older

Continuation of therapy:

1. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance) NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy AND
2. Documentation of decreased viral load and increased CD4 count from baseline – indicating clinically significant disease response and improvement AND
3. Member continues to take an optimized background regimen of antiretroviral therapy in combination with Rukobia

Medicaid State:

1. Patient is 18 years old and older
2. Prescribed in consultation with an infectious disease specialist
3. Resistance, intolerance, or contraindications to at least 4 antiretroviral therapies, including

Medication/Dose	Details of Failure	Chart Note Pg #
Nucleoside Reverse-Transcriptase Inhibitor (NRTI) Medication:		
Non-Nucleoside Reverse-Transcriptase Inhibitor (NNRTI) Medication:		
Protease inhibitor Medication:		
Fusion inhibitor Medication:		

4. Rukobia will be used concomitantly with other antiretroviral(s) indicated for the treatment of HIV-1 infection. Medication(s): _____ Chart note page #: ____
5. Patient is NOT taking CYP3A inducers concomitantly, which may significantly reduce fostemsavir plasma concentration, resulting in a loss of virologic response. These drugs include, but are not limited to:
    - Androgen receptor inhibitor: enzalutamide
    - Anticonvulsants: carbamazepine, phenytoin
    - Antimycobacterial: rifampin
    - Antineoplastic: mitotane o Herbal product: St John's wort (Hypericum perforatum)

Reauthorization: Updated letter with medical justification or updated chart notes demonstrating maintenance of virological suppression with HIV-1 RNA less than 50 copies/mL

Initial authorization: Up to 6 months
Re-authorization: Up to 1 year

Sotyktu (deucravacitinib)

-for treatment of moderate-to-severe plaque psoriasis, 6mg tablet once daily

Coverage criteria:

South Dakota Medicaid general psoriasis PA criteria:

1. Diagnosis of chronic plaque psoriasis **AND**
2. Patient is ≥ XX years of age **AND**
3. Prescribed by or in consultation with a dermatologist **AND**
4. The medication will not be used in combination with another biologic agent **AND**
5. Patient has had an inadequate response to, intolerance to, or contraindication to conventional therapy with at least one of the following: phototherapy or one or more oral systemic treatments (i.e., methotrexate, cyclosporine, acitretin, sulfasalazine, calcipotriene, tazarotene, corticosteroid)

State A:

1. Member is 18 years old and older
2. Diagnosis of psoriasis
3. Previous trial and failure of at least two other targeted immunomodulators
4. Patient does not have a history of targeted immunomodulator

State B:

1. Medical records confirming diagnosis of moderate to severe plaque psoriasis
2. Medical records confirming one of the following:
    a. At least 3% body surface area (BSA) involvement
    b. Severe scalp psoriasis
    c. Palmoplantar (i.e., palms, soles), facial, or genital involvement
3. Minimum duration of a 4-week trial and failure, contraindication, or intolerance to one of the following topical therapies
    a. corticosteroids (e.g., calcitriol, calcipotriene)
    b. tazarotene
    c. calcineurin inhibitors (e.g., tacrolimus, pimecrolimus)
    d. anthralin
    e. coal tar
4. Prescribed by or in consultation with a dermatologist
5. Trial and failure of preferred product
6. Not used in combination with other potent immunosuppressants (e.g., azathioprine, cyclosporine)

Reauthorization

1. Submission of medical records confirming positive clinical response to therapy as evidenced by one of the following:
    a. Reduction of body surface area (BSA) involvement from baseline
    b. Improvement in symptoms (e.g., pruritus, inflammation) from baseline

State C:

1. Diagnosis of plaque psoriasis
2. Trial and failure, contraindication, or intolerance to at least one topical treatment from the following:
    a. corticosteroid
    b. calcipotriene
    c. tazarotene
3. Trial and failure, contraindication, or intolerance to two preferred immunomodulators with the same indication.

Optum Rx®

Therapeutic Class Overview

Immunomodulators

Introduction

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), alopecia areata, and uveitis (UV), as well as several less common conditions. Immunomodulators that treat CD and UC are covered in a separate review (Inflammatory Bowel Disease Agents). In addition, immunomodulators that treat atopic dermatitis are covered in a separate review (Atopic Dermatitis Agents).
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (*Choy et al 2001*). This has led to the development of biologic agents to target these areas. The Food and Drug Administration (FDA) has currently approved 5 originator TNF inhibitors: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), and Simponi/Simponi Aria (golimumab), as well as numerous biosimilar TNF inhibitors: Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), Yusimry (adalimumab-aqvh), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda). Other immunomodulators targeting different cells and cytokines in the inflammatory and immune process are also FDA-approved. These include:
  - Orencia (abatacept), which inhibits CD28-B7 mediated costimulation of the T-cell.
  - Rituxan (rituximab), which targets CD20, a molecule that is found on the surface of B-cells.
    - Biosimilar products have also been approved: Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), and Riabni (rituximab-arrx).
  - Actemra (tocilizumab) and Kevzara (sarilumab), which have activity directed against the IL-6 receptor.
  - Kineret (anakinra), which targets the IL-1 receptor.
  - Ilaris (canakinumab), which binds to the IL-1ß receptor.
  - Stelara (ustekinumab), which targets the IL-12 and IL-23 cytokines.
  - Cosentyx (secukinumab) and Taltz (ixekizumab), which bind and neutralize IL-17A.
  - Siliq (brodalumab), an IL-17 receptor antagonist.
  - Tremfya (guselkumab), Skyrizi (risankizumab), and Ilumya (tildrakizumab-asmn), which are IL-23 antagonists.
- Oral immunomodulator agents on the market include:
  - Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Rinvoq (upadacitinib), and Olumiant (baricitinib), which target Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
  - Otezla (apremilast), a small-molecule phosphodiesterase 4 (PDE-4) inhibitor.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but not discussed in detail. These include:
  - Ilaris for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); 4) familial Mediterranean fever (FMF); and 5) adult-onset Still's disease.
  - Kineret for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA) and CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID).
  - Actemra for giant cell arteritis (GCA), cytokine release syndrome (CRS), and systemic sclerosis-associated interstitial lung disease (SSc-ILD).
  - Cimzia, Cosentyx, Rinvoq, and Taltz for non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
  - Orencia for prophylaxis of acute graft-versus-host disease (GVHD).
  - Otezla for treatment of adults with oral ulcers associated with Behçet disease.
  - Cosentyx (secukinumab) for enthesitis-related arthritis in patients 4 years and older.
- Rituxan and biosimilar products are also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA), and pemphigus vulgaris. These indications will not be discussed in this review.

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- Olumiant (baricitinib) has been approved for the treatment of COVID-19 in hospitalized patients requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Information on COVID-19-related indications will not be addressed in this review.
- Tysabri (natalizumab), an integrin receptor antagonist, is indicated for multiple sclerosis and CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; it is not included as a drug product in this review (*Tysabri prescribing information 2021*). Arcalyst (rilonacept), an interleukin-1 blocker indicated for CAPS, including FCAS and MWS, DIRA, and recurrent pericarditis is also not included in this review (*Arcalyst prescribing information 2021*).
- Although FDA-approved, the launch plans for many biosimilar drugs are pending and may be delayed; therefore, these agents are not currently included in this review (Purple Book: Database of Licensed Biological Products 2023).
- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*	Type of Agent
Actemra (tocilizumab)	-	Human monoclonal antibody targeting the IL-6 receptor
Amjevita (adalimumab-atto)	N/A‖	TNFα inhibitor
Avsola (infliximab-axxq)	N/A*	TNFα inhibitor
Cimzia (certolizumab)	-	TNFα inhibitor
Cosentyx (secukinumab)	-	Human monoclonal antibody to IL-17A
Enbrel (etanercept)	-‡	sTNFR fusion protein, TNFα inhibitor
Humira (adalimumab)	-†	TNFα inhibitor
Ilaris (canakinumab)	-	Human monoclonal antibody that binds to IL-1ß
Ilumya (tildrakizumab-asmn)	-	Human monoclonal antibody to IL-23
Inflectra (infliximab-dyyb)	N/A*	TNFα inhibitor
Kevzara (sarilumab)	-	Human monoclonal antibody targeting IL-6 receptor
Kineret (anakinra)	-	IL-1 receptor antagonist
Olumiant (baricitinib)	-	Small molecule Janus kinase (JAK) inhibitor
Orencia (abatacept)	-	sCTLA-4-Ig recombinant fusion protein
Otezla (apremilast)	-	Small-molecule phosphodiesterase 4 inhibitor
Riabni (rituximab-arrx)	N/A§	Anti-CD20 monoclonal antibody
Remicade (infliximab)	-*	TNFα inhibitor
Renflexis (infliximab-abda)	N/A*	TNFα inhibitor
Rinvoq (upadacitinib)	-	Small molecule Janus kinase (JAK) inhibitor
Rituxan (rituximab)	-§	Anti-CD20 monoclonal antibody
Ruxience (rituximab-pvvr)	N/A§	Anti-CD20 monoclonal antibody
Siliq (brodalumab)	-	Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA)
Simponi/Simponi Aria (golimumab)	-	TNFα inhibitor
Skyrizi (risankizumab-rzaa)	-	Human monoclonal antibody to IL-23
Stelara (ustekinumab)	-	Human monoclonal antibody targeting the IL-12 and IL-23 cytokines
Taltz (ixekizumab)	-	Human monoclonal antibody to IL-17A
Tremfya (guselkumab)	-	Human monoclonal antibody to IL-23 cytokine
Truxima (rituximab-abbs)	N/A§	Anti-CD20 monoclonal antibody

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Drug	Alternative Available (same molecular entity)*	Type of Agent
Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib)	-	Small molecule Janus kinase (JAK) inhibitor

**For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.
*Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), and Avsola (infliximab-axxq) have been FDA-approved as biosimilar agents to Remicade (infliximab).
†Abrilada (adalimumab-afzb), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), and Yusimry (adalimumab-aqvh have been FDA-approved as biosimilars to Humira (adalimumab). Cyltezo (adalimumab-adbm) is the only biosimilar product in this review that is designated interchangeable with its reference product, Humira (adalimumab). Further information regarding adalimumab biosimilars will be added to this review as these products launch.
‡Erelzi (etanercept-szzs) and Eticovo (etanercept-ykro) have been FDA-approved as biosimilars to Enbrel (etanercept). Further information on etanercept biosimilars will be included in this review as these products launch.
§Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), and Riabni (rituximab-arrx) have been FDA-approved as biosimilar agents to Rituxan (rituximab).
ǂAmjevita (adalimumab-atto) has been FDA-approved as biosimilar to Humira (adalimumab).

(Drugs@FDA, 2023; Purple Book: Database of Licensed Biological Products 2023)

Indications

Table 2. Food and Drug Administration Approved Indications (see footnotes for less common indications: oral ulcers associated with Behçet disease, CAPS, CRS, ERA, FMF, GCA, prophylaxis of acute GVHD, HIDS/MKD, NRAS, and TRAPS)***

Drug	Rheumatoid Arthritis (RA)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Hidradenitis Suppurativa (HS)	Uveitis (UV)	Alopecia areata
Actemraˠ (tocilizumab)	✔ *	✔ **	✔ **						
Amjevita (adalimumab-atto)	✔ ‡‡		✔ ∫	✔ ‡	✔ ∫∫	✔			
Avsola (infliximab-axxq)	✔ ⊥			✔ ‡‡‡	✔	✔			
Cimzia~~ (certolizumab)	✔			✔ ‡	✔	✔			
Cosentyx~~,▼▼▼ (secukinumab)				✔ ‡	✔ **	✔			

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Enbrel (etanercept)	✔ †		✔ **	✔ ‡	✔ †	✔			
Humira (adalimumab)	✔ ‡‡		✔ ∫	✔ ‡	✔ ∫∫	✔	✔ ↑	✔ ▼	
Ilaris” (canakinumab)		✔ **							
Ilumya (tildrakizumab-asmn)				✔ ‡					
Inflectra (infliximab-dyyb)	✔ ⊥			✔ ‡‡‡	✔	✔			
Kevzara (sarilumab)	✔ *								
Kineret▼▼ (anakinra)	✔ ∞								
Olumiant (baricitinib)	✔ *,⌂⌂								✔ ⌂⌂⌂⌂
Orencia∞∞∞ (abatacept)	✔ ∞∞		✔ ⌂		✔				

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Otezla~~~ (apremilast)				✔ △△△	✔				
Remicade (infliximab)	✔ ⊥			✔ ‡‡‡	✔	✔			
Renflexis (infliximab-abda)	✔ ⊥			✔ ‡‡‡	✔	✔			
Riabni'''' (rituximab-arrx)	✔ ǂ								
Rinvoq (upadacitinib)	✔ *,△△				✔ *,△△	✔ *,△△			
Rituxan''' (rituximab)	✔ ǂ								
Ruxience (rituximab-pvvr)	✔ ǂ								
Siliq (brodalumab)				✔ ǂǂ					
Simponi (golimumab)	✔ ┤				✔ ┤┤	✔			

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Drug	Rheumatoid Arthritis (RA)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Hidradenitis Suppurativa (HS)	Uveitis (UV)	Alopecia areata
Simponi Aria (golimumab)	✔ †		✔ **		✔ **	✔			
Skyrizi (risankizumab-rzaa)				✔ ‡	✔				
Sotyktu (deucravacitinib)				✔ ‡					
Stelara (ustekinumab)				✔ ‡	✔ ▼▼▼▼				
Taltz~~ (ixekizumab)				✔ ‡	✔	✔			
Tremfya (guselkumab)				✔ ‡	✔				
Truxima (rituximab-abbs)''''	✔ ǂ								
Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib)	✔ *,⌂⌂		✔ *,**,⌂⌂		✔ *,⌂⌂	✔ *,⌂⌂			

ŸActemra is also indicated for treatment of giant cell arteritis in adults, chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients ≥ 2 years, and adults with systemic sclerosis-associated interstitial lung disease.

*Patients with moderately to severely active RA who have had an inadequate response or intolerance to ≥ 1 disease-modifying anti-rheumatic drugs (DMARDs) (Actemra, Kevzara) or ≥ 1 tumor necrosis factor (TNF) antagonists (Olumiant, Rinvoq, Xeljanz).

**Patients 2 years and older.

†In combination with methotrexate (MTX) or used alone.

‡Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy, with the exception of Enbrel, which is indicated for the treatment of patients 4 years and older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy; Taltz and Cosentyx, which are indicated for the treatment of patients 6 years and older with moderate-to-severe PsO who are candidates for systemic therapy or phototherapy; Stelara, which is indicated for the treatment of patients 6 years and older with moderate to severe PsO.

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‡‡Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. Can be used alone or in combination with MTX or other DMARDs.
‡‡‡ Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
∫Indicated for reducing signs and symptoms of juvenile idiopathic arthritis (JIA) for patients 2 years of age and older. Can be used alone or in combination with MTX.
∫∫Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. Can be used alone or in combination with non-biologic DMARDs.
▼ Treatment of non-infectious intermediate, posterior and panuveitis in adult and pediatric patients 2 years of age or older.
↑ Treatment of moderate to severe hidrandenitis suppurative in patients 12 years of age or older.
▼▼Kineret is also indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS), including neonatal-onset multisystem inflammatory disease (NOMID), and for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA).
"Ilaris also indicated for the treatment of CAPS in adults and children 4 years of age and older including: familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients; hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients; familial Mediterranean fever (FMF) in adult and pediatric patients; and adult-onset Still's disease.
∞Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age or older who have failed one or more DMARDs. Can be used alone or in combination with DMARDs other than TNF blocking agents.
∞∞Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. May be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
⌂ Indicated for reducing signs and symptoms in pediatric patients 2 years and older with moderate to severely active polyarticular juvenile idiopathic arthritis (PJIA). May be used as monotherapy or with MTX.
⊥In combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.
'''Rituxan and Ruxience are also indicated for Non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA); Rituxan is additionally indicated for pemphigus vulgaris.
╪In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to ≥ 1 TNF antagonist therapies.
╪╪Treatment of moderate to severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.
┼ In combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA.
┼┼ Alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA.
┼┼┼ In combination with nonbiologic DMARDs.
~~Cimzia, Cosentyx, Rinvoq, and Taltz are also indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
~~~Otezla also indicated for treatment of adults with oral ulcers associated with Behçet disease.
''''Truxima and Riabni are also indicated for adults with NHL, CLL, GPA (Wegener's Granulomatosis) and MPA.
***Ruxience is indicated for NHL, CLL, GPA (Wegener's Granulomatosis) and MPA.
▼▼▼Cosentyx is also indicated for treatment of active ERA in patients 4 years of age and older.
∞∞∞Indicated for prophylaxis of acute graft vs host disease in combination with a calcineurin inhibitor and MTX in adults and pediatric patients ≥ 2 years undergoing hematopoietic stem cell transplantation from a matched or 1 allele-mismatched unrelated donor.
⌂⌂ Use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
⌂⌂⌂ Indicated for the treatment of adult patients who are candidates for phototherapy or systemic therapy.
⌂⌂⌂⌂ Indicated for severe alopecia areata in adults.
▼▼▼▼ Indicated for patients 6 years or older with active PsA.

(*Prescribing information: Actemra 2022; Amjevita 2022; Avsola 2021; Cimzia 2022; Cosentyx 2021; Enbrel 2022; Humira 2021; Ilaris 2020; Ilumya 2022; Inflectra 2022; Kevzara 2018; Kineret 2020; Olumiant 2022; Orencia 2021; Otezla 2021; Remicade 2021; Renflexis 2022; Riabni 2022; Rinvoq 2022; Rituxan 2021; Ruxience 2021; Siliq 2020; Simponi 2019; Simponi Aria 2021; Skyrizi 2022; Sotyktu 2022; Stelara 2022; Taltz 2022; Tremfya 2020; Truxima 2022; Xeljanz/Xeljanz XR/Xeljanz oral solution 2022)*

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

Clinical Efficacy Summary

Rheumatoid arthritis (RA)

- The approval of the subcutaneous (SQ) formulation of Orencia (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20) was not significantly different between the groups (*Genovese et al 2011*).

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- Orencia (abatacept), Remicade (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (n = 431). Enrolled patients had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after 6 months of treatment, some differences in favor of abatacept were evident after 1 year of treatment. After 1 year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (*Schiff et al 2008*).
- Treatment with Orencia (abatacept) was directly compared to treatment with Humira (adalimumab), when added to MTX, in a multicenter, investigator-blind, randomized controlled trial (n = 646) of RA patients with inadequate response to MTX. After 2 years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the 2 groups after 2 years of treatment. Rates of AEs were similar between treatment groups (*Schiff et al 2014*).
- Amjevita (adalimumab-atto) was compared with US-licensed Humira in patients with moderate to severe RA despite treatment with methotrexate in a randomized, double-blind, equivalence study *(Cohen et al 2017)*. Patients were randomized to Amjevita or adalimumab (40 mg) every 2 weeks. At week 24, the primary endpoint of ACR20 occurred in 74.6% and 72.4% of patients treated with Amjevita or Humira, respectively; because the 90% CI for risk ratio of ACR lay between 0.738 and 1.355, biosimilarity of Amjevita to Humira was established.
- The RAPID-1 and RAPID-2 studies compared Cimzia (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (*Keystone et al 2008, Smolen et al 2009a*). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks 0, 2, and 4 then 200 or 400 mg every 2 weeks attained greater ACR 20, ACR 50 and ACR 70 responses compared to patients on placebo and MTX, respectively, after 24 weeks ($p \leq 0.01$). The response rates were sustained with active treatment over 52 weeks (*Keystone et al 2008*). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (*Keystone et al 2008, Smolen et al 2009a*). A trial evaluated Cimzia (certolizumab) monotherapy vs placebo in patients with active disease who had failed at least 1 prior DMARD. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; $p < 0.001$). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy (*Fleischmann et al 2009*).
- More Cimzia (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, $p \leq 0.05$) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least 6 months (*Smolen et al 2015a*).
- A randomized, double-blind, placebo-controlled trial (n = 316) conducted in Japan compared Cimzia (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤ 12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (*Atsumi et al 2016*). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; $p < 0.001$). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population. In a long-term extension, a higher percentage of patients treated with certolizumab plus MTX experienced inhibition of radiographic progression (change from baseline in mTSS) at week 104 vs MTX alone (84.2% vs 67.5%; $p < 0.001$) (*Atsumi et al 2017*).
- The FDA approval of Simponi (golimumab) for RA was based on 3 multicenter, double-blind, randomized, controlled trials in 1,542 patients ≥ 18 years of age with moderate to severe active disease. A greater percentage of patients from all 3 trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 vs patients treated with MTX alone (*Emery et al 2009, Keystone et al 2009, Smolen et al 2009b*). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean

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Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI) (*Keystone et al 2009, Smolen et al 2009b*). Response with golimumab + MTX was sustained for up to 5 years (*Keystone et al 2013a, Smolen et al 2015b*).

- Simponi Aria (golimumab) was studied in patients with RA. In 1 trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg intravenously (IV) every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; p < 0.001) (*Kremer et al 2010*). In the GO-FURTHER trial (n = 592), golimumab 2 mg/kg IV or placebo was given at weeks 0, 4 and then every 8 weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [p < 0.001]) (*Weinblatt et al 2013*). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (*Bingham et al 2015*). In the GO-MORE trial, investigators treated patients with golimumab SQ for 6 months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ + IV group and the SQ golimumab group (*Combe et al 2014*).
- The efficacy and safety of Actemra (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients age ≥ 18 years with active RA. Patients were diagnosed according to ACR criteria, with at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given every 4 weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (*Emery et al 2008, Genovese et al 2008, Jones et al 2010, Kremer et al 2011, Smolen et al 2008*).
  - AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to 1 of 3 treatment arms, tocilizumab 8 mg/kg every 4 weeks, MTX 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (Jones et al 2010).
  - LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had 3 times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at 6 months as compared to MTX (33% vs 4%), and these rates continued to increase over time to 1 year (47% vs 8%) (*Kremer et al 2011*). These benefits were maintained or improved at 2 years with no increased side effects (*Fleishmann et al 2013*).
  - OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every 4 weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with < 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 (p < 0.001). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well (p < 0.001). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; p < 0.0296 for 4 mg/kg and p < 0.0082 for 8 mg/kg) (*Smolen et al 2008*).
  - TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful

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improvements in physical function when compared to placebo (60% vs 30%; p value not reported) (*Genovese et al 2008*).
  - RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to ≥ 1TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every 4 weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with Humira (adalimumab) and Remicade (infliximab), irrespective of the type or number of failed TNF antagonists (Emery et al 2008). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (*Gabay et al 2013*).
- More recently, results of a randomized, double-blind trial evaluating Actemra (tocilizumab) in early RA were published (*Bijlsma et al 2016*). Patients (n = 317) had been diagnosed with RA within 1 year, were DMARD-naïve, and had a DAS28 score of ≥ 2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 < 2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p < 0.0001 for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p = 0.06 for tocilizumab plus MTX vs MTX; p = 0.0356 for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the SQ formulation of Actemra (tocilizumab) was based on 1 multicenter, double-blind, randomized, controlled trial in patients (n = 1262) with RA. Weekly tocilizumab SQ 162 mg was found to be noninferior to tocilizumab IV 8 mg/kg every 4 weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (*Burmester et al 2014a*). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥ 0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (*Burmester et al 2016*). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ Actemra administered every other week (*Kivitz et al 2014*).
- A Phase 3 trial (MONARCH) evaluating the efficacy of Kevzara (sarilumab) monotherapy vs Humira (adalimumab) monotherapy for the treatment of patients with active RA with an inadequate response or intolerance to MTX reported superiority of sarilumab over adalimumab based on change from baseline in DAS28-ESR at week 24 (-3.28 vs -2.20; difference, -1.08; 95% CI, -1.36 to -0.79; p < 0.0001) (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab. Aside from the MONARCH trial, sarilumab has not been directly compared to any other biologic or tofacitinib. Nonetheless, 2 pivotal trials have shown the agent to be superior in achievement of ACR 50 when compared to MTX plus placebo, in both MTX inadequate responders and TNF inhibitor inadequate responder patients (*Genovese et al 2015, Fleischmann et al 2017*). Additionally, a meta-analysis of 4 randomized controlled trials (RCTs) has shown that ACR 50 response rates were significantly higher with sarilumab 200 mg and sarilumab 200 mg plus MTX when compared to MTX plus placebo (OR, 4.05; 95% CI, 2.04 to 8.33 and OR, 3.75; 95% CI, 2.37 to 5.72, respectively). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) suggested that sarilumab 200 mg was most likely to achieve ACR 50 response rate, followed by sarilumab 200 mg plus MTX, sarilumab 150 mg plus MTX, adalimumab 40 mg, and MTX plus placebo (*Bae et al 2018).*
- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the Xeljanz (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant decreases

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in fatigue and pain (*Fleishmann et al 2012*). In another Phase 3 study, Xeljanz (tofacitinib), when administered with background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to Humira (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab. Safety of tofacitinib continues to be monitored for long term effects (*van Vollenhoven et al 2012*). The ORAL Scan trial showed the ACR 20 response rates at month 6 for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo ($p < 0.0001$ for both comparisons) (*van der Heijde et al 2013*). Treatment effects were maintained through month 24 in the ORAL Scan trial, with an ACR 20 response rate of 50.5% and 58.3% for tofacitinib 5 mg and 10 mg twice daily, respectively (*van der Heijde et al 2019[a]*). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; $p < 0.001$) (*Lee et al 2014*). No radiographic progression was defined as a change from baseline in the modified total Sharp score of < 0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.

- In the ORAL Step study, patients with RA who had an inadequate response to ≥ 1 TNF inhibitors were randomized to Xeljanz (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (*Burmester et al 2013a, Strand et al 2015a*). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5 mg (41.7%; 95% CI, 6.06 to 28.41; $p = 0.0024$) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; $p < 0.0001$) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; $p < 0.0001$) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; $p < 0.0001$) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.
- The approval of Olumiant (baricitinib) was based on 2 confirmatory, 24-week, Phase 3 trials in patients with active RA. In RA-BEACON, enrolled patients (N = 527) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 TNF antagonist(s) (*Genovese et al 2016*). Patients received baricitinib once daily or placebo along with continuing a stable dose of a conventional DMARD. The primary endpoint, ACR 20 response at week 12, was achieved by 49% and 27% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$). In RA-BUILD, enrolled patients (N = 684) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 conventional DMARD(s) (*Dougados et al 2017*). Patients received baricitinib once daily or placebo; concomitant conventional DMARDs were permitted but not required. The primary endpoint, ACR20 response at week 12, was achieved by 66% and 39% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$). Disease control with baricitinib was maintained at 3 years follow up with no new safety signals (*Smolen et al 2021*).
- Approval of Rinvoq (upadacitinib) was based on clinical trials from the SELECT program in patients with RA. In SELECT-EARLY (n = 947), 52% of MTX-naïve patients treated with upadacitinib 15 mg daily achieved ACR 50 vs 28% treated with MTX at week 12, and at week 24, significantly more patients treated with upadacitinib 15 mg daily had no radiographic progression (87.5% vs 77.7%; $p < 0.01$) *(van Vollenhoven et al 2018)*. In SELECT-MONOTHERAPY (n = 648), 68% of patients with an inadequate response or intolerance to MTX (MTX-IR) treated with upadacitinib 15 mg daily achieved ACR 20 vs 41% treated with continued MTX at week 14 *(Smolen et al 2019)*. In SELECT-COMPARE, which evaluated MTX-IR patients (n = 1629), ACR 20 was significantly more frequent with upadacitinib 15 mg daily vs placebo and vs adalimumab at week 12 (70.5% vs 36.4% and 63%, respectively; $p < 0.001$ and $p < 0.05$) and at week 26 (67.4% vs 35.6% and 57.2%, respectively; $p <0.001$ and $p <0.01$). At week 26, significantly more patients treated with upadacitinib had no radiographic progression vs placebo (83.5% vs 76.0%; $p < 0.001$) *(Fleischman et al 2018)*. Differences between upadacitinib and adalimumab were maintained for up to 3 years of treatment (*Fleischmann et al 2022*). In SELECT-BEYOND (n = 499), 65% of biologic-IR patients treated with upadacitinib 15 mg daily plus conventional DMARDs achieved ACR 20 vs 28% treated with placebo plus conventional DMARDs at week 12 ($p <0.0001$) *(Genovese et al 2018)*. A network meta-analysis of the SELECT trials found that upadacitinib plus MTX was more effective than MTX alone, and upadacitinib 15 mg plus MTX was most likely to achieve the best ACR 20 response rate (followed by upadacitinib 30 mg plus MTX, adalimumab 40 mg plus MTX, upadacitinib 30 mg, upadacitinib 15 mg, and MTX, in order) (*Song and Lee 2020*).
- A meta-analysis investigated the relative efficacy and safety profiles of tofacitinib, baricitinib, upadacitinib, and filgotinib (not approved in the US) in patients with active RA refractory to biologics (*Lee et al 2021*). The ranking probability based on the SUCRA suggested that upadacitinib had the highest probability of being the best treatment for achieving ACR20, followed by filgotinib (200 mg), baricitinib, filgotinib (100 mg), and tofacitinib. For achievement of ACR50, the SUCRA suggested that baricitinib was the best treatment, followed by filgotinib (200 mg), tofacitinib, upadacitinib, and filgotinib

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(100 mg). Tofacitinib was superior to filgotinib (100 mg) and upadacitinib for achievement of ACR70. Tofacitinib and filgotinib (200 mg) showed a significantly lower serious adverse event rate than upadacitinib.

- A 24-week, Phase 3, double-blind trial explored the efficacy of upadacitinib compared with abatacept in 612 patients with RA. The mean change in the Disease Activity Score for 28 joints based on C-reactive protein (DAS28-CRP) was -2.52 in the upadacitinib group and -2.00 in the abatacept group from baseline to week 12 (difference, -0.52 points; 95% CI, -0.69 to -0.35; p < 0.001 for noninferiority; p < 0.001 for superiority). Additionally, 30% of patients in the upadacitinib group and 13.3% of patients in the abatacept group achieved remission (difference, 16.8%; 95% CI, 10.4 to 23.2; p < 0.001 for superiority) (*Rubbert-Roth et al 2020*).
- Inflectra (infliximab-dyyb) was evaluated and compared to Remicade (infliximab; European Union formulation) in PLANETRA (N=606), a double-blind, multicenter, randomized trial (*Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the Remicade and Inflectra groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the 2 products.
  - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
  - In the extension study (n = 302) through 102 weeks, all patients received Inflectra. Response rates were maintained, with no differences between the Inflectra maintenance group and the group who switched from Remicade to Inflectra.
- Renflexis (infliximab-abda) was evaluated and compared to Remicade (infliximab; European Union formulation) in 584 patients in a double-blind, multicenter, randomized Phase 3 trial (*Choe et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 64.1% and 66.0% of patients in the Renflexis and Remicade groups, respectively (TD, -1.88%; 95% CI, -10.26% to 6.51%) (per-protocol population). Equivalence was demonstrated between the 2 products.
  - Secondary endpoints were also very similar between the 2 groups.
  - At week 54 of this trial, patients transitioned into the switching/extension phase, in which patients initially taking Remicade were re-randomized to continue Remicade or switch to Renflexis; patients initially taking Renflexis continued on the same treatment. Although slight numerical differences were observed, there was consistent efficacy over time across treatments and the proportions of patients achieving ACR responses were comparable between groups (*Renflexis FDA clinical review 2017*).
- Avsola (infliximab-axxq) was evaluated and compared to Remicade (infliximab) in 558 patients in a double-blind, multicenter, randomized equivalence trial (*Genovese et al 2020*). The primary endpoint, ACR 20 at week 22, was achieved by 68.1% and 59.1% of patients in the Avsola and Remicade groups, respectively (TD, 9.37%; 90% CI, 2.67% to 15.96%). The upper bound exceeded the pre-specified equivalence criteria by 0.96% such that superiority could not be ruled out statistically. In a post hoc analysis with adjustment for imbalances in baseline factors, the CI was narrowed (90% CI, 0.75% to 13.62%). Secondary endpoints were also very similar between the 2 groups.
- Two studies, 1 double-blind and 1 open-label, evaluated Rituxan (rituximab) in patients who had failed treatment with a TNF blocker (*Cohen et al 2006, Haraoui et al 2011*). All patients continued to receive MTX. Both studies showed > 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (*Lopez-Olivo et al 2015*) examined Rituxan (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression (70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life (QoL).
- In the open-label ORBIT study (n = 295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either Rituxan (rituximab) (n = 144) or a TNF inhibitor (physician/patient choice of Enbrel [etanercept] or Humira [adalimumab]; n = 151) (*Porter et al 2016*). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.
  - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified noninferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was noninferior to initial TNF inhibitor treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high

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percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).

- Truxima (rituximab-abbs) was compared to Rituxan (rituximab) in 372 patients in a double-blind, multicenter, randomized Phase 3 trial (*Park et al 2018*). The primary efficacy endpoint, change from baseline in DAS28 based on C-reactive protein (CRP) at week 24, was -2.13 and -2.09 for Truxima and Rituxan, respectively (TD, -0.04; 95% CI, -0.29 to 0.21). Equivalence was demonstrated between the 2 products. Secondary endpoints were also very similar between the 2 groups.
  - In an extension of this study, 330 patients received a second 24-week course of their assigned study drug (Truxima or Rituxan) (Suh et al 2019). Mean change in DAS28-CRP from baseline to week 48 was similar between groups (-2.7 and -2.6 for Truxima and Rituxan, respectively). ACR 20/50/70 responses were also similar between groups at week 48.
  - After week 48, 295 patients entered a second extension phase that continued until week 72; during this extension phase, patients who were previously receiving Truxima or Rituxan (European Union formulation) received Truxima, while patients who were previously receiving Rituxan (United States formulation) were randomized 1:1 to continue receiving Rituxan (United States formulation) or switch to Truxima (Shim et al 2019). All patients experienced similar improvements in disease activity parameters, including DAS28 and ACR response rates. Switching from Rituxan to Truxima did not result in any clinically meaningful efficacy differences.
- Riabni (rituximab-arrx) was compared to Rituxan (rituximab) in a double-blind, multicenter, randomized controlled trial (*Burmester et al 2020*). The primary efficacy endpoint, change from baseline in DAS28-CRP at week 24, was -2.197 and -2.125 for Riabni and Rituxan, respectively (difference between means, -0.02%; 90% CI, -0.225 to 0.264). Equivalence was demonstrated between the 2 products.
- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (*Gottenberg et al 2016*). Patients (n = 300) were randomized to receive a second TNF inhibitor (n = 150) or a non-TNF-targeted biologic (n = 150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), and Remicade (infliximab), and the non-TNF biologics included Actemra (tocilizumab), Rituxan (rituximab), and Orencia (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of > 1.2 points resulting in a score of ≤ 3.2.
  - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (p = 0.003 or p = 0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious AEs (p = 0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.
- Another recent randomized trial (*Manders et al 2015*) evaluated the use of Orencia (abatacept) (n = 43), Rituxan (rituximab) (n = 46), or a different TNF inhibitor (n = 50) in patients (n =139) with active RA despite previous TNF inhibitor treatment. Actemra (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined Orencia (abatacept) for the treatment of RA. ACR 50 response was not significantly different at 3 months but was significantly higher in the abatacept group at 6 and 12 months compared to placebo (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (*Maxwell et al 2009*).
- The safety and efficacy of Humira (adalimumab) for the treatment of RA were assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses, respectively, at 6 months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious (*Navarro-*

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Sarabia et al 2005). In another study, patients received adalimumab 20 mg or 40 mg every other week for 1 year, and then could receive 40 mg every other week for an additional 9 years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (*Keystone et al 2013b*).

- A Phase 3, open-label study evaluated the long-term efficacy of Humira (adalimumab) for RA. Patients receiving adalimumab in 1 of 4 early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis; however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (*Furst et al 2015*).
- A Cochrane review was performed to compare Kineret (anakinra) to placebo in adult patients with RA. Significant improvements in both primary (ACR 20, 38% vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (*Mertens et al 2009*).
- In another Cochrane review, Enbrel (etanercept) was compared to MTX or placebo in adult patients with RA and found that at 6 months, 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39% and 15%, respectively, in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups, respectively. Etanercept 10 mg twice weekly was only associated with significant ACR 20 (51% vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24% vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (*Blumenauer et al 2003*). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (*O'Dell et al 2013*).
- A more recent Cochrane review (*Singh et al 2016a*) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included Xeljanz (tofacitinib) and 9 biologics (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Rituxan [rituximab], and Actemra [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:
  - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
  - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
  - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS < 1.6 or DAS28 < 2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
  - Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
  - Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.
- A similar Cochrane review focused on the use of biologic or Xeljanz (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (*Singh et al 2016[b]*). A total of 41 randomized trials (n = 14,049) provided data for this review. Key results are as follows:
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.

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  - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or Xeljanz (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (*Singh et al 2017[a]*). The review included 12 randomized trials (n = 3,364). Key results are as follows:
  - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.
  - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.
  - There were no published data for tofacitinib monotherapy vs placebo.
  - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- In another meta-analysis, ACR 20 and ACR 70 response rates for Xeljanz (tofacitinib) 5 mg and 10 mg were comparable to the other monotherapies (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Actemra [tocilizumab]) at 24 weeks (*Bergrath et al 2017*). ACR 50 response rates were also comparable for tofacitinib 10 mg and other monotherapies. At 24 weeks, ACR 20/50/70 response rates for the combination of tofacitinib 5 mg or 10 mg plus conventional DMARD were comparable to other biologic plus conventional DMARD therapies except tofacitinib 5 mg plus conventional DMARD and tofacitinib 10 mg plus conventional DMARD were both superior to certolizumab 400 mg every 4 weeks plus conventional DMARD for achieving ACR 70 response (OR, 59.16; [95% CI, 2.70 to infinity]; and OR, 77.40; [95% CI, 3.53 to infinity], respectively).
- A Bayesian network meta-analysis of 5 randomized trials (n = 1,547) examined the efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib (not approved in the U.S.) and peficitinib (not approved in the U.S.) in patients with RA. The ranking probability based on SUCRA revealed the following agents with the highest probability to achieve the ACR 20 response rate: peficitinib 150 mg (highest probability) followed by peficitinib 100 mg, filgotinib 200 mg, filgotinib 100 mg, tofacitinib 5 mg, upadacitinib 15 mg, baricitinib 4 mg, and placebo *(Ho Lee at al 2020)*.
- A meta-analysis of 20 randomized trials (n = 8,982) assessed the efficacy of tofacitinib, baricitinib, and upadacitinib in patients with RA. Tofacitinib 10 mg (RR, 2.48; 95% CI, 1.97 to 3.14; $p < 0.001$) had to the highest ACR20 response rates followed by tofacitinib 5 mg (RR, 2.16; 95% CI, 1.81 to 2.58; $p < 0.001$). Tofacitinib displayed higher ACR 20 response rates compared with baricitinib and upadacitinib (*Wang et al 2020*).
- Another recent Cochrane review (*Hazelwood et al 2016*) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or Xeljanz (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effect was small.
- A network meta-analysis of individual patient data from 38 randomized controlled trials compared various MTX-biologic combinations for RA in patients with an inadequate response to MTX alone (*Janke et al 2020*). Anakinra plus MTX showed relatively less benefit than other combinations in terms of clinical remission or low disease activity, and certolizumab plus MTX showed relatively higher rates of serious adverse events or infections; however, differences between combinations were generally minor.
- An additional Cochrane review evaluated biologics for RA in patients naïve to MTX in 19 studies (*Singh et al 2017[b]*). Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), Remicade (infliximab), Orencia (abatacept), and Rituxan (rituximab). When combined with MTX, use of biologics showed a benefit in ACR 50 vs comparator (MTX/MTX plus methylprednisolone) (RR, 1.40; 95% CI, 1.30 to 1.49) and in RA remission rates (RR, 1.62; 95% CI, 1.33 to 1.98), but no difference was found for radiographic progression. When used without MTX, there was no significant difference in efficacy between biologics and MTX.
- A meta-analysis evaluated the efficacy of Remicade (infliximab) in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared

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to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03) (*Wiens et al 2009*).

- Another meta-analysis of randomized controlled trials included Humira (adalimumab), Kineret (anakinra), Enbrel (etanercept), and Remicade (infliximab) with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.7 (95% CI, 0.9 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) and with etanercept 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed, and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.5; $p < 0.05$) (*Nixon et al 2007*).
- The Agency for Healthcare Research and Quality published a review of drug therapy to treat adults with RA (*Donahue et al 2012*). They concluded that there is limited head-to-head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of 2 biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- A meta-analysis of 6 trials (n = 1,927) evaluated the efficacy of withdrawing biologics from patients with RA who were in sustained remission or had low disease activity (*Galvao et al 2016*). The biologics in the identified trials were TNF inhibitors, most commonly Enbrel (etanercept) or Humira (adalimumab). Compared to withdrawing the medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.

Ankylosing spondylitis (AS)

- The FDA approval of Humira (adalimumab) for the treatment of AS was based on 1 randomized, double-blind, placebo-controlled study (n = 315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab (58% vs 21% with placebo; $p < 0.001$). A greater than 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness that is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients ($p < 0.001$) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group ($p < 0.001$) (*van der Heijde et al 2006*).
- In 2 double-blind, randomized, placebo-controlled trials, the efficacy of Enbrel (etanercept) was evaluated in patients with AS (*Calin et al 2004, Gorman et al 2002*). Etanercept had a significantly greater response to treatment compared to placebo ($p < 0.001$) (*Gorman et al 2002*). More patients achieved an ASAS 20 response compared to placebo ($p < 0.001$) (*Calin et al 2004*). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while efficacy endpoints included ASAS 20 response, ASAS 5/6 response and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache, and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144, and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance (*Davis et al 2008*). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 ($p < 0.0001$). There were also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group ($p < 0.0001$ for both) (*Braun et al 2011*).
- The FDA approval of Simponi (golimumab) for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least 3 months (n = 356). Golimumab with or without a DMARD was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of

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AS demonstrated by the percentage of patients achieving an ASAS 20 response at week 14 (*Inman et al 2008*). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to 5 years in an open-label extension trial (*Deodhar et al 2015*). Safety profile through 5 years was consistent with other TNF inhibitors.

- The efficacy of Remicade (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There were significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks ($p < 0.0001$) (*Braun et al 2002*), At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group ($p < 0.001$) (*van der Heijde et al 2005*).
- Inflectra (infliximab-dyyb) was evaluated alongside Remicade (infliximab; European Union formulation) for the treatment of AS in PLANETAS (n = 250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between Inflectra and Remicade. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the Remicade and Inflectra groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
  - In the extension study (n = 174) through 102 weeks, all patients received Inflectra. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.
- The efficacy of Cimzia (certolizumab) for the treatment of AS was established in 1 randomized, double-blind, placebo-controlled study (n = 325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every 2 weeks and certolizumab 400 mg every 4 weeks compared to placebo at 12 weeks (*Landewe et at 2014*). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (*Sieper et al 2015a*). A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis, which includes AS (*Sieper et al 2015b*).
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (*Baeten et al 2015*). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, $p < 0.001$ for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20 responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo group ($p < 0.001$ for secukinumab 150 mg vs placebo; $p = 0.10$ for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52. In a long-term extension of MEASURE 1, ASAS 20 response rates were 73.7% with secukinumab 150 mg and 68.0% with 75 mg at week 104 and in MEASURE 2, ASAS 20 response rates were 71.5% with both doses at week 104 (*Braun et al 2017, Marzo-Ortega et al 2017*). In a 3-year extension of MEASURE-1, ASAS 20/40 response rates were 80.2%/61.6% for secukinumab 150 mg and 75.5%/50.0% for secukinumab 75 mg at week 156 (*Baraliakos et al 2017*). Four-year results from MEASURE-1 demonstrated sustained efficacy with ASAS 20/40 response rates of 79.7%/60.8% and 71%/43.5% with secukinumab 150 mg and 75 mg, respectively, at week 208 (*Braun et al 2018*).
- The efficacy and safety of Taltz (ixekizumab) were evaluated in the Phase 3 randomized, double-blind, placebo-controlled COAST-V and COAST-W trials. In total, 657 patients were studied in these trials, including biologic DMARD-naïve patients in COAST-V and patients with previous inadequate response or intolerance to TNF inhibitors in COAST-W. The primary endpoint in both trials, ASAS 40 response at week 16, was significantly improved with ixekizumab every 4 weeks vs placebo (48% vs 18% in COAST-V, $p < 0.0001$; 25% vs 13% in COAST-W, $p < 0.017$). Common adverse events included nasopharyngitis, upper respiratory tract infection, neutropenia, and infection *(van der Heijde et al 2018[a]; Deodhar et al 2019[a])*. The ASAS 40 response seen at week 16 was sustained through week 52 in both trials and through 3 years in 1 trial (*Dougados et al 2020, van der Heijde et al 2022[a]*).
- Efficacy and safety of Xeljanz (tofacitinib) in AS were assessed in a placebo-controlled, randomized, double-blind trial in 269 patients with active disease *(Deodhar et al 2021)*. Patients were randomized to double-blind tofacitinib 5 mg twice daily or placebo for 16 weeks, followed by an additional 32 weeks of treatment with tofacitinib 5 mg twice daily in all patients. The primary endpoint of ASAS 20 response at week 16 was significantly improved in patients treated with tofacitinib compared with placebo (56% vs 29%, respectively; $p < 0.0001$).

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- Efficacy and safety of Rinvoq (upadacitinib) in AS were assessed in 2 randomized controlled trials, SELECT-AXIS 1 and SELECT-AXIS 2 (*van der Heijde et al 2019[b]; van der Heijde et al 2022[b]*). SELECT-AXIS 1 randomized 187 biologic-naïve patients with active AS to receive upadacitinib 15 mg daily or placebo and found that more patients in the upadacitinib group achieved an ASAS 40 response at week 14 (52% vs 26%; p = 0.0003) (*van der Heijde et al 2019[b]*). Clinical response was maintained for up to 2 years in the open label extension phase of SELECT-AXIS 1 (*van der Heijde et al 2022[c]*). SELECT-AXIS 2 randomized 420 patients with active AS and inadequate response to biologic DMARDs to receive upadacitinib 15 mg daily or placebo and found that more patients in the upadacitinib group achieved an ASAS 40 response at week 14 (45% vs 18%; p < 0.0001) (*van der Heijde et al 2022[b]*).
- In 2 systematic reviews of TNF blockers for the treatment of AS, patients taking Simponi (golimumab), Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21 (95% CI, 1.91 to 2.56) (*Machado et al 2013*). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (*Maxwell et al 2015*). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, Cosentyx (secukinumab), and Actemra (tocilizumab; not FDA-approved for AS) (*Chen et al 2016*). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.
- A Bayesian network meta-analysis of 6 randomized controlled trials compared upadacitinib, secukinumab, tofacitinib, and filgotinib (not approved in the US) for the treatment of AS and found no statistically significant difference in ASAS response rates between these agents (*Lee 2022*).

Hidradenitis suppurativa (HS)

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated Humira (adalimumab) for the treatment of HS (*Kimball et al 2016*). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of 2 treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week 0, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
  - The primary endpoint was HS 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 count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (p = 0.003) and 58.9% vs 27.6% in PIONEER II (p < 0.001).
  - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
  - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

Juvenile idiopathic arthritis (JIA)

- In a trial of pediatric patients (6 to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with Orencia (abatacept) (p = 0.0003). The time to flare was significantly different favoring abatacept (p = 0.0002) (*Ruperto et al 2008*).
- Humira (adalimumab) was studied in a group of patients (4 to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to MTX use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX,

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flares occurred in 43% receiving adalimumab and 71% receiving placebo (p = 0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (p = 0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment (*Lovell et al 2008*).

- A double-blind, multicenter, randomized controlled trial compared Humira (adalimumab) and placebo in 46 children ages 6 to 18 years with enthesitis-related arthritis (*Burgos-Vargas et al 2015*). Patients were TNF inhibitor naïve. At week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, p = 0.039). A total of 7 patients (3 placebo; 4 adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo -32.1; p = 0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.
- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, Enbrel (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; p = 0.003) (*Lovell et al 2000*). Ninety-four percent of patients who remained in an open-label 4 year extension trial met ACR Pedi 30; CRP levels, articular severity scores, and patient pain assessment scores all decreased. There were 5 cases of serious AEs related to etanercept therapy after 4 years (*Lovell et al 2006*).
- The approval of Actemra (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (n = 112). Children aged 2 to 17 years of age with active SJIA and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85% vs 24%; p < 0.0001) (*De Benedetti et al 2012*). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (*Brunner et al 2015*). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; p < 0.0024). Disease control with tocilizumab was maintained at 2 years follow up with no new safety signals (*Brunner et al 2021*).
- The approval of Simponi Aria (IV golimumab) for polyarticular JIA was based on an open-label Phase 3 study (n = 127). Children 2 to < 18 years of age with active polyarticular course JIA and inadequate response to MTX were enrolled. The primary endpoints were pharmacokinetic exposure and model-predicted steady-state area under the curve (AUC_{ss}) over an 8-week dosing interval at weeks 28 and 52. Other endpoints included ACR response rates. The ACR 30, 50, 70, and 90 response rates were 84%, 80%, 70%, and 47%, respectively, at week 28. Golimumab serum concentrations and AUC_{ss} were 0.40 mcg/mL and 399 mcg•day/mL at week 28. ACR response rates, serum concentrations, and AUC_{ss} were maintained at week 52 (*Ruperto et al 2021[a]*).
- The approval of Xeljanz/Xeljanz oral solution (tofacitinib) for polyarticular JIA was based on a 44-week study (n = 225) that enrolled patients 2 to 17 years old with polyarticular course JIA and inadequate responses to at least 2 DMARDs. The primary endpoint was the occurrence of disease flare at week 44. Compared with patients receiving placebo, patients receiving tofacitinib experienced significantly fewer disease flares (31% with tofacitinib vs 55% with placebo; difference in proportions -25% [95% CI, -39% to -10%]; p = 0.0007) (*Xeljanz prescribing information 2022, Ruperto et al 2021[b]*).
- In 2 trials in patients with SJIA, Ilaris (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (*Ruperto et al 2012*). Patients enrolled in these trials were eligible for an open-label extension and were followed for 5 years. At 3 years, aJIA-ACR 50/70/90 response rates were 54.8%, 53.7%, and 49.7%, respectively (*Ruperto et al 2018*).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; 1 each for Kineret (anakinra), Ilaris (canakinumab), and Actemra (tocilizumab), and 2 for rilonacept (not FDA-approved for JIA and not included in this review) (*Tarp et al 2016*). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.

Plaque psoriasis (PsO)

- In a randomized, double-blind, double-dummy trial, Humira (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the

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adalimumab group achieved the primary endpoint compared to patients in the MTX ($p < 0.001$) and placebo ($p < 0.001$) groups, respectively (*Saurat et al 2008*).

- Amjevita (adalimumab-atto) was compared with US-licensed Humira in a randomized, double-blind, multicenter study in patients with moderate to severe psoriasis and intolerance or non-response to ≥ 1 conventional systemic therapy *(Papp et al 2017[a])*. At week 16, the primary endpoint of PASI change from baseline was within the predefined equivalence margin of ± 15 (least-squares mean difference, -2.18; 95% CI, -7.39 to 3.02), demonstrating similarity of Amjevita to Humira.
  - At week 16, patients treated with Amjevita who had ≥ 50% improvement in the PASI score continued Amjevita, whereas Humira-treated patients were rerandomized to either Amjevita or Humira *(Papp et al 2017[b])*. At up to 52 weeks of treatment, patients who were rerandomized to transition from Humira to Amjevita achieved similar improvement in PASI scores as those who continued treatment with Humira.
- More than 2,200 patients were enrolled in 2 published, pivotal, Phase 3 trials that served as the primary basis for the FDA approval of Stelara (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks 0, 4, and every 12 weeks thereafter (*Leonardi et al 2008, Papp et al 2008, Langley et al 2015*). In PHOENIX 1, patients who were initially randomized to ustekinumab at week 0 and achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 ($p < 0.0001$ for both). PASI 75 response was better maintained to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 ($p < 0.0001$) (*Leonardi et al 2008*). In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compared to patients receiving placebo ($p < 0.0001$). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every 8 weeks. More partial responders at week 28 who received 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no such response to changes in dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (*Papp et al 2008*). A total of 70% (849 of 1212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (*Langley et al 2015*).
- In a study comparing Enbrel (etanercept) and Stelara (ustekinumab), a greater proportion of PsO patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; $p = 0.01$ vs ustekinumab 45 mg; $p < 0.001$ vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7% vs 0.7% of all ustekinumab patients) (*Griffiths et al 2010).*
- Approval of Otezla (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1,257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a 75% improvement on the PASI 75. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs 5.3%; $p < 0.0001$) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; $p < 0.0001$) at 16 weeks (*Papp et al 2015, Paul et al 2015a*).
  - Additional analyses of the ESTEEM trials have been published. In 1 analysis (*Thaçi et al 2016*), the impact of apremilast on HRQoL, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (Rich et al 2016), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50% reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.
- Otezla (apremilast) has additionally been studied in patients with moderate to severe PsO of the scalp in the Phase IIIb, double-blind, randomized, placebo-controlled STYLE trial. In this trial, 303 patients with moderate to severe scalp PsO

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who had an inadequate response to 1 or more topical scalp therapies were randomized 2:1 to receive apremilast 30 mg twice daily (with a titration period) or placebo for 16 weeks. The primary endpoint was the proportion of patients achieving ScPGA response (score of 0 or 1 with a ≥ 2-point reduction from baseline) at week 16. Patients receiving apremilast were more likely to achieve ScPGA response at week 16 (43.3% vs 13.7%; p < 0.0001) (*Van Voorhees et al 2020*).

- Otezla (apremilast) has also been studied in patients with mild to moderate PsO in a double-blind, placebo-controlled study *(Stein Gold et al 2022)*. Patients with inadequate response or intolerance to ≥ 1 topical therapy (N = 595) were randomized to apremilast 30 mg twice daily or placebo. At week 16, the primary endpoint of static Physician Global Assessment response was significantly greater with apremilast compared with placebo (21.6% vs 4.1%; p < 0.0001).
- Cosentyx (secukinumab) was evaluated in 2 large, Phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
  - In ERASURE (n = 738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
  - In FIXTURE (n = 1306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, Enbrel (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
- Two smaller, Phase 3, double-blind, placebo-controlled trials evaluated Cosentyx (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
  - In FEATURE (n = 177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (*Blauvelt et al 2015*).
  - In JUNCTURE (n = 182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (*Paul et al 2015b*).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of Cosentyx (secukinumab) (*Blauvelt et al 2015, Langley et al 2014, Paul et al 2015b*).
- In the CLEAR study, Cosentyx (secukinumab) 300 mg SQ every 4 weeks and Stelara (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (*Thaçi et al 2015*). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; p < 0.0001). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; p < 0.0001). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.
- Cosentyx (secukinumab) and Stelara (ustekinumab) were also compared in the 16-week randomized, double-blind CLARITY trial, which included 1102 patients with moderate to severe PsO. The co-primary endpoints were proportion of patients achieving PASI 90 response at week 12 and modified IGA score of 0/1 at week 12. Secukinumab was found be to superior to ustekinumab for both PASI 90 response (66.5% vs 47.9%; p < 0.0001) and modified IGA score of 0/1 (72.3% vs 55.3%; p < 0.0001) (*Bagel et al 2018*). The significant trend of benefit for secukinumab over ustekinumab was maintained at 52 weeks with no new safety signals (*Bagel et al 2021*).
- The efficacy of Cosentyx (secukinumab) in children 6 years of age and older with moderate to severe PsO was established in a multicenter, randomized, double-blind, active-controlled trial that enrolled 162 patients (*Bodemer et al 2021*). Patients were randomized to secukinumab low- or high-dose groups, etanercept, or placebo. In the secukinumab groups, patients with body weight < 25 kg received 75 mg (categorized as both low-dose [LD] and high-dose [HD] for this weight range), those with body weight 25 to < 50 kg received either 75 mg (LD) or 150 mg (HD), and those with body weight ≥ 50 kg received either 150 mg (LD) or 300 mg (HD). There was a significant trend of benefit in favor of LD and HD secukinumab over placebo for PASI 75 at week 12 (80.0% and 77.5%, respectively vs 14.6%; p < 0.0001 for both comparisons to placebo) and IGA score improvement to 0 or 1 (70% and 60%, respectively, vs 4.9%; p < 0.0001

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for both comparisons to placebo). Statistical significance in favor of LD and HD secukinumab was also reached for comparisons to etanercept with regard to IGA score improvement to 0 or 1 (70% and 60%, respectively vs 34.1%; $p < 0.05$) and PASI 90 (72.5% and 67.5% vs 29.3%; $p < 0.05$).

- A meta-analysis of 7 Phase 3 clinical trials demonstrated the efficacy of Cosentyx (secukinumab) vs placebo and vs Enbrel (etanercept) in patients with PsO (*Ryoo et al 2016*). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the 1-year trials.
- The use of Taltz (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
  - UNCOVER-1 (n = 1296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (*Gordon et al 2016*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively ($p < 0.001$ for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively ($p < 0.001$ for both doses vs placebo). Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.
  - UNCOVER-2 (n = 1224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (*Griffiths et al 2015*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
  - UNCOVER-3 (n = 1346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (*Griffiths et al 2015*). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
  - Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (*Gordon et al 2016*). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.
- The IXORA-Q study (n = 149) evaluated the efficacy of Taltz (ixekizumab) to placebo in patients with moderate-to-severe genital psoriasis. At week 12, ixekizumab was superior to placebo for the primary endpoint of the proportion of patients achieving a score of 0 or 1 on the static PGA of genitalia (73% vs 8%, $p < 0.001$) (*Ryan et al 2018*).
- The IXORA-S study (n = 676) was a head-to-head study that compared Taltz (ixekizumab) (160 mg LD, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks) to Stelara (ustekinumab) (45 mg or 90 mg weight-based dosing per label) (*Reich et al 2017[b]).* The primary endpoint, PASI 90 response at week 12, was achieved by 72.8% and 42.2% of patients in the ixekizumab and ustekinumab groups, respectively ($p < 0.001$); superior efficacy of ixekizumab

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was maintained through week 24. Response rates for PASI 75, PASI 100, and PGA 0 or 1 also favored ixekizumab over ustekinumab (adjusted p < 0.05).

- The IXORA-R study (n = 1027) compared Taltz (ixekizumab) to Tremfya (guselkumab) in adults with moderate-to-severe PsO (*Blauvelt et al 2021*). At week 24, ixekizumab was found noninferior to guselkumab for achievement of PASI 100 (50% vs 52%, respectively; difference, -2.3%; 95% CI, -8.4 to 3.8 [within the 11.4% noninferiority margin]); statistical significance was not reached for this comparison (p = 0.41).
- The use of Siliq (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
  - AMAGINE-1 (n = 661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12 (*Papp et al 2016*). This 12-week induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥ 2 and those initially receiving placebo received brodalumab 210 mg every 2 weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥ 3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).
  - AMAGINE-2 (n = 1831) and AMAGINE-3 (n = 1881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, Stelara (ustekinumab), and placebo (*Lebwohl et al 2015*). Brodalumab was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every 2 weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
    - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.08 for brodalumab 140 mg vs ustekinumab). After week 52, patients receiving ustekinumab or placebo were switched to brodalumab and treatment was continued to week 120 (*Puig et al 2020*). At 120 weeks, 84.4%, 75.6%, and 61.1% of patients achieved PASI 75, PASI 90, and PASI 100, respectively, with brodalumab treatment.
    - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.007 for brodalumab 140 mg vs ustekinumab).
    - In both studies, the 2 brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA

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success rates, maintenance with brodalumab 210 mg or 140 mg every 2 weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

- The use of Tremfya (guselkumab) for the treatment of moderate to severe PsO was evaluated in the VOYAGE 1, VOYAGE 2, NAVIGATE, and ECLIPSE trials. All were Phase 3, double-blind, randomized trials.
  - Patients in both VOYAGE 1 and VOYAGE 2 were initially assigned to receive guselkumab (100 mg at weeks 0 and 4, then every 8 weeks), placebo, or Humira (adalimumab) (80 mg at week 0, 40 mg at week 1, then every 2 weeks). Patients in the placebo group were switched to guselkumab at week 16. The coprimary endpoints included the proportion of patients achieving an IGA score of 0 or 1 at week 16 as well as the proportion of patients achieving a PASI 90 response at week 16 in the guselkumab group compared with placebo. Comparisons between guselkumab and adalimumab were assessed as secondary endpoints at weeks 16, 24, and 48. To evaluate maintenance and durability of response in VOYAGE 2, subjects randomized to guselkumab at week 0 and who were PASI 90 responders at week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or be withdrawn from therapy (ie, receive placebo).
    - In VOYAGE 1 (n = 837), IGA 0 or 1 was achieved in more patients treated with guselkumab (85.1%) compared to placebo (6.9%) at week 16 ($p < 0.001$), and a higher percentage of patients achieved PASI 90 with guselkumab (73.3%) compared to placebo (2.9%; $p<0.001$) (*Blauvelt et al 2017*). Additionally, IGA 0 or 1 was achieved in more patients with guselkumab vs adalimumab at week 16 (85.1% vs 65.9%), week 24 (84.2% vs 61.7%), and week 48 (80.5% vs 55.4%; $p < 0.001$). PASI 90 score was also achieved in a higher percentage of patients with guselkumab vs adalimumab at week 16 (73.3% vs 49.7%), week 24 (80.2% vs 53%), and week 48 (76.3% vs 47.9%; $p < 0.001$). In a long-term extension of this study, PASI and IGA response rates were maintained to week 204 with continuous guselkumab treatment (*Griffiths et al 2022*).
    - In VOYAGE 2 (n = 992), IGA 0 or 1 and PASI 90 were achieved by a higher proportion of patients who received guselkumab (84.1% and 70%) vs placebo (8.5% and 2.4%) ($p < 0.001$ for both comparisons). At week 16, IGA score of 0 or 1 and PASI 90 were achieved in more patients with guselkumab (84.1% and 70%) vs adalimumab (67.7% and 46.8%) ($p < 0.001$). PASI 90 was achieved in 88.6% of patients who continued on guselkumab vs 36.8% of patients who were rerandomized to placebo at week 48. In patients who were nonresponders to adalimumab and switched to guselkumab, PASI 90 was achieved by 66.1% of patients.
  - In NAVIGATE (n = 871), patients were assigned to open-label ustekinumab 45 or 90 mg at weeks 0 and 4 (*Langley et al 2018*). Patients with IGA 0 or 1 at week 16 were continued on ustekinumab, while patients with an inadequate response to ustekinumab at week 16 (IGA ≥ 2) were randomized to blinded guselkumab 100 mg or ustekinumab. Patients treated with guselkumab had a higher mean number of visits with IGA of 0 or 1 and ≥ 2-grade improvement (relative to week 16) compared to randomized ustekinumab from week 28 to 40 (1.5 vs 0.7; $p < 0.001$). A higher proportion of patients achieved IGA of 0 or 1 with ≥ 2 grade improvement at week 28 with guselkumab (31.1%) vs randomized ustekinumab (14.3%; $p = 0.001$). At week 52, 36.2% of guselkumab-treated patients achieved this response vs 17.3% of the ustekinumab-treated patients. The proportion of patients with PASI 90 response at week 28 was 48.1% for the guselkumab group vs 22.6% for the ustekinumab group ($p \leq 0.001$).
  - In ECLIPSE (n = 1048), patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) 100 mg SQ at weeks 0 and 4 and then every 8 weeks (n = 534) or Cosentyx (secukinumab) 300 mg SQ at weeks 0, 1, 2, 3, and 4, and then every 4 weeks (n = 514) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; $p < 0.0001$). The proportion of patients with adverse events, infections, and serious adverse events were similar between the treatments.
- The approval of Ilumya (tildrakizumab-asmn) was based on 2 randomized, double-blind, multicenter, Phase 3 trials: reSURFACE1 (772 patients) and reSURFACE2 (1,090 patients). Enrolled adult patients with moderate-to-severe chronic PsO received tildrakizumab-asmn 200 mg, tildrakizumab-asmn 100 mg, or placebo in both studies; reSURFACE 2 also included an Enbrel (etanercept) arm. Only the tildrakizumab-asmn 100 mg dose was approved by the FDA. The coprimary endpoints included the proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥ 2 reduction from baseline) at week 12 (*Reich et al 2017[a]*).
  - In reSURFACE 1, PASI 75 response was achieved by 64% and 6% of the tildrakizumab-asmn 100 mg and placebo arms at week 12, respectively; a PGA response was achieved by 58% vs 7% of the tildrakizumab-asmn 100 mg and placebo groups, respectively ($p < 0.0001$ for both comparisons).
  - In reSURFACE 2, PASI 75 response was achieved by 61% and 6% of the tildrakizumab-asmn 100 mg and placebo arms, respectively; a PGA response was achieved by 55% vs 4% of the tildrakizumab-asmn 100 mg and placebo groups, respectively ($p < 0.0001$ for both comparisons). A higher proportion of patients in the tildrakizumab 100 mg

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group achieved PASI 75 vs etanercept (61% vs 48%, respectively; p = 0.001), but the rates of PGA responses did not differ significantly between groups (55% vs 48%, respectively; p = 0.0663).

- The approval of Skyrizi (risankizumab-rzaa) was based on 4 randomized, double-blind, multicenter trials. In two replicate placebo- and active-controlled trials (UltIMMa-1 and -2), patients with moderate to severe chronic PsO (n = 997) assigned to risankizumab 150 mg every 12 weeks experienced significantly higher rates of PASI 90 response at week 16 (75.3% and 74.8% in UltIMMa-1 and -2, respectively) vs patients assigned to placebo (4.9% and 2.0% in UltIMMa-1 and -2, respectively) and Stelara (ustekinumab) 45 or 90 mg (42.0% and 47.5% in UltIMMa-1 and -2, respectively; p < 0.0001 for both comparisons from both trials) *(Gordon et al 2018)*. In an active controlled trial (IMMvent) in patients with moderate-to-severe chronic PsO (n = 605), PASI 90 was achieved by 72% of patients receiving risankizumab-rzaa vs 47% receiving Humira (adalimumab) (p < 0.0001) at week 16 (*Reich et al 2019[b]*). In a trial with a randomized withdrawal and retreatment design (IMMhance) (n = 507), PASI 90 was achieved by 73.2% of risankizumab-rzaa-treated patients vs 2.0% of placebo-treated patients (p < 0.001) at week 16 (*Langley et al 2019)*
- The Phase 3 IMMerge randomized noninferiority trial compared Skyrizi (risankizumab) 150 mg (n = 164) and Cosentyx (secukinumab) 300 mg (n = 163) in patients with moderate to severe PsO (*Warren et al 2021*). Risankizumab demonstrated noninferiority to secukinumab in the proportion of patients achieving PASI 90 at week 16 (73.8% vs 65.6%, respectively; difference, 8.2%; 96.25% CI, -2.2 to 18.6 [within the 12% noninferiority margin] and was superior to secukinumab at week 52 (86.6% vs 57.1%, respectively; difference, 29.8%; 95% CI, 20.8 to 38.8; p < 0.001).
- The approval of Sotyktu (deucravacitinib) was based on 2 randomized, double-blind, multicenter trials (POETYK PSO-1 and PSO-2) *(Armstrong et al 2023, Strober et al 2023)*. Adults with moderate to severe PsO who were eligible for systemic therapy or phototherapy were randomized to either deucravacitinib 6 mg once daily, placebo, or apremilast 30 mg twice daily. In both trials, deucravacitinib was superior to placebo for the co-primary endpoints of static Physician's Global Assessment (sPGA) 0/1 (PSO-1: 54% vs 7% and PSO-2: 50% vs 9%, p < 0.0001 for both) and PASI 75 (PSO-1: 58% vs 13% and PSO-2: 53% vs 9%, p < 0.0001 for both) responses at week 16. In both trials, deucravacitinib was superior to apremilast for sPGA 0/1 (PSO-1: 54% vs 32% and PSO-2: 50% vs 34%, p < 0.0001 for both) and PASI 75 (PSO-1: 58% vs 35% [p < 0.0001] and PSO-2: 53% vs 40% [p = 0.0004]) responses at week 16. In both trials, efficacy was maintained to week 52.
- For most immunomodulators that are FDA-approved for the treatment of PsO, the indication is limited to adults. In 2016, Enbrel (etanercept) received FDA approval for treatment of PsO in pediatric patients age ≥ 4 years. Limited information from published trials is also available on the use of Stelara (ustekinumab) and Taltz (ixekizumab) in pediatric patients (age 6 to 17 years).
  - A 48-week, double-blind, placebo-controlled trial (n = 211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (*Paller et al 2008*). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 (p < 0.001). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including 3 infections) occurred in 3 patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (n = 182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (*Paller et al 2016*).
  - A 52-week, double-blind, placebo-controlled trial (n = 110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (*Landells et al 2015*). Patients received a weight-based standard dose (SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) (p < 0.001 for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively (p < 0.001 for both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively (p < 0.001 for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable

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treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.
  - An open-label, single arm, multicenter, Phase 3 trial evaluated the efficacy and safety of ustekinumab in patients 6 to < 12 years of age with moderate to severe PsO (*Philipp et al 2020*). A total of 44 patients received weight-based ustekinumab at weeks 0 and 4, then every 12 weeks through week 40. At week 12, 77% of patients achieved PGA 0 or 1, 84% achieved PASI 75, and 64% achieved PASI 90. No new safety concerns were identified.
  - The IXORA-PEDS study (n = 171) evaluated the efficacy of Taltz (ixekizumab) in pediatric patients aged 6 to < 18 years with moderate to severe PsO (*Paller et al 2020*). At week 12, weight-based ixekizumab every 4 weeks was superior to placebo for the co-primary endpoints of proportion of patients achieving PASI 75 (89% vs 25%; p < 0.001) and proportion of patients achieving PGA 0 or 1 (81% vs 11%; p < 0.001). Responses were sustained through week 108 (*Paller et al 2022*).
- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (*Feldman 2015*). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with Enbrel (etanercept) plus MTX may be beneficial for therapy-resistant patients (*Busard et al 2014; Gottlieb et al 2012*).
- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, Humira (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response (p < 0.00001) while Enbrel (etanercept) 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo (p < 0.00001 for both strengths vs placebo). The Remicade (infliximab) group had the greatest response with a risk difference of 77% compared to the placebo group (p < 0.0001). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab (*Schmitt et al 2008*).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥ 24 weeks) for moderate-to-severe PsO (*Nast et al 2015*). A total of 25 randomized trials (N = 11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for Remicade (infliximab), 11.97 (95% CI, 8.83 to 16.23) for Cosentyx (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for Stelara (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for Humira (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for Enbrel (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for Otezla (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.
- In a meta-analysis of 41 RCTs that used hierarchical clustering to rate efficacy and tolerability, Humira (adalimumab), Cosentyx (secukinumab), and Stelara (ustekinumab) were characterized by high efficacy and tolerability, Remicade (infliximab) and Taltz (ixekizumab) were characterized by high efficacy and poorer tolerability, and Enbrel (etanercept), MTX, and placebo were characterized by poorer efficacy and moderate tolerability in patients with PsO (*Jabbar-Lopez et al 2017*).
- A Cochrane review evaluated biologics in patients with moderate to severe PsO in 167 studies (*Sbidian et al 2022*). The network meta-analysis showed that compared to placebo, the biologics infliximab, bimekizumab (not yet approved in the US), ixekizumab, and risankizumab, were the best choices for achieving PASI 90 in patients with moderate-to-severe PsO on the basis of high-certainty evidence.
- A network meta-analysis of 41 randomized clinical trials (N = 19,248) assessed the proportion of patients with moderate-to-severe PsO who achieved PASI 100, PASI 90, and PASI 75 at weeks 10, 12, and 16 while using agents such as infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, risankizumab or guselkumab. The results revealed higher rates of PASI 100 and PASI 90 with brodalumab, ixekizumab, and risankizumab (*Tada et al 2020*).

Psoriatic arthritis (PsA)

- In 2 trials, PsA patients receiving Humira (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this endpoint by week 12 (p = 0.012) in a trial (n = 100); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial (p < 0.001) (*Genovese et al 2007, Mease et al 2005*). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; p < 0.001) (*Mease et al 2005*).

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- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of Enbrel (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo ($p < 0.0001$). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 ($p = 0.0154$) and 13% ($p < 0.0001$) of placebo-treated patients (*Mease et al 2000*). In a second trial, the mean annualized rate of change in the mTSS with Enbrel (etanercept) was -0.03 unit, compared to 1 unit with placebo ($p < 0.0001$). At 24 weeks, 23% of etanercept patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients ($p = 0.001$). Additionally, HAQ scores were significantly improved with etanercept (54%) over placebo (6%; $p < 0.0001$). Injection site reaction occurred at a greater rate with etanercept than placebo (36% vs 9%; $p < 0.001$) (*Mease et al 2004*).
- A 24-week trial of adult patients with PsA randomized 851 patients to oral methotrexate monotherapy, etanercept monotherapy, or combination therapy. At week 24, ACR 20 response rates were significantly greater with etanercept monotherapy (60.9%) compared to methotrexate monotherapy (50.7%), but combination therapy (65%) did not provide any significant improvement over etanercept monotherapy (*Mease et al 2019*).
- The FDA approval of Simponi (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA despite NSAID or DMARD therapy (n = 405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy (*Kavanaugh et al 2009*).
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year 5 were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every 4 weeks (*Kavanaugh et al 2014b*).
  - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥5 of 7 PsA outcomes measures [≤1 swollen joint, ≤1 tender joint, PASI ≤1, patient pain score ≤15, patient global disease activity score ≤20, HAQ disability index [HAQ DI] ≤0.5, and ≤1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (*Kavanaugh et al 2016*).
- In another trial, more Remicade (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients ($p < 0.001$) (*Antoni et al 2005*).
- The efficacy of Cimzia (certolizumab) in the treatment of PsA was established in 1 multicenter, double-blind, placebo controlled trial (n = 409). Patients were randomized to receive placebo, Cimzia 200 mg every 2 weeks, or Cimzia 400 mg every 4 weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (*Mease et al 2014*).
- The FDA-approval of Stelara (ustekinumab) for PsA was based on the results of 2 randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In PSUMMIT 1 (n = 615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; $p < 0.0001$ for both comparisons); responses were maintained at week 52 (*McInnes et al 2013*). Similar results were observed in the PSUMMIT 2 trial (n = 312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response ($p < 0.001$) (*Ritchlin et al 2014*).
  - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (*McInnes et al 2013*). At week 100 (*Kavanaugh et al 2015a*), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and HRQoL were sustained over time, with median decreases in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.
  - The approval of ustekinumab for PsA in patients aged 6 to 17 years was based on evidence from adequate and well-controlled studies in adults with PsO and PsA, along with pharmacokinetic data and safety data from 2 clinical

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studies in 44 patients aged 6 to 11 years with PsO and 110 patients aged 12 to 17 years with PsO (*Stelara prescribing information 2022*).

- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on 2 multicenter, double-blind, placebo-controlled randomized controlled trials – FUTURE 1 and FUTURE 2 *(Mease et al 2015, McInnes et al 2015*). The FUTURE 1 study randomized patients to secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
  - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; $p < 0.0001$ vs placebo).
  - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.
  - At week 104 in a long-term extension study of FUTURE 1, ACR 20 was achieved in 66.8% of patients with secukinumab 150 mg and 58.6% of patients with secukinumab 75 mg (*Kavanaugh et al 2017*).
  - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively ($p < 0.0001$ for secukinumab 300 mg and 150 mg; $p < 0.05$ for 75 mg vs placebo).
  - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- An additional randomized controlled trial (CHOICE) compared secukinumab at 2 doses to placebo in biologic-naïve patients with PsA and found that secukinumab 300 mg every 4 weeks was associated with a higher ACR 20 response rate than placebo at week 16 (51.5% vs 23.1%; $p = 0.001$) (*Nguyen et al 2022*). Secukinumab 150 mg every 4 weeks had a numerically higher ACR 20 response rate than placebo (36.9%) but the difference did not reach statistical significance.
- The efficacy of Otezla (apremilast) was demonstrated in 4 placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the Otezla groups had ≥ 20% improvement in symptoms, as defined by ACR response criteria (*Cutolo et al 2013, Edwards et al 2016, Kavanaugh et al 2014a, Wells et al 2018*). Clinical improvements observed at 16 weeks were sustained at 52 weeks (*Edwards et al 2016, Kavanaugh et al 2015b, Wells et al 2018*). In a long-term extension study, clinical improvements with Otezla were sustained up to 260 weeks (*Wells et al 2022*).
- Orencia (abatacept) gained FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2011, Mease et al 2017[a]*). In a Phase 2 dose-finding trial (n = 170), patients received abatacept 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 doses of 30 mg/kg then 10 mg/kg) on days 1, 15, 29 and then every 28 days (*Mease et al 2011*). Compared to placebo (19%), the proportion of patients achieving ACR 20 was significantly higher with abatacept 10 mg/kg (48%; $p = 0.006$) and 30/10 mg/kg (42%; $p = 0.022$) but not 3 mg/kg (33%). A Phase 3 trial (n = 424) randomized patients to abatacept 125 mg weekly or placebo (*Mease et al 2017[a]*). At week 24, the proportion of patients with ACR 20 response was significantly higher with abatacept (39.4%) vs placebo (22.3%; $p < 0.001$).
- Rinvoq (upadacitinib) received FDA approval for the treatment of PsA based on the results of 2 randomized, double-blind, placebo-controlled studies in adults with moderately to severely active PsA (SELECT-PsA 1 and SELECT-PsA 2) *(McInnis et al 2021, Mease et al 2020[a])*. Patients with a previous inadequate response or intolerance to ≥ 1 non-biologic DMARD (SELECT-PsA 1) or ≥ 1 biologic DMARD (SELECT-PsA 2) were randomized to upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, adalimumab (SELECT-PsA 1), or placebo as monotherapy or in combination with ≤ 2 non-biologic DMARDs for 24 weeks. The primary endpoint of both studies, ACR 20 at week 12, was significantly improved with upadacitinib 15 mg once daily (FDA-approved dose) compared with placebo in SELECT-PsA 1 (70.6% vs 36.2%; difference, 34.5%; 95% CI, 28.2 to 40.7; $p < 0.001$) and SELECT-PsA 2 (56.9% vs 24.1%; difference, 32.8%; 95% CI, 24.0 to 41.6; $p < 0.001$).
- Skyrizi (risankizumab) received FDA approval for the treatment of PsA based on the results of 2 randomized, double-blind, placebo-controlled studies, KEEPsAKE 1 and KEEPsAKE 2, in patients with active PsA (*Kristensen et al 2022*, *Östör et al 2022*). In KEEPsAKE 1, all patients had a previous inadequate response or intolerance to non-biologic DMARD therapy and were biologic-naïve. In KEEPsAKE 2, patients had an inadequate response or intolerance to ≤ 2 biologic therapies and/or ≥ 1 non-biologic DMARD therapy. Risankizumab was associated with significantly higher rates of the primary endpoint of ACR 20 response at week 24 in KEEPsAKE 1 (57.3% vs 33.5%; $p < 0.001$) and KEEPsAKE 2

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(51.3% vs 26.5%; p < 0.001). Significant improvements were reported in both trials for ACR 50 and ACR 70 response at week 24. Results at 52 weeks of treatment in both KEEPsAKE 1 and KEEPsAKE 2 indicated no new safety concerns *(Kristensen et al 2022, Östör et al 2022)*.

- Taltz (ixekizumab) received FDA approval for the treatment of PsA based on 2 double-blind clinical trials, SPIRIT-P1 and SPIRIT-P2 (*Mease et al 2017[b], Nash et al 2017*). SPIRIT-P1 randomized 417 biologic naïve patients to placebo, adalimumab 40 mg every 2 weeks, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 62.1% and 57.9%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (30.2%; p ≤ 0.001). The active reference treatment, adalimumab, had an ACR 20 at week 24 of 57.4% (*Mease et al 2017[b]*). SPIRIT-P2 randomized 363 patients who had a previous inadequate response to a TNF inhibitor to placebo, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 48% and 53%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (20%; p < 0.0001) (*Nash et al 2017*).
  - An open-label extension of the SPIRIT-P1 trial followed patients through week 52, demonstrating sustained efficacy with ixekizumab. The ACR 20, ACR 50, and ACR 70 response rates for the every 4 week and every 2 weeks groups were 69.1% and 68.8%, 54.6% and 53.1%, and 39.2% and 39.6% at week 52, respectively (*van der Heijde et al 2018[b]*).
  - An additional open-label extension of the SPIRIT-P1 trial followed patients through week 156. The ACR 20, ACR 50, and ACR 70 response rate for the every 2 weeks and every 4 weeks groups were 62.5% and 69.8%, 56.1% and 51.8%, and 43.8% and 33.4%, respectively (*Chandran et al 2020*).
- SPIRIT-H2H is a 52-week multicenter, open-label study comparing ixekizumab with adalimumab in patients with PsA and without prior use of biologic DMARDs. At week 52, a higher proportion of patients treated with ixekizumab achieved the combined ACR 50 and PASI 100 response (39% vs 26%, p < 0.001) and PASI 100 response (64% vs 41%, p < 0.001) compared with the patients treated with adalimumab. Both agents yielded similar outcomes for ACR 50 (49.8% vs 49.8%, p = 0.924) (*Smolen et al 2020[b]*).
- Xeljanz (tofacitinib) received FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2017[c], Gladman et al 2017*). The OPAL Broaden trial randomized 422 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg every 2 weeks, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 61% in the tofacitinib 10 mg group, 33% in the placebo group (p = 0.01 vs 5 mg; p < 0.001 vs 10 mg), and 52% in the adalimumab group (*Mease et al 2017[c]*). The OPAL Beyond trial randomized 395 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 47% in the tofacitinib 10 mg group, and 24% in the placebo group (p < 0.001 for both comparisons) (*Gladman et al 2017*).
- Tremfya (guselkumab) received FDA approval for the treatment of PsA based on 2 randomized, double-blind, placebo controlled trials (*Deodhar et al 2020[c], Mease et al 2020[b]*). The DISCOVER-1 trial randomized 381 patients with active PsA despite standard therapies to receive guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, ACR 20 response rates for guselkumab every 4 weeks and every 8 weeks were 59% and 52%, respectively, which was significantly greater than the ACR 20 response rate with placebo (22%; p < 0.0001) (*Deodhar et al 2020[c]*). The DISCOVER-2 trial randomized 741 biologic-naïve patients with PsA to receive guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, ACR 20 response rates for guselkumab every 4 weeks and every 8 weeks were 64% and 64%, respectively, which was significantly greater than the ACR 20 response rate with placebo (33%; p < 0.0001) (*Mease et al 2020[b]*). Clinical improvements were maintained through 2 years of treatment (*McInnes et al 2022*). An additional placebo-controlled trial (COSMOS) in patients with inadequate response to TNF inhibitors found that guselkumab significantly improved ACR 20 response rates at week 24 in these patients (44.4% vs 19.8% with placebo; p < 0.001) (*Coates et al 2022[a]*).
- A small, single-center randomized trial (N = 100) compared Remicade (infliximab), Enbrel (etanercept), and Humira (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (*Atteno et al 2010*). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest improvement in

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PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.

- The multicenter, randomized, double-blind EXCEED study compared Cosentyx (secukinumab) to Humira (adalimumab) in 853 biologic-naïve patients with active PsA and an inadequate response to DMARDs (*McInnes et al 2020*). The ACR 20 response rates at week 52 were 67% with secukinumab and 62% with adalimumab (p = 0.0719). Secukinumab did not show statistical superiority over adalimumab.
- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of Humira (adalimumab), Enbrel (etanercept), Remicade (infliximab), and Simponi (golimumab) over 24 weeks for the treatment of PsA (*Fénix et al 2013*). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.
- A meta-analysis of 9 randomized controlled trials and 6 observational studies evaluated Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with moderate to severe PsA (*Lemos et al 2014*). Patients who used adalimumab, etanercept and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.
- A meta-analysis of 8 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), and Stelara (ustekinumab) in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with PsA (*Bilal et al 2018*). Patients who used these agents were more likely to achieve ACR 20, ACR 50, and ACR70 after 24 weeks of treatment. Another network meta-analysis of 6 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), and Stelara (ustekinumab) over 24 weeks in patients with active PsA (*Wu et al 2018*). The investigators found that all agents improved ACR20 and ACR50 at week 24 compared to placebo. A different network meta-analysis of 8 studies evaluated Orencia (abatacept), Otezla (apremilast), Stelara (ustekinumab), and Cosentyx (secukinumab) in the achievement of ACR 20 and ACR 50 in adults with moderate to severe PsA (*Kawalec et al 2018*). The investigators found a significant difference in ACR20 response rate between Cosentyx (secukinumab) 150 mg and Otezla (apremilast) 20 mg (RR, 2.55; 95% CI, 1.24 to 5.23) and Cosentyx (secukinumab) 300 mg and Otezla (apremilast) 20 mg (RR, 3.57; 95% CI, 1.48 to 8.64) or Otezla (apremilast) 30 mg (RR, 2.84; 95% CI, 1.18 to 6.86).
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.
  - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (*Ungprasert et al 2016a*). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: Enbrel [etanercept], Remicade [infliximab], Humira [adalimumab], and Simponi [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving Cimzia (certolizumab), Otezla (apremilast), or Stelara (ustekinumab). Patients receiving Cosentyx (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
  - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (Orencia [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF inhibitors (*Ungprasert et al 2016[b]*). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
  - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.
- In a network meta-analysis of 8 randomized trials (N = 3086), the efficacy and safety of apremilast were compared with tofacitinib in patients with active PsA, including treatment with tofacitinib 10 mg or 5 mg, apremilast 20 or 30 mg, and placebo *(Song et al 2019)*. Tofacitinib 10 mg and apremilast 30 mg were among the most effective treatments, followed by tofacitinib 5 mg and apremilast 20 mg. Tofacitinib 10 mg was most likely to be most effective in ACR 20 response (SUCRA = 0.785), followed by apremilast 30 mg (SUCRA = 0.670), tofacitinib 5 mg (SUCRA = 0.596), and apremilast 20 mg (SUCRA = 0.448). There were no significant differences in adverse event rates.
- A network meta-analysis of 30 randomized trials (N = 10,191) compared the efficacy of infliximab, apremilast, adalimumab, tofacitinib, ustekinumab, golimumab, abatacept, secukinumab, certolizumab, brodalumab, etanercept, and ixekizumab in PsA (*Qiu et al 2020*). Direct and indirect comparisons were performed. In direct comparisons, most

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agents were better than placebo in terms of ACR 20 response rate (except adalimumab, tofacitinib, and abatacept), and no agent was significantly different from placebo in terms of serious adverse events. In the network meta-analysis, etanercept and infliximab were more effective than golimumab for ACR 20 response, and infliximab was more effective than certolizumab for PASI 75 response. Etanercept and infliximab were ranked as the most effective treatments.

- A network meta-analysis of 30 randomized trials (only 12 randomized trials for peripheral arthritis outcome) assessed the efficacy of adalimumab, etanercept, infliximab, golimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, guselkumab, brodalumab, risankizumab, and tildrakizumab on peripheral arthritis by using ACR 70 criteria and on skin by reporting PASI 100 (*Torres et al 2021*). Secukinumab and ixekizumab had the highest probability for reaching both ACR 70 and PASI 100 responses.
- A meta-analysis of 11 randomized studies (N = 5382) revealed that TNF inhibitors, IL inhibitors, and abatacept are more likely to achieve radiographic non-progression compared with placebo (*Wu et al 2020*). Ixekizumab and adalimumab had a similar proportion of non-progressors.
- A meta-analysis of 33 trials in patients with PsA found that guselkumab was comparable to IL-17A inhibitors and TNF inhibitors for achievement of ACR20, ACR50, and ACR70 (*Mease et al 2022*). There was a trend of benefit for guselkumab vs most other active agents for achievement of PASI 90. For PASI 100, van der Heijde-Sharp score, and serious adverse events, guselkumab was comparable to other active agents.
- A network meta-analysis of 11 trials evaluated the comparative efficacy in prevention of radiographic progression PsA of biologic DMARDs, including abatacept, adalimumab, certolizumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, secukinumab, and ustekinumab *(Wang et al 2022)*. All interventions were more effective than placebo in achieving radiographic non-progression except for secukinumab 150 mg, ustekinumab, and guselkumab. SUCRA values indicated that adalimumab, certolizumab, and etanercept may be most effective in achievement of radiographic non-progression. SUCRA analysis showed that infliximab ranked the best in reducing the total radiographic score, followed by etanercept.

Uveitis (UV)

- The safety and efficacy of Humira (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in 2 randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
  - VISUAL I (n = 217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥ 2 weeks (*Jaffe et al 2016*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).
  - VISUAL II (n = 226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (*Nguyen et al 2016*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [>18 months] vs 8.3 months; hazard ratio, 0.57, 95% CI, 0.39 to 0.84; p = 0.004). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.
- The SYCAMORE study established the efficacy and safety of Humira (adalimumab) in pediatric patients with JIA-associated UV. The double-blind trial evaluated 90 children and adolescents ≥ 2 years of age and randomized them to adalimumab or placebo until treatment failure or 18 months had elapsed. The primary endpoint was the time to treatment failure. Sixteen treatment failures (27% of patients) occurred with adalimumab compared to 18 failures (60% of patients) with placebo (HR, 0.25; 95% CI, 0.12 to 0.90). Adverse events occurred more frequently with adalimumab (10.07 events per patient year [PY] vs 6.51 events per PY with placebo) (*Ramanan et al 2017*).

Multiple indications

- The efficacy of infliximab-dyyb (European Union formulation) in patients (n = 481) with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab (European Union formulation) for ≥ 6 months was assessed in the NOR-SWITCH trial (*Jørgensen et al 2017*). Twenty-five percent of patients in the infliximab originator group experienced disease worsening compared to 30% of patients in the infliximab-dyyb group (TD, -4.4%; 95% CI, -12.7% to 3.9%; noninferiority margin, 15%). The authors concluded that infliximab-dyyb was noninferior to originator infliximab.

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Alopecia areata, Behçet disease, CAPS, CRS, DIRA, ERA, FMF, GCA, GVHD, HIDS/MKD, NOMID, NRAS, SSc-ILD, and TRAPs

- The efficacy of Otezla (apremilast) for Behçet disease was evaluated in a randomized, double-blind, placebo-controlled trial in 207 adults with Behçet disease with active oral ulcers who were previously treated with at least one nonbiologic therapy (*Hatemi et al 2019*). At week 12, apremilast 30 mg twice daily was associated with a 42.7 point mean reduction from baseline in oral ulcer pain on a visual analog scale (VAS), compared with an 18.7 point reduction with placebo. The area under the curve (AUC) of the total mean number of ulcers during the 12 week period was 129.5 in the apremilast vs 222.1 in the placebo group ; p < 0.001). The proportion of patients who were oral ulcer-free at week 12 was 53% and 22% with apremilast vs placebo, respectively. Adverse events with apremilast included diarrhea, nausea, and headache.
- The efficacy of Kineret (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n = 11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (*Kineret prescribing information 2020*). A cohort study of 26 patients followed for 3 to 5 years demonstrated sustained improvement in disease activity and inflammatory markers (*Sibley et al 2012*).
- The efficacy of Kineret (anakinra) for DIRA was evaluated in a long-term natural history study of 9 patients (ages 1 months to 9 years) with genetically-confirmed DIRA who were treated with anakinra for up to 10 years. All patients achieved inflammatory remission (defined as CRP ≤ 5 mg/dL and absence of pustulosis, inflammatory bone disease, or glucocorticoid use) (*Kineret prescribing information 2020*).
- Cosentyx (secukinumab) was evaluated in a double-blind, placebo-controlled trial in 86 patients 2 to < 18 years of age with active ERA or juvenile PsA *(Cosentyx prescribing information 2021, Ruperto et al 2021[c])*. The JIA subtypes at baseline were 60.5% ERA and 39.5% juvenile PsA. Patients were treated with secukinumab during an open-label portion, followed by a randomized withdrawal phase and then open-label treatment. In patients with ERA, the primary endpoint of time to disease flare during the randomized withdrawal period demonstrated reduced risk in patients treated with secukinumab compared with placebo (hazard ratio, 0.47; 95% CI, 0.17 to 1.32).
- The efficacy of Cimzia (certolizumab) was evaluated in a Phase 3, randomized, double-blind, placebo-controlled trial in 317 patients with NRAS. Patients were randomized to certolizumab (400 mg at weeks 0, 2, and 4, followed by 200 mg every 2 weeks) or placebo in addition to nonbiologic background medication. At week 52, treatment with certolizumab was associated with a significantly higher proportion of patients achieving major improvement (≥ 2 point decrease in Ankylosing Spondylitis Disease Activity Score; 47.2% vs 7.0%; p < 0.0001) *(Deodhar et al 2019[b])*.
- The efficacy and safety of Rinvoq (upadacitinib) were evaluated in a Phase 3, randomized, double-blind, placebo-controlled trial in adults with active NRAS and inadequate response to at least 2 NSAIDs or intolerance or contraindication to NSAIDs. Patients were randomized to upadacitinib (15 mg daily; n = 156) or placebo (n = 157). At 14 weeks, the primary endpoint of ASAS 40 response was significantly improved with upadacitinib compared with placebo (44.9% vs 22.3%, respectively; difference, 22.5%; 95% CI, 12.4 to 32.5; p < 0.0001) *(Deodhar et al 2022[a])*.
- The efficacy and safety of Taltz (ixekizumab) were evaluated in NRAS in the 52 week, randomized, double-blind, placebo-controlled, parallel-group, multicenter COAST-X trial (*Deodhar et al 2020[a]*). In COAST-X, 303 adults with NRAS and an inadequate response or intolerance to NSAIDs were randomly assigned to ixekizumab 80 mg SQ every 4 weeks (n = 96), every 2 weeks (n = 102), or placebo (n = 105). Both primary endpoints were met with ixekizumab: ASAS 40 at week 16 (35% every 4 weeks vs 40% every 2 weeks vs 19% placebo; p = 0.0094 and p = 0.0016, respectively) and ASAS 40 at week 52 (30% every 4 weeks vs 31% every 2 weeks vs 13% placebo; p = 0.0045 and p = 0.0037, respectively). The most common treatment-emergent adverse events were nasopharyngitis and injection site reaction.
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in NRAS in the randomized, double-blind, placebo-controlled, Phase 3 PREVENT study (*Deodhar et al 2020[b]*). In this trial, 555 adults with NRAS were randomized to receive secukinumab with a loading dose, secukinumab without a loading dose, or placebo (secukinumab was dosed as 150 mg at weeks 0, 1, 2, and 3, then every 4 weeks starting at week 4). The primary analyses were performed in TNF inhibitor-naïve patients (n = 501). Both primary endpoints were met. At week 16, more patients in the secukinumab plus loading dose group achieved ASAS 40 compared with placebo (41.5% vs 29.2%; p < 0.05). At week 52, more patients in the secukinumab without loading dose group achieved ASAS 40 compared with placebo (39.8% vs 19.9%; p < 0.05).
- The efficacy and safety of Ilaris (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, FMF, and adult-onset Still's disease.

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- Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open-label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (Ilaris prescribing information 2020). Published data supports the use of canakinumab for these various CAPS phenotypes (*Koné-Paut et al 2011, Kuemmerle-Deschner et al 2011, Lachmann et al 2009*).
- Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period (45% vs 8%, 35% vs 6%, and 61% vs 6%, respectively). Resolution of the flare was defined as a PGA score <2 (minimal or no disease) and CRP within normal range (or reduction ≥70% from baseline) (*De Benedetti et al 2018*). In the open-label extension phase of this trial, canakinumab was effective for controlling disease activity and flares over 72 weeks; 64% of patients experienced no flares during the 72-week trial period, and 20% had 1 flare, as compared with a median of 12 flares per year reported at baseline (*Jeyaratnam et al 2022*).
- Efficacy and safety in adult-onset Still's disease were evaluated in a randomized, double-blind, placebo-controlled study of 36 patients with adult-onset Still's disease and active joint involvement. The primary endpoint, proportion of patients achieving a significant reduction in DAS28 at week 12, was achieved in 67% of canakinumab-treated patients and 41% of placebo-treated patients (p = 0.18). Proportions of patients achieving the secondary endpoints of ACR 30, 50, and 70 were significantly greater in the canakinumab group (61%, 50%, and 28% with canakinumab vs 20%, 6.7%, and 0% with placebo; p = 0.033, 0.009, and 0.049 for canakinumab vs placebo, respectively). The study was terminated prematurely due to recruitment difficulties (*Kedor et al 2020*).

- The efficacy and safety of Actemra (tocilizumab) has been evaluated for treatment of GCA, CRS, and SSc-ILD.
  - Efficacy and safety of tocilizumab in GCA were evaluated in a double-blind, placebo-controlled Phase 3 trial (GiACTA) in patients ≥ 50 years old with active GCA and a history of elevated ESR (*Stone et al 2017*). Patients received tocilizumab every week or every other week with a 26-week prednisone taper, or received placebo with a 26-week or 52-week prednisone taper. Patients who received tocilizumab every week and every other week experienced higher sustained remission rates at week 52 compared to placebo (p < 0.01).
  - The efficacy of tocilizumab in CRS was based on the result of a retrospective analysis of pooled outcome data from clinical trials of chimeric antigen receptor (CAR) T-cell therapies for hematological cancers (*Actemra prescribing information 2022*). Patients aged 3 to 23 years received tocilizumab with or without high-dose corticosteroids for severe or life-threatening CRS. Sixty-nine percent of patients treated with tocilizumab achieved a response. In a second study using a separate study population, CRS resolution within 14 days was confirmed.
  - The efficacy of tocilizumab in SSc-ILD was evaluated in a randomized, double-blind, placebo-controlled clinical trial of 210 adults with SSc-ILD (Khanna et al 2020). While this trial did not meet its primary endpoint (change from baseline to week 48 in the modified Rodnan Skin Score [mRSS], a standard outcome measure for skin fibrosis in SSc-ILD), there was a trend of benefit in favor of tocilizumab for preservation of lung function (a > 10% decrease in FVC% predicted occurred in 24% of patients in the placebo group and only 13% of patients in the tocilizumab group; HR 0.55, 95% CI, 0.3 to 1.11; p = 0.08). Treatment failure was also less likely with tocilizumab (22%) vs placebo (35%; p = 0.08). Benefits in preservation of lung function were maintained through week 96 in an open-label extension of this study (*Khanna et al 2022*).
- The efficacy and safety of Orencia (abatacept) in the prophylaxis of acute GVHD was assessed in a Phase 2 trial of adults and children with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor *(Watkins et al 2021)*. A cohort of patients with 8/8 HLA-matched HSCT (N = 142) were randomized to blinded abatacept or placebo, each in addition to a calcineurin inhibitor (CNI) and MTX. At day 100, abatacept was associated with numeric improvements in the primary endpoint of severe (grade 3 to 4) acute GVHD (hazard ratio, 0.45; 95% CI, 0.22 to 0.90). At day 180, severe acute GVHD-free-survival (SGFS) was 93.2% for CNI/MTX plus abatacept vs 82% for CNI/MTX plus placebo (p = 0.05). In an open-label single-arm cohort of patients undergoing 7/8 HLA-matched HSCT (n = 43), grade 3 to 4 acute GVHD was 2.3% for CNI/MTX plus abatacept, which compared favorably with a nonrandomized matched cohort of CNI/MTX (30.2%, p < 0.001); the SGFS was also better (97.7% vs 58.7%, p < 0.001).
  - A study using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) of patients 6 years and older who underwent HSCT from a 1 allele-mismatched unrelated donor demonstrated that treatment with

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abatacept in addition to CNI and MTX was associated with greater overall survival at day 180 post-HSCT compared with patients not treated with abatacept (98% vs 75%) (*Orencia prescribing information 2021*).

- The efficacy and safety of baricitinib for alopecia areata were assessed in 2 randomized, placebo-controlled, Phase 3 trials (BRAVE-AA1 and BRAVE-AA2) (*King et al 2022*). Both trials enrolled adults with severe alopecia areata and randomized patients to receive either baricitinib 4 mg daily, baricitinib 2 mg daily, or placebo. The primary outcome was a Severity of Alopecia Tool (SALT) score of 20 or less at week 36. In BRAVE-AA1 (N = 654), the primary outcome was achieved in 38.8%, 22.8%, and 6.2% of patients assigned to baricitinib 4 mg, baricitinib 2 mg, and placebo, respectively ($p < 0.001$ for both doses vs placebo). In BRAVE-AA2 (N = 546), the primary outcome was achieved in 35.9%, 19.4%, and 3.3% of patients assigned to baricitinib 4 mg, baricitinib 2 mg, and placebo, respectively ($p < 0.001$ for both doses vs placebo).
- A systematic literature review of 38 studies determined that anakinra, canakinumab, and etanercept are the most commonly studied biologics for treating familial Mediterranean fever, while studies with adalimumab, tocilizumab, rilonacept, and infliximab remain limited (*Kuemmerle-Deschner et al 2020*). The available evidence suggests that anakinra and canakinumab are effective in treating familial Mediterranean fever.

Clinical Guidelines

- RA:
  - The America College of Rheumatology (ACR) recommends the use of conventional DMARDs, a TNF inhibitor, a non-TNF inhibitor biologic (tocilizumab, sarilumab, abatacept, or rituximab [only in patients that have had an inadequate response to TNF inhibitors or have a history of lymphoproliferative disorder]), or a JAK inhibitor (tofacitinib, baricitinib, upadacitinib). For patients who are not at target, switching to a medication in a different class is conditionally recommended over switching to a medication in the same class for patients receiving a biologic or JAK inhibitor. Biosimilars are considered equivalent to FDA-approved originator biologics. Anakinra was excluded from the ACR guideline because of its low use and lack of new data. (*Fraenkel et al 2021*).
  - EULAR guidelines for RA management were recently updated (*Smolen et al 2023*). EULAR recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first conventional synthetic DMARD (csDMARD) strategy, in the absence of poor prognostic factors, other csDMARDs should be considered. If poor prognostic factors are present with csDMARD failure, a biological DMARD should be added; JAK inhibitors may be considered, but pertinent risk factors should be taken into account. In patients who cannot use csDMARDs as a comedication, IL-6 inhibitors and targeted synthetic DMARDs may have some advantages compared with other biologic DMARDs. If a biologica or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF or IL-6 inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF or IL-6 inhibitor.
  - The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (*ACR 2018*). Similarly, the Task Force on the Use of Biosimilars to Treat Rheumatological Disorders recommends that both healthcare providers and patients should take part in the decision-making process for switching amongst biosimilars (*Kay et al 2018*).
  - EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
  - The ACR/Arthritis Foundation guidelines for the management of osteoarthritis of the hand, hip, and knee strongly recommends against the use of biologics (eg, TNF inhibitors, IL-1 receptor antagonists) for any form of osteoarthritis (*Kolasinski et al 2020*).
- JIA:
  - The ACR and Arthritis Foundation published a guideline for the treatment of JIA in 2019 focusing on therapy for non-systemic polyarthritis, sacroiliitis, and enthesitis. In children and adolescents with JIA and polyarthritis with moderate to high disease activity, addition of a biologic (TNF inhibitor, abatacept, or tocilizumab) is conditionally recommended. Patients with continued disease activity and primary TNF inhibitor failure are conditionally recommended to receive abatacept or tocilizumab over a second TNF inhibitor. Children and adolescents with JIA and active sacroiliitis despite treatment with NSAIDs are strongly recommended to add TNF inhibitor therapy over continuing NSAID monotherapy (*Ringold et al 2019*).

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- A 2021 guideline from the ACR addresses the treatment of oligoarthritis, temporomandibular joint arthritis, and SJIA (*Onel et al 2022*). For SJIA, an IL-1 inhibitor or IL-6 inhibitor is conditionally recommended for initial treatment; no specific agent is preferred. Monotherapy with an NSAID may also be considered for initial treatment of SJIA without macrophage activation syndrome. Systemic glucocorticoids are conditionally recommended as part of initial therapy for patients with macrophage activation syndrome. If residual arthritis is present despite these therapies, a conventional synthetic DMARD may be added or a different biologic therapy may be tried. Patients without macrophage activation syndrome who experience incomplete response or intolerance to an initial IL-1 or IL-6 inhibitor may be switched to an alternative IL-1 or IL-6 inhibitor.

- PsO and PsA:
  - Joint guidelines from the American Academy of Dermatology (AAD)/National Psoriasis Foundation (NPF) state that topical medications (eg, corticosteroids, vitamin D analogues) are the most common agents used to treat mild to moderate PsO. They are commonly used as adjunctive therapy to phototherapy, systemic agents, and biologics (*Elmets et al 2021*). Phototherapy is viewed as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications (*Elmets et al 2019*). Although biologic therapies have changed the treatment landscape, non-biologic systemic agents (eg, methotrexate) either as monotherapy or in combination with biologics, are still widely used due to benefit for widespread disease, comparatively low cost, increased availability, and ease of administration (*Menter et al 2020[a]*).
  - Joint guidelines from the AAD/NPF on the treatment of psoriasis with biologics address the effectiveness of these drugs as monotherapy or in combination to treat moderate-to-severe disease in adults. The guideline does not provide relevant ranking for preferences of individual biologics, but does recommend that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab can all be recommended as a monotherapy option for patients. Further recommendations on specific presentations of the disease, combination therapy, and dosing recommendations are included in the guidance (*Menter et al 2019*).
  - The AAD/NPF guideline on PsO in pediatric patients states that etanercept, adalimumab, and ustekinumab are effective biologic therapies for moderate to severe pediatric psoriasis. Infliximab can be recommended as monotherapy or in combination with MTX for use in pediatric patients with severe plaque or pustular psoriasis that is unresponsive to other systemic medications, rapidly progressive, unstable, and/or life threatening (*Menter et al 2020[b]*).
  - EULAR 2019 PsA guidelines recommend biologic DMARDs in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX. For patients with peripheral arthritis, an inadequate response to at least 1 synthetic DMARD, and relevant skin involvement, biologics targeting IL-12/23 or IL-17 pathways may be considered. In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD and at least one biologic DMARD, JAK inhibitors may be considered; JAK inhibitors may also be considered in patients for whom biologic DMARD therapy is not appropriate. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics and JAK inhibitors are not appropriate (*Gossec et al 2020, Kerschbaumer et al 2020*).
  - The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, an IL-12/23 inhibitor, an IL-23 inhibitor, an IL-17 inhibitor, a JAK inhibitor, or a PDE-4 inhibitor (*Coates et al 2022[b]*).
  - The American College of Rheumatology/National Psoriasis Foundation guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy (MTX, sulfasalazine, leflunomide, cyclosporine, or apremilast) can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics (secukinumab, ixekizumab, brodalumab), IL-12/23 biologics (ustekinumab), abatacept, and tofacitinib (*Singh et al 2019*).
  - In 2020, the International Psoriasis Council Biosimilar Working Group published a consensus statement for the use of biosimilars in the treatment of patients with psoriasis (*Cohen et al 2020*). There was consensus from the Group that prescribing biosimilars to biologic-naïve patients or switching a stable patient from a reference product to a biosimilar product is appropriate if the patient and physician agree to do so. Furthermore, switching between different biosimilars should be performed with caution, until more evidence is generated supporting this practice, and multiple switches between various biosimilars and reference biologics is not the preferred option but is acceptable. Lastly, treatment switches should not occur in less than an adequate period of time (usually 6 months) from initiation of the reference product, allowing full assessment of its therapeutic effect.

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- AS:
  - The American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network joint recommendations for treatment of AS and NRAS were updated in 2019. Patients with active AS or NRAS who do not respond to initial NSAID therapy are conditionally recommended to be treated with sulfasalazine, MTX, or tofacitinib; sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNF inhibitors are not available. Patients who do not respond to NSAID therapy are strongly recommended to receive treatment with a TNF inhibitor, although no particular TNF inhibitor is preferred. Treatment with a TNF inhibitor is conditionally recommended over tofacitinib, secukinumab, and ixekizumab in these patients. In patients with active disease who have primary nonresponse with a TNF inhibitor, treatment with secukinumab or ixekizumab is strongly recommended, and treatment with tofacitinib is conditionally recommended. Patients with secondary nonresponse to treatment with a TNF inhibitor are conditionally recommended to receive treatment with an alternative TNF inhibitor. In patients with AS and inflammatory bowel disease or recurrent iritis, TNF inhibitors are conditionally recommended over treatment with other biologics. In patients with stable disease who are treated with an originator TNF inhibitor, the guideline strongly recommends continuing the originator TNF inhibitor over mandated switching to its biosimilar (*Ward et al 2019*).
  - Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR and were updated in 2022. The guideline notes that radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis are part of the same disease spectrum, and therefore uses the term axial spondyloarthritis in recommendations. The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered, but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. TNF inhibitors, IL-17A inhibitors, or JAK inhibitors should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with a TNF inhibitor or IL-17A inhibitor. In patients with a history of recurrent uveitis or active IBD, preference should be given to a monoclonal antibody against TNF. In patients with significant psoriasis, an IL-17 inhibitor may be preferred. Following failure of the first biologic or targeted synthetic DMARD, switching to another biologic DMARD (TNF inhibitor or IL-17A inhibitor) or a JAK inhibitor should be considered. For patients in sustained remission, tapering of a biologic DMARD can be considered (*Ramiro et al 2023*).
- Ocular inflammatory disorders:
  - Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (*Levy-Clarke et al 2014*). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
  - A 2019 guideline by the ACR and Arthritis foundation focusing on children with JIA-associated UV conditionally recommended starting a monoclonal antibody TNF inhibitor over etanercept in children and adolescents with chronic anterior UV. Children and adolescents with inadequate response to one monoclonal TNF inhibitor are conditionally recommended to be treated with an escalated dose and/or frequency of the TNF inhibitor over switching to another TNF inhibitor; patients failing dose escalation are conditionally recommended to switch to another monoclonal TNF inhibitor. Children and adolescents failing MTX and 2 monoclonal TNF inhibitors are conditionally recommended to receive abatacept or tocilizumab as biologic DMARD options (*Angeles-Han et al 2019*).
- Additional indications:
  - Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, and infliximab may be considered a second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
  - For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to the maximum tolerated dose of colchicine. TNF inhibitors have also been used in colchicine-resistant patients, with good responses seen in observational studies (*Ozen et al 2016*).
  - For the management of HS, the US and Canadian Hidradenitis Suppurativa Foundation recommend adalimumab to improve disease severity and QoL in patients with moderate-to-severe disease (*Alikhan et al 2019*). Additionally,

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infliximab is recommended for moderate-to-severe disease; however, the optimal dose is not currently known. Anakinra and ustekinumab may be effective agents for HS as well.
- For the management of GCA, EULAR recommendations state that tocilizumab (or methotrexate as an alternative) should be used as an adjunctive therapy in patients who have refractory or relapsing disease or who are at an increased risk of glucocorticoid-related adverse effects or complications (*Hellmich et al 2020*). A joint guideline from the ACR and Vasculitis Foundation recommends the use of oral or IV glucocorticoids, tocilizumab, and other non-glucocorticoid immunosuppressive drugs (eg, methotrexate, abatacept); specific recommendations depend on various factors such as the patient's clinical presentation, comorbidities, and prior therapies (*Maz et al 2021*).
- A EULAR guideline states that cyclophosphamide should be considered for treatment of SSc-ILD, in particular for patients with progressive disease (*Kowal-Bielecka et al 2017*).
- In children and adolescents with JIA and active enthesitis, ACR guidelines conditionally recommend TNF inhibitor therapy over methotrexate or sulfasalazine (*Ringold et al 2019*).
- A EULAR guideline for the management of IL-1-mediated autoinflammatory disorders provides recommendations for the management of CAPS, TRAPS, MKD, and DIRA (*Romano et al 2022*). The guideline states that IL-1 inhibitor therapy has become the preferred treatment for these disease states; a therapeutic trial with an IL-1 inhibitor may be started when strong clinical suspicion of CAPS, TRAPS, MKD, or DIRA exists. For CAPS, IL-1 inhibitors (anakinra, canakinumab, and rilonacept) are considered standard of care; anakinra may be the most effective treatment for CNS disease. For TRAPS, IL-1 inhibitors are more effective than traditional DMARDs or other biologic DMARDs. For MKD, IL-1 inhibitors are first-line; if these therapies are not effective or available, TNF inhibitors may be considered. For DIRA, anakinra and rilonacept are recommended.
- No recent guidelines were identified for alopecia areata, CRS, or Still's disease.

Safety Summary

- Contraindications:
  - Actemra (tocilizumab), Avsola (infliximab-axxq), Cimzia (certolizumab), Cosentyx (secukinumab), Ilaris (canakinumab), Ilumya (tildrakizumab-asmn), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Kineret (anakinra), Otezla (apremilast), Remicade (infliximab), Renflexis (infliximab-abda), Skyrizi (risankizumab), Stelara (ustekinumab), and Taltz (ixekizumab) in patients with hypersensitivity to any component of the product.
  - Enbrel (etanercept) in patients with sepsis.
  - Kineret (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
  - Remicade (infliximab), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda) in patients with hypersensitivity to murine proteins; and doses >5 mg/kg in patients with moderate to severe heart failure.
- Boxed Warnings:
  - Actemra (tocilizumab), Avsola (infliximab-axxq), Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Rinvoq (upadacitinib), Simponi / Simponi Aria (golimumab), and Xeljanz / Xeljanz XR/Xeljanz oral solution (tofacitinib) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.
  - In addition, Avsola (infliximab-axxq), Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Rinvoq (upadacitinib), Simponi / Simponi Aria (golimumab), and Xeljanz (tofacitinib) all have warnings for increased risk of malignancies.
  - Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib) have warnings for increased risk of thrombosis and death, including sudden cardiovascular death. Rinvoq (upadacitinib) and Olumiant (baricitinib), other JAK inhibitors, also carry a boxed warning for this risk.
    - In September 2021, the FDA announced that its review of a large randomized safety clinical trial comparing Xeljanz (tofacitinib) vs a TNF inhibitor in RA found an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with tofacitinib. The final results showed an increased risk of adverse events with the lower dose as well as the higher dose. The FDA believes that baricitinib and upadacitinib have similar risks because they share the same mechanism of action. The FDA has limited all approved uses of baricitinib, tofacitinib, and upadacitinib to certain patients who have not responded or cannot tolerate 1 or more TNF inhibitors.

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- Rituxan (rituximab), Riabni (rituximab-arrx), Ruxience (rituximab-pvvr), and Truxima (rituximab-abbs) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).
- Siliq (brodalumab) has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with Siliq. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.
- Olumiant (baricitinib) has a boxed warning for thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis.

- Warnings/Precautions (applying to some or all of the agents in the class):
  - Reactivation of HBV or other viral infections
  - Serious infections including tuberculosis
  - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
  - Cytopenias and pancytopenia
  - Worsening and new onset congestive heart failure
  - Hypersensitivity reactions
  - Lupus-like syndrome
  - Malignancy and lymphoproliferative disorders
  - Avoiding live vaccinations and therapeutic infectious agents
  - Noninfectious pneumonia with Stelara (ustekinumab)
  - Increased lipid parameters and liver function tests with Actemra (tocilizumab), Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib) and Kevzara (sarilumab)
  - Increased incidence of CD and UC with Cosentyx (secukinumab) and Taltz (ixekizumab); risk of new-onset CD or exacerbation of CD with Siliq (brodalumab)
  - Diarrhea, nausea, and vomiting with Otezla (apremilast)
  - Depression with Otezla (apremilast)
  - Gastrointestinal perforations with Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Olumiant (baricitinib), Actemra (tocilizumab), Kevzara (sarilumab), Rituxan (rituximab), Riabni (rituximab-arrx), Ruxience (rituximab-pvvr), and Truxima (rituximab-abbs)
  - Thrombosis with Olumiant (baricitinib)
  - Embryo-fetal toxicity with Rinvoq (upadacitinib)
  - Hepatotoxicity with Actemra (tocilizumab)
  - Cardiovascular and cerebrovascular reactions during and after infusion (infliximab)
  - Macrophage activation syndrome with Ilaris (canakinumab)
  - Posterior reversible encephalopathy syndrome (PRES) with Stelara (ustekinumab)
  - Consult prescribing information for other drug-specific warnings/precautions
  - Cytomegalovirus and Epstein-Barr Virus reactivation (abatacept)
- Adverse Reactions:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension, and headache.
  - Consult prescribing information for other drug-specific AEs
- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a 5-year study in RA and a 10-year study in patients with early RA (*Keystone et al 2014a, Burmester et al 2014b*). In the 5-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 PY and 2.8 events per 100 PY, respectively. The rate of serious events was highest in the first 6 months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over 5 years in patients with RA (*Keystone et al 2014b*). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 PY), and upper respiratory infections (rate of 7.3 per 100 PY). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 PY for malignancies.

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- Abatacept has been evaluated in 2 long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the 7 year follow-up and a 52-week double-blind study (*Westhovens et al 2014*). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 PY), malignancies (3.2 events per 100 PY), and autoimmune events (1.2 events per 100 PY). In a 5-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99 events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year 1 and year 5, respectively.
- A randomized controlled noninferiority trial compared tofacitinib to TNF inhibitors in terms of risk for major cardiovascular adverse events and malignancy (*Ytterberg et al 2022*). A total of 1455 patients with active RA and at least 1 additional cardiovascular risk factor were randomized to receive tofacinitib 5 or 10 mg twice daily or a TNF inhibitor. During a median follow-up of 4 years, major cardiovascular adverse events were more common among patients receiving tofacitinib (3.4% vs 2.5%; hazard ratio, 1.33; 95% CI, 0.91 to 1.94), as were malignancies (4.2% vs 2.9%; hazard ratio, 1.48; 95% CI, 1.04 to 2.09). Noninferiority was not established for tofacitinib vs TNF inhibitors for either endpoint.
- Data from 5 RCTs of Actemra (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4009 patients with moderate to severe RA received at least 1 dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 PY. The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (*Genovese et al 2013*).
- A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the Enbrel (etanercept) plus DMARD group and the DMARD alone group at 6 months, 12 months, and 2 years. At 3 years, withdrawals were significantly reduced in the etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at 6 months, flu-like syndrome at 6 months and 2 years, infection at 6 months and 2 years, malignancy at 12 months and 2 years, pneumonia at 12 months, and serious infection at 12 months and 2 years between the etanercept plus DMARD group and the DMARD group (*Lethaby et al 2013*).
- A systematic review analyzed 66 randomized controlled trials and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (*Strand et al 2015b*). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.
- A meta-analysis analyzed 50 randomized controlled trials and long-term extension studies evaluating biologic DMARDs and tofacitinib to compare the risks of malignancies in patients with RA (*Maneiro et al 2017*). The overall risk of malignancies was 1.01 (95% CI, 0.72 to 1.42) for all TNF antagonists, 1.12 (95% CI, 0.33 to 3.81) for abatacept, 0.54 (95% CI, 0.20 to 1.50) for rituximab, 0.70 (95% CI, 0.20 to 2.41) for tocilizumab, and 2.39 (95% CI, 0.50 to 11.5) for tofacitinib. The authors concluded that treatment with biologic DMARDs or tofacitinib does not increase the risk of malignancies.
- A systematic review and network meta-analysis analyzed 42 randomized controlled trials and found no significant difference between the available JAK inhibitors in terms of major adverse cardiovascular events or venous thromboembolic events (*Alves et al 2022*).
- A pooled analysis of 9 RA trials evaluating baricitinib included 3492 patients (7860 PY exposure). The incidence rate for major adverse cardiovascular events was comparable between placebo (0.5 per 100 PY) and baricitinib 4 mg (0.8 per 100 PY). Incidence rates for arterial thrombotic events and congestive heart failure were also similar between baricitinib and placebo. The occurrence of a deep vein thrombosis or pulmonary embolism occurred more frequently in the baricinitib 4 mg group (6 events in 997 patients) vs placebo (0 events in 1070 patients) (*Taylor et al 2019*). Another pooled analysis of 10 RA trials including 3770 patients (14,744 patient-years exposure) examined the safety of baricitinib over a median of 4.6 years and a maximum of 9.3 years. In this analysis, the incidence rates for serious infections, herpes zoster, major cardiovascular adverse events, malignancy, and deep vein thrombosis/pulmonary embolism were 2.6, 3.0, 0.5, 1.0, and 0.5 per 100 patient-years, respectively (*Taylor et al 2022*).

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- PsO
  - A total of 3,117 patients treated with at least 1 dose of Stelara (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least 4 years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with ≥ 5 years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year 5. The causes of death were considered related to cardiovascular events (n = 5), malignancy (n = 5), infection (n = 3) and other causes (n = 7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year 1 to year 5, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (*Papp et al 2013*).
  - In a 5-year extension study, a total of 2510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (*Kimball et al 2015*). Serious AEs were reported as a cumulative incidence of the entire 5-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month 6 and remained stable through 5 years.
  - In a ≥ 156-week extension study, a total of 1,184 patients treated with apremilast in ESTEEM 1 and 2 were evaluated for long-term safety and tolerability (*Crowley et al 2017*). Serious AEs (≥ 2 patients) were coronary artery disease (n = 6), acute myocardial infarction (n = 4), osteoarthritis (n = 4), and nephrolithiasis (n = 4). The exposure-adjusted incidence rate for major cardiac events was 0.5/100 patients years, for malignancies was 1.2/100 patient years, for serious infections was 0.9/100 patient-years, and for suicide attempts was 0.1/100 patient-years.
  - In a 5-year extension study, 1349 patients treated with guselkumab in VOYAGE 1 and VOYAGE 2 were evaluated for long-term safety; during 7166 patient-years of follow-up, the incidence rates for serious infections, nonmelanoma skin cancer, malignancy other than nonmelanoma skin cancer, and major adverse cardiovascular events were 0.85, 0.34, 0.45, and 0.29 per 100 patient-years, respectively (*Blauvelt et al 2022*).
  - A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (*Kalb et al 2015*). Patients were followed for up to 8 years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; $p < 0.001$) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; $p = 0.002$) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.
- PsA
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (*Kavanaugh et al 2014b*). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.
  - An integrated safety analysis of 4 clinical trials examined the safety of ixekizumab in 1401 patients with PsA (2247.7 patient-years of exposure) (*Deodhar et al 2022[b]*). In this study, the exposure-adjusted incidence rates of serious infections, malignancies, inflammatory bowel disease, depression, and major cerebrocardiovascular events were 1.2, 0.7, 0.1, 1.6, and 0.5 per 100 PY, respectively. No new safety signals were observed.
- AS
  - A meta-analysis of 25 randomized controlled studies with 2403 patients with AS or non-radiographic axial spondyloarthritis treated with agents such as adalimumab, certolizumab, etanercept, golimumab, infliximab, sarilumab, tocilizumab, and secukinumab showed no significant increase in the risk of serious infections with biologic agents compared to controls (OR, 1.42; 95% CI, 0.58 to 3.47) (*Wang et al 2018*).

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- Another meta-analysis of 14 randomized controlled trials with 2032 patients with AS that were treated with adalimumab, certolizumab, etanercept, golimumab, or infliximab revealed no significant difference between TNF inhibitors and placebo for overall serious adverse events (OR, 1.34; 95% CI, 0.87 to 2.05), risk of serious infections (OR, 1.59; 95% CI, 0.63 to 4.01), risk of malignancy (OR, 0.98; 95% CI, 0.25 to 3.85), and discontinuation due to adverse events (OR, 1.55; 95% CI, 0.95 to 2.54) (*Hou et al 2018*).

- Multiple indications
  - One study looked at 23,458 patients who were treated with Humira (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (*Burmester et al 2013b*).
  - Pooled data from 5 Phase 3 trials of SQ golimumab over at least 3 years demonstrated a safety profile consistent with other TNF inhibitors (*Kay et al 2015*). A total of 1179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
  - A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (*Capogrosso Sansone et al 2015).* All but 1 trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.
  - The safety of ustekinumab was examined in a pooled analysis of 12 trials in patients with PsO, PsA, and CD. A total of 5584 patients were evaluated, equating to 4521 PYs. Respective incidences per 100 PY of infections (125.4 vs 129.4), major cardiovascular adverse events (0.5 vs 0.3), malignancies (0.4 vs 0.2), and death (0.1 vs 0.0) were similar between ustekinumab and placebo, respectively (*Ghosh et al 2019*).
  - Several meta-analyses evaluated the safety of TNF inhibitors.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up 1 to 36 months) and 7 open-label extension studies (follow-up 6 to 48 months) (*Minozzi et al 2016*). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up 2 to 36 months) and 6 open-label extension trials (follow-up 6 to 48 months) (*Bonovas et al 2016*). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.

- Drug interactions
  - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
  - Do not give 2 immunomodulators together.
  - For Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), adjust dose with potent inhibitors of cytochrome P450 (CYP) 3A4 and medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Coadministration with potent CYP3A4 inducers and potent immunosuppressive drugs is not recommended.
  - For Olumiant (baricitinib), adjust dose when used with potent inhibitors of organic anion transporter (OAT) 3.
- Risk Evaluation and Mitigation Strategy (REMS)
  - Siliq (brodalumab) is available only through the Siliq REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
    - Prescribers must be certified with the program.

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- Patients must enroll in the program.
- Pharmacies must be certified with the program and must only dispense to patients who are enrolled in the program.

Dosing and Administration

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Actemra (tocilizumab)	Vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL Prefilled syringe or autoinjector: 162 mg/0.9 mL	**RA:** IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800 mg. SQ: < 100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response; ≥ 100 kg, 162 mg administered SQ every week. **PJIA:** IV: < 30 kg, 10 mg/kg IV every 4 weeks; ≥ 30 kg, 8 mg/kg IV every 4 weeks. SQ: < 30 kg, 162 mg SQ every 3 weeks; ≥ 30 kg, 162 mg SQ every 2 weeks. **SJIA:** IV: < 30 kg, 12 mg/kg IV every 2 weeks; ≥ 30 kg, 8 mg/kg IV every 2 weeks SQ: < 30 kg, 162 mg SQ every 2 weeks; ≥ 30 kg, 162 mg SQ once weekly. **GCA:** IV: 6 mg/kg IV every 4 weeks with tapering glucocorticoids. SQ: 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations. **CRS:** < 30 kg, 12 mg/kg IV; ≥ 30 kg, 8	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. **GCA:** Can use alone after discontinuation of glucocorticoids. **CRS:** Can give with corticosteroids. May repeat up to 3 additional doses if no clinical improvement, with at least 8 hours between doses. **RA, PJIA, and SJIA, SSc-ILD, and GCA**: Adjust dose for liver enzyme abnormalities, low platelet count, infection, and low ANC. **PJIA**: Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate.	Give as a single 60-minute intravenous infusion. < 30 kg, use a 50 mL infusion bag. ≥ 30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs. Patients can self-inject with the prefilled syringe or autoinjector. Rotate injection sites. SQ administration with the prefilled autoinjector has not been studied in SSc-ILD. IV administration is not approved for SSc-ILD. Laboratory abnormalities in patients with GCA may warrant dose interruption with IV administration and dose interruption or reduction with SQ administration. Doses > 600 mg per infusion not recommended in GCA.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		mg/kg IV; maximum, 800 mg per infusion. **SSc-ILD:** 162 mg SQ once weekly		
Amjevita (adalimumab-atto)	Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL Prefilled autoinjector: 40 mg/0.8 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week or 80 mg every other week if not on MTX. **PJIA:** 15 kg to < 30 kg: 20 mg SQ every other week; ≥ 30 kg, 40 mg SQ every other week **PsO:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose.	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued.	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room temperature prior to injecting.
Avsola (infliximab-axxq)	Vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen, and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Cimzia (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	**CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks. **RA, PsA:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks.	Patients can self-inject with the prefilled syringe.	When a 400 mg dose is required, give as 2 200 mg SQ injections in separate sites in the thigh or abdomen.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		PsO: 400 mg SQ every other week or 400 mg SQ initially and at weeks 2 and 4, followed by 200 mg every other week (for body weight ≤ 90 kg) **AS, NRAS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks.		
Cosentyx (secukinumab)	Sensoready pen: 150 mg/1 mL Prefilled syringe: 150 mg/1 mL, 75 mg/0.5 mL Vial: 150 mg lyophilized powder	**PsO:** 300 mg by SQ injection at weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks; for some patients, 150 mg may be acceptable. **PsO in pediatric patients ≥ 6 years of age:** Dose is based on weight (< 50 kg, 75 mg; ≥ 50 kg, 150 mg) and administered at weeks 0, 1, 2, 3 and 4, followed every 4 weeks. **PsA, AS, NRAS:** With a loading dose (not required): 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg every 4 weeks. **PsA in pediatric patients:** Dose is based on weight (≥ 15 kg and < 50 kg, 75 mg; ≥ 50 kg, 150 mg) and administered at weeks 0, 1, 2, 3 and 4, followed by every 4 weeks. **ERA:** Dose is based on weight (≥ 15 kg and < 50 kg, 75 mg; ≥ 50 kg, 150 mg) and administered at weeks 0, 1, 2, 3 and 4,	**PsA:** For PsA patients with coexistent moderate to severe PsO, dosing for PsO should be followed. If active PsA or AS continues in adults, consider 300 mg dose every 4 weeks.	Each 300 mg dose is given as 2 subcutaneous injections of 150 mg. Patients may self-administer with the pen or prefilled syringe. The vial is for healthcare professional use only.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		followed by every 4 weeks.		
Enbrel (etanercept)	Prefilled syringe: 25 mg/0.5 mL and 50 mg/mL Prefilled SureClick autoinjector: 50 mg/mL Multiple-use vial: 25 mg lyophilized powder Solution: 50 mg/mL in Enbrel Mini® cartridge for use with reusable autoinjector only Single-dose vial: 25 mg/0.5 mL	**RA, AS, PsA:** 50 mg SQ weekly. **PsO (adults):** 50 mg SQ twice weekly for 3 months, then 50 mg weekly. **PJIA and PsO (pediatrics):** ≥ 63 kg, 50 mg SQ weekly; < 63 kg, 0.8 mg/kg SQ weekly.	**RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued. **JIA:** NSAIDs glucocorticoids, or analgesics may be continued.	Patients may be taught to self-inject. May bring to room temperature prior to injecting.
Humira (adalimumab)	Prefilled syringe: 10 mg/0.1 mL 10 mg/0.2 mL 20 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL Single-use pen: 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL Single-use vial: 40 mg/0.8 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week or 80 mg every other week if not on MTX. **PJIA or pediatric uveitis:** 10 kg to < 15 kg: 10 mg SQ every other week; 15 kg to < 30 kg: 20 mg SQ every other week; ≥ 30 kg, 40 mg SQ every other week **HS:** 160 mg SQ on Day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29), begin 40 mg weekly or 80 mg every other week. **PsO and UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose. **HS in adolescent patients ≥ 12 years and older:** 30 kg to < 60 kg: 80 mg on day 1, 40 mg on day 8;	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued.	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room temperature prior to injecting.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		maintenance dose is 40 mg every other week. ≥ 60 kg: 160 mg on day 1, 80 mg on day 15, 40 mg on day 29; maintenance dose is 40 mg every week.		
Ilaris (canakinumab)	Single-dose vial: 150 mg injection solution	**SJIA and adult-onset Still's disease:** ≥ 7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg). **CAPS**: ≥ 15 to ≤ 40 kg, 2 mg/kg SQ; > 40 kg, 150 mg SQ; frequency every 8 weeks. **TRAPS, HIDS/MKD, and FMF**: ≤ 40 kg, 2 mg/kg SQ; > 40 kg, 150 mg SQ; frequency every 4 weeks.	**For CAPS:** children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg. **For TRAPS, HIDS/MKD, and FMF:** If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤ 40 kg) or 300 mg (weight > 40 kg).	Do not inject into scar tissue.
Ilumya (tildrakizumab-asmn)	Prefilled syringe: 100 mg/mL	**PsO:** 100 mg SQ at weeks 0 and 4, and then every 12 weeks.		Should be administered only by a healthcare provider. Bring to room temperature (30 minutes) prior to injecting.
Inflectra (infliximab-dyyb)	Vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		maintenance regimen of 5 mg/kg every 6 weeks.		
Kevzara (sarilumab)	Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL Prefilled pen: 150 mg/1.14 mL 200 mg/1.14 mL	**RA:** 200 mg SQ every 2 weeks.	**RA:** give with or without MTX or other conventional DMARDs Reduce dose for neutropenia, thrombocytopenia, and elevated liver enzymes.	Patients may be taught to self-inject. Bring to room temperature (30 minutes [pre-filled syringe] or 60 minutes [pre-filled pen]) prior to injecting. Rotate injection sites.
Kineret (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID) and DIRA:** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day.	**NOMID**: dose can be given once or twice daily. CrCl < 30 mL/min: give dose every other day	Patients may be taught to self-inject. A new syringe must be used for each dose.
Olumiant (baricitinib)	Tablet: 1 mg, 2 mg, and 4 mg	**RA:** 2 mg once daily. **Alopecia areata:** 2 mg once daily; increase to 4 mg once daily if response is inadequate	**Alopecia areata**: for patients with nearly complete or complete scalp hair loss, consider treating with 4 mg once daily; once patients achieve an adequate response to treatment with 4 mg, decrease the dosage to 2 mg daily Dosage modification may be required for cytopenias or anemia, or when used concomitantly with potent OAT3 inhibitors. Avoid use in combination with other JAK inhibitiors, biologic DMARDs, or potent immunosuppressants such as azathioprine and cyclosporine.	May be taken with or without food. Tablets may be crushed and dispersed in water for patients unable to swallow whole tablets.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			Renal: Use not recommended in patients with estimated glomerular filtration rate < 30 mL/min/1.73m^2; adjust dosage in patients with estimated glomerular filtration rate between 30 and 60 mL/min/1.73 m^2.	
Orencia (abatacept)	Vial: 250 mg Prefilled syringe: 50 mg/0.4 mL 87.5 mg/0.7 mL 125 mg/1 mL ClickJect autoinjector: 125 mg/mL	**RA:** IV: < 60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; > 100 kg, 1,000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first 125 mg SQ injection within a day of the IV infusion and then once weekly. **PJIA:** IV: 6 to 17 years and < 75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter. > 75 kg, follow adult RA IV schedule; maximum dose = 1,000 kg. SQ: 2 to 17 years, 10 to < 25 kg, 50 mg once weekly; 25 to < 50 kg, 87.5 mg once weekly, ≥ 50 kg, 125 mg once weekly. **PsA:** IV: follow adult RA IV schedule.	Before administering for treatment of GVHD, administer recommended antiviral prophylaxis.	IV infusion should be over 30 minutes. Use 100 mL bag for IV infusion. Do not administer with other drugs. Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		SQ: 125 mg once weekly without IV dose. **GVHD:** IV: ≥ 6 years: 10 mg/kg (maximum 1000 mg) on the day before transplantation, then administration on days 5, 14, and 28 after transplantation. ≥ 2 to < 6 years: 15 mg/kg (maximum 1000 mg) on the day before transplantation, then 12 mg/kg on days 5, 14, and 28 after transplantation.		
Otezla (apremilast)	Tablet: 10 mg, 20 mg, and 30 mg	**PsA, PsO, Behçet's:** Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: 30 mg twice daily.	Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms. Dosage should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl <30 mL/min as estimated by the Cockcroft-Gault equation). For initial dosing in these patients, use only the morning titration schedule listed above (evening doses should be excluded).	May be taken with or without food. Do not crush, split, or chew the tablets.
Remicade (infliximab)	Vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.		Infuse over 2 hours. Do not administer with other drugs.
Renflexis (infliximab-abda)	Vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Riabni (rituximab-arrx)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.
Rinvoq (upadacitinib)	Extended release tablet: 15 mg, 30 mg, and 45 mg	**RA, PsA, AS, NRAS:** 15 mg once daily.		May be administered with or without food.
Rituxan (rituximab)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		no sooner than every 16 weeks.		
Ruxience (rituximab-pvvr)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.
Siliq (brodalumab)	Prefilled syringe: 210 mg/1.5 mL	**PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks.	**PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation.	Patients may self-inject when appropriate and after proper training. The syringe should be allowed to reach room temperature before injecting.
Simponi/Simponi Aria (golimumab)	SmartJect autoinjector: 50 mg/0.5 mL and 100 mg/mL Prefilled syringe: 50 mg/0.5 mL and 100 mg/mL Aria, Vial: 50 mg/4 mL	**RA, PsA, and AS**: 50 mg SQ once monthly **UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks. **Aria (RA, PsA, and AS)**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks. **Aria (PJIA):** 80 mg/m^2 IV at weeks 0 and 4, and then every 8 weeks.	**RA:** give with MTX. **PsA and AS**: may give with or without MTX or other DMARDs. Needle cover of the syringe contains dry rubber (latex). **Aria (RA)**: give with MTX (**PsA, AS)**: give with or without MTX or other non-biologic DMARDs. Corticosteroids, NSAIDs, and/or analgesics may be continued. Efficacy and safety of switching between IV and SQ formulations have not been established.	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated. For SQ, bring to room temperature for 30 minutes prior to injecting. **Aria**: IV infusion should be over 30 minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL. Do not administer with other drugs.
Skyrizi (risankizumab-rzaa)	Prefilled syringe: 75 mg/0.83 mL, 150 mg/mL	**PsO, PsA:** 150 mg SQ at week 0, week 4, and every 12 weeks thereafter.	Product is not made with natural rubber latex.	Each dose must be administered in different anatomic locations.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Prefilled pen (autoinjector): 150 mg/mL Prefilled cartridge with on-body injector (for CD only): 360 mg/2.4 mL Vial (for IV infusion in CD only): 600 mg/10 mL		**PsA**: give with or without non-biologic DMARD.	Patients may be taught to self-inject using the prefilled syringes or pen.
Sotyktu (deucravacitinib)	Tablet: 6 mg	**PsO:** 6 mg once daily	Not recommended in severe hepatic impairment.	May take with or without food.
Stelara (ustekinumab)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL	**PsO**: ≤ 100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. > 100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg > 100 kg, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **PsA (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 kg or more, 45 mg > 100 kg with concomitant moderate-to-severe PsO, 90 mg; administer recommended dose	**Co-existent moderate-to-severe PsO with PsA weighing >100 kg**: 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. Needle cover of the syringe contains dry rubber (latex).	Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is recommended that Stelara be administered by a healthcare provider. Stelara for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infused over at least 1 hour. Rotate injection sites.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		initially, 4 weeks later, then every 12 weeks.		
Taltz (ixekizumab)	Prefilled syringe: 80 mg/mL Autoinjector: 80 mg/mL	**PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. **PsO (6 to < 18 years old):** < 25 kg, 40 mg SQ at week 0 then 20 mg every 4 weeks; 25 to 50 kg, 80 mg SQ at week 0 then 40 mg every 4 weeks; > 50 kg, 160 mg SQ at week 0, then 80 mg every 4 weeks. **PsA, AS:** 160 mg by SQ injection at week 0, followed by 80 mg every 4 weeks. **NRAS:** 80 mg by SQ injection every 4 weeks. NOTE: For patients with PsA with coexistent moderate-to-severe PsO, use dosing regimen for PsO.		Patients weighing >50 kg may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites. Doses for patients weighing ≤50 kg must be administered by a healthcare professional. Contents of a prefilled syringe should be transferred to a sterile vial, and the appropriate dose drawn out of the vial into a new syringe.
Tremfya (guselkumab)	Prefilled syringe or single-dose patient-controlled autoinjector: 100 mg/mL	**PsO, PsA:** 100 mg by SQ injection at week 0, week 4, and then every 8 weeks	For **PsA**, Tremfya may be used alone or in combination with MTX.	Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting.
Truxima (rituximab-abbs)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Xeljanz/Xeljanz XR (tofacitiib)	Tablet: 5 mg, 10 mg Extended-release Tablet: 11 mg, 22 mg Oral solution: 1 mg/mL	**RA, AS:** 5 mg PO twice daily or 11 mg PO once daily **PsA:** 5 mg PO twice daily or 11 mg once daily used in combination with nonbiologic DMARDs **PJIA:** 3.2 mg (3.2 mL oral solution) twice daily if weight ≥ 10 kg but < 20 kg; 4 mg (4 mL oral solution) twice daily if weight ≥ 20 kg but < 40 kg; and 5 mg (tablet or 5 mL oral solution) twice daily if weight ≥ 40 kg.	Patients may switch from Xeljanz 5 mg twice daily to Xeljanz XR 11 mg once daily the day following the last dose of Xeljanz 5 mg. Xeljanz XR is not interchangeable or substitutable with Xeljanz oral solution. Dose adjustment needed in patients taking CYP450 inhibitors, and with moderate or severe renal impairment, moderate hepatic impairment, lymphopenia, neutropenia, and anemia. Moderate to severe impairment: Patients with RA, PsA, or AS receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with PJIA on Xeljanz tablets or oral solution should reduce dosing to once daily if taking 3.2 mg, 4 mg, or 5 mg twice daily. For patients on hemodialysis, administer doses after the dialysis session. Do not take supplemental doses if a dose was taken before dialysis.	May take with or without food. Swallow Xeljanz XR tablets whole; do not crush, split, or chew. Xeljanz should not be initiated in patients with absolute lymphocyte count < 500 cells/mm^3, absolute neutrophil count < 1000 cells/mm^3, or hemoglobin < 9 g/dL. Administer Xeljanz oral solution with the included press-in bottle adapter and oral dosing syringe.

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Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			Hepatic impairment: Patients with RA, PsA, or AS receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with PJIA on Xeljanz tablets or oral solution should reduce dosing to once daily if taking 3.2 mg, 4 mg, or 5 mg twice daily. Not recommended in severe hepatic impairment.	

ANC=absolute neutrophil count; AS=ankylosing spondylitis; CRS=cytokine release syndrome; DIRA=deficiency of interleukin-1 receptor antagonist; DMARD=disease-modifying anti-rheumatic drug; ERA=enthesitis-related arthritis; GCA=giant cell arteritis; GVHD: graft-vs-host disease; HS=hidradenitis suppurative; IV=intravenous infusion; JAK=Janus kinase; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID=neonatal-onset multisystem inflammatory disease; NRAS=nonradiographic axial spondyloarthritis; NSAID=non-steroidal anti-inflammatory drug; PJIA=polyarticular juvenile idiopathic arthritis; PO=orally; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; SQ=subcutaneously; SSc-ILD=systemic sclerosis-associated interstitial lung disease.
See the current prescribing information for full details.

Conclusion

- Immunomodulators are available for a variety of conditions associated with inflammation. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Limited head-to-head clinical trials between the agents have been completed.
  - In patients with RA, abatacept and infliximab showed comparable efficacy at 6 months, but abatacept demonstrated greater efficacy after 1 year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (*Schiff et al 2008*).
  - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over 2 years in a single-blind study (*Schiff et al 2014*).
  - In patients with RA, upadacitinib was superior to abatacept for changes in the DAS28-CRP and the achievement of remission (*Rubbert-Roth et al 2020*).
  - In patients with RA and an inadequate response or intolerance to MTX, sarilumab significantly improved change from baseline in DAS28-ESR over adalimumab (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab.
  - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (*Gabay et al 2013*). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
  - In patients with RA and inadequate response or intolerance to MTX, upadacitinib was associated with significantly greater ACR 20 response compared with adalimumab at weeks 12 and 26 *(Fleischman et al 2018).*
  - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have noninferior efficacy to initial TNF inhibitor treatment (*Porter et al 2016*).

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- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (*Gottenberg et al 2016*). Another recent randomized trial did not demonstrate clinical efficacy differences between abatacept, rituximab, and use of a second TNF inhibitor in this patient population *(Manders et al 2015*).
- Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR and CLARITY studies, which were double-blind, randomized controlled trials in 676 and 1102 patients, respectively, with moderate to severe PsO (*Bagel et al 2018, Thaçi et al 2015*). In both studies, the proportion of patients achieving PASI 90 was significantly higher with secukinumab compared to ustekinumab (CLEAR: 79% vs 57.6%, $p < 0.0001$; CLARITY: 66.5% vs 47.9%, $p < 0.0001$) at week 16 in CLEAR and at week 12 in CLARITY.
- In the IXORA-S study, the proportion of patients achieving PASI 90 at week 12 was significantly higher with ixekizumab compared to ustekinumab (72.8% vs 42.2%, respectively; $p < 0.001$) (*Reich et al 2017[b]).*
- In the IXORA-R study, ixekizumab was found noninferior to guselkumab for achievement of PASI 100 at week 24 (50% vs 52%, respectively; statistical significance was not reached for this comparison ($p = 0.41$) (*Blauvelt et al 2021).*
- A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; $p = 0.01$ vs ustekinumab 45 mg; $p < 0.001$ vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema than ustekinumab (14.7% vs 0.7%) (*Griffiths et al 2010*).
- In the FIXTURE study in patient with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (*Langley et al 2014*).
- In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
- In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (*Lebwohl et al 2015*).
- In the VOYAGE 1 and VOYAGE 2 studies, the proportions of patients with moderate to severe PsO achieving IGA 0 or 1 and PASI 90 were higher with guselkumab compared to those treated with adalimumab *(Blauvelt et al 2017, Reich et al 2017[a]*).
- In two trials of patients with moderate to severe chronic PsO, risankizumab was associated with significant improvement in PASI 90 response at week 16 vs ustekinumab *(Gordon et al 2018)*.
- In the IMMerge trial, risankizumab was noninferior to secukinumab for the proportion of patients achieving PASI 90 at week 16 (73.8% vs 65.6%, respectively) and was superior to secukinumab at week 52 (86.6% vs 57.1%, respectively; $p < 0.001$) (*Warren et al 2021*).
- In ECLIPSE, patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) or Cosentyx (secukinumab) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; $p < 0.0001$).
- No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (*Park et al 2013, Park et al 2016, Park et al 2017, Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). Similarly, no meaningful differences between infliximab and infliximab-abda were found in treatment of RA in clinical studies to establish biosimilarity (*Choe et al 2017, Shin et al 2015*).
- In patients with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab for ≥ 6 months, infliximab-dyyb was noninferior to infliximab originator group for disease worsening (*Jørgensen et al 2017*).
- In the SPIRIT-H2H study, ixekizumab led to a higher proportion of patients with PsA achieving the combined ACR 50 and PASI 100 and PASI 100 alone compared with adalimumab (*Smolen et al 2020[b]*)
- More comparative studies are needed.

- For RA, the ACR recommends the use of conventional DMARDs, a TNF inhibitor, a non-TNF inhibitor biologic (tocilizumab, sarilumab, abatacept, or rituximab [only in patients that have had an inadequate response to TNF inhibitors or have a history of lymphoproliferative disorder]), or a JAK inhibitor (tofacitinib, baricitinib, upadacitinib). Biosimilars are considered equivalent to FDA-approved originator biologics (*Fraenkel et al 2021*). EULAR guidelines for RA management were recently updated (*Smolen et al 2023*). EULAR recommends that therapy with DMARDs should be

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initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, others should be considered. If poor prognostic factors are present with treatment failure, a biological DMARD should be added; JAK inhibitors may be considered, but pertinent risk factors must be taken into account. In patients who cannot use csDMARDs as a comedication, IL-6 inhibitors and targeted synthetic DMARDs may have some advantages compared with other biologic DMARDs. If a biological or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF or IL-6 inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF or IL-6 inhibitor. EULAR has also released guidelines for use of antirheumatic drugs in pregnancy, which state that the TNF inhibitors etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).

- EULAR 2019 PsA guidelines recommend biologic DMARDs in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX (*Gossec et al 2020, Kerschbaumer et al 2020*). For patients with peripheral arthritis, an inadequate response to at least 1 synthetic DMARD, and relevant skin involvement, biologics targeting IL-12/23 or IL-17 pathways may be considered. In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD and at least one biologic DMARD, JAK inhibitors may be considered; JAK inhibitors may also be considered in patients for whom biologic DMARD therapy is not appropriate. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics and JAK inhibitors are not appropriate.
- Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, JAK inhibitors, and PDE-4 inhibitors (*Coates et al 2022[b]*). Joint guidelines from the AAD/NPF on the treatment of PsO with biologics do not provide ranking for preferences of individual biologics, but do note that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab can be recommended as a monotherapy option for patients with moderate to severe PsO (*Menter et al 2019*).
- The ACR/NPF guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics, IL-12/23 biologics, abatacept, and tofacitinib (*Singh et al 2019*).
- The ACR guideline for SJIA conditionally recommends an IL-1 inhibitor or IL-6 inhibitor for initial treatment; no specific agent is preferred (*Onel et al 2022*). Patients with JIA and active sacroiliitis or enthesitis are recommended to receive TNF inhibitor therapy, and patients with non-systemic polyarthritis are recommended to receive TNF inhibitor therapy, abatacept, or tocilizumab. Patients with continued disease activity and primary TNF inhibitor failure are recommended to receive abatacept or tocilizumab *(Ringold et al 2019)*.
- Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, with infliximab a potential second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
- Joint guidelines from ASAS and EULAR state that TNF inhibitors, IL-17A inhibitors, or JAK inhibitors should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with a TNF inhibitor or IL-17A inhibitor (*Ramiro et al 2023*). The 2019 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over another for AS for most patients. Secukinumab or ixekizumab are recommended in patients with active disease who have primary nonresponse with a TNF inhibitor (*Ward et al 2019*).
- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (*Levy-Clarke et al 2016*).
- Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. Tocilizumab, TNF inhibitors, tofacitinib, sarilumab, baricitinib, and upadacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors, tofacitinib, baricitinib, and upadacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior. Tofacitinib (10 mg twice daily dose), upadacitinib, and baricitinib also have boxed warnings regarding thrombosis risk.
  - A final FDA review of a large randomized safety clinical trial comparing Xeljanz (tofacitinib) vs a TNF inhibitor found an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with tofacitinib. The final results showed an increased risk of adverse events with the lower dose as well as the higher

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dose. The FDA believes that baricitinib and upadacitinib have similar risks because they share the same mechanism of action. The FDA required revisions to the Boxed warning, several sections of the prescribing information, and the patient medication guide and limited all approved uses to certain patients who have not responded or cannot tolerate 1 or more TNF inhibitors for tofacitinib and, because they share the same mechanism of action, baricitinib and upadacitinib (*FDA Drug Safety Communication 2021*).

- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast, baricitinib, tofacitinib, and upadacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast, baricitinib, tofacitinib, and upadacitinib are given orally.
- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

References

- Actemra prescribing information. Genentech, Inc. South San Francisco, CA. December 2022.
- Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations. Part II: topical, intralesional, and systemic medical management. *J Am Acad Dermatol*. 2019;81(1):91-101. doi: 10.1016/j.jaad.2019.02.068.
- Alves C, Penedones A, Mendes D, Marques FB. Risk of cardiovascular and venous thromboembolic events associated with janus kinase inhibitors in rheumatoid arthritis: a systematic review and network meta-analysis. *J Clin Rheumatol*. 2022;28(2):69-76. doi:10.1097/RHU.0000000000001804.
- American College of Rheumatology. Position statement on biosimilars. March 2018. https://www.rheumatology.org/portals/0/files/biosimilars-position-statement.pdf. Accessed February 6, 2022.
- Amjevita prescribing information. Amgen, Inc, Thousand Oaks, CA. July 2022.
- Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis. *Arthritis Care Res (Hoboken)*. 2019;71(6):703-716. doi: 10.1002/acr.23871.
- Antoni C, Krueger GG, de Vam K, et al. IMPACT 2 Trial Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis*. 2005;64(8):1150-7.
- Arcalyst prescribing information. Regeneron Pharmaceuticals, Inc. Tarrytown, NY. May 2021.
- Armstrong AW, Gooderham M, Warren RB, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. *J Am Acad Dermatol*. 2023;88(1):29-39. doi:10.1016/j.jaad.2022.07.002
- Atsumi T, Tanaka Y, Yamamoto K, et al. Clinical benefit of 1-year certolizumab pegol (CZP) add-on therapy to methotrexate treatment in patients with early rheumatoid arthritis was observed following CZP discontinuation: 2-year results of the C-OPERA study, a phase III randomised trial. *Ann Rheum Dis*. 2017;76(8):1348-1356.
- Atsumi T, Yamamoto K, Takeuchi T, et al. The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naïve early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. Ann Rheum Dis. 2016;75:75-83.
- Atteno M, Peluso R, Costa L, et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. *Clin Rheumatol.* 2010;29:399-403.
- Avsola prescribing information. Amgen, Inc. Thousand Oaks, CA. September 2021.
- Bae SC, Lee YH. Comparative efficacy and tolerability of sarilumab 150 and 200 mg in patients with active rheumatoid arthritis : A Bayesian network meta-analysis of randomized controlled trials. *Z Rheumatol*. 2018;77(5):421-428. doi: 10.1007/s00393-017-0292-6.
- Baeten D, Sieper J, Braun J, et al for the MEASURE 1 Study Group and MEASURE 2 Study Group. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *N Engl J Med*. 2015; 373(26):2534-48.
- Bagel J, Blauvelt A, Nia J, et al. Secukinumab maintains superiority over ustekinumab in clearing skin and improving quality of life in patients with moderate to severe plaque psoriasis: 52-week results from a double-blind phase 3b trial (CLARITY). *J Eur Acad Dermatol Venereol*. 2021;35(1):135-142. doi:10.1111/jdv.16558.
- Bagel J, Nia J, Hashim PW, et al. Secukinumab is superior to ustekinumab in clearing skin in patients with moderate to severe plaque psoriasis (16-week CLARITY results). *Dermatol Ther (Heidelb)*. 2018;8(4):571-579. doi: 10.1007/s13555-018-0265-y.
- Baraliakos X, Kivitz AJ, Deodhar AA, et al; MEASURE 1 Study Group. Long-term effects of interleukin-17A inhibition with secukinumab in active ankylosing spondylitis: 3-year efficacy and safety results from an extension of the Phase 3 MEASURE 1 trial. *Clin Exp Rheumatol*. 2018;36(1):50-55.
- Bergrath E, Gerber RA, Gruben D, Lukic T, Makin C, Wallenstein G. Tofacitinib versus biologic treatments in moderate-to-severe rheumatoid arthritis patients who have had an inadequate response to nonbiologic DMARDs: systematic literature review and network meta-analysis. *Int J Rheumatol*. 2017;2017:8417249.
- Bijlsma JW, Welsing PM, Woodworth TG, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. *Lancet*. 2016;388:343-55.
- Bilal J, Bin Riaz I, Kamal MU, et al. A systematic review and meta-analysis of efficacy and safety of novel interleukin inhibitors in the management of psoriatic arthritis. *J Clin Rheumatol*. 2018; 24(1):6-13. doi: 10.1097/RHU.0000000000000583.
- Bingham CO, Mendelsohn AM, Kim L, et al. Maintenance of clinical and radiographic benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: week-112 efficacy and safety results of the open-label long-term extension of a phase III, double-blind, randomized, placebo-controlled trial. *Arthritis Care Res*. 2015;67:1627-1636.
- Blauvelt A, Leonardi C, Elewski B, et al. A head-to-head comparison of ixekizumab vs guselkumab in patients with moderate-to-severe plaque psoriasis: 24-week efficacy and safety results from a randomized, double-blinded trial. *Br J Dermatol*. 2021;184(6):1047-1058. doi:10.1111/bjd.19509.

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- Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol.* 2017;76(3):405-417.
- Blauvelt A, Prinz JC, Gottlieb AB, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). *Br J Dermatol.* 2015;172(2):484-93.
- Blauvelt A, Tsai TF, Langley RG, et al. Consistent safety profile with up to 5 years of continuous treatment with guselkumab: pooled analyses from the phase 3 VOYAGE 1 and VOYAGE 2 trials of patients with moderate-to-severe psoriasis. *J Am Acad Dermatol*. 2022;86(4):827-834. doi:10.1016/j.jaad.2021.11.004.
- Bodemer C, Kaszuba A, Kingo K, et al. Secukinumab demonstrates high efficacy and a favourable safety profile in paediatric patients with severe chronic plaque psoriasis: 52-week results from a Phase 3 double-blind randomized, controlled trial. *J Eur Acad Dermatol Venereol*. 2021;35(4):938-947. doi:10.1111/jdv.17002.
- Boehringer Ingelheim. VOLTAIRE-X phase III data in patients with moderate-to-severe chronic plaque psoriasis support interchangeability application. Boehringer Ingelheim. Published April 23, 2021. https://www.boehringer-ingelheim.us/press-release/voltaire-x-phase-iii-data-patients-moderate-severe-chronic-plaque-psoriasis-support. Accessed February 6, 2023.
- Bonovas S, Minozzi S, Lytras T, et al. Risk of malignancies using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. *Expert Opin Drug Saf*. 2016;15(sup1):35-54.
- Braun J, Baraliakos X, Deodhar A, et al. Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. *Ann Rheum Dis*. 2017;76(6):1070-1077.
- Braun J, Baraliakos X, Deodhar A, et al. Secukinumab shows sustained efficacy and low structural progression in ankylosing spondylitis: 4-year results from the MEASURE 1 study. *Rheumatology (Oxford)*. 2019;58(5):859-868. doi: 10.1093/rheumatology/key375.
- Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomized controlled multicentre trial. *Lancet.* 2002;359(9313):1187-93.
- Braun J, van der Horst-Bruinsma IE, Huang F, et al. Clinical efficacy and safety of etanercept vs sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. *Arthritis Rheum.* 2011;63(6):1543-51.
- Brunner H, Ruperto N, Zuber Z, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomized, double-blind withdrawal trial. *Ann Rheum Dis*. 2015;74:1110-117. doi:10.1136/annrheumdis-2014-205351.
- Burmester GR, Blanco R, Charles-Schoeman C, et al for the ORAL Step Investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomized phase 3 trial. *Lancet.* 2013[a];381:451-60.
- Brunner HI, Ruperto N, Zuber Z, et al. Efficacy and safety of tocilizumab for polyarticular-course juvenile idiopathic arthritis in the open-label two-year extension of a phase III trial. *Arthritis Rheumatol*. 2021;73(3):530-541. doi:10.1002/art.41528.
- Burmester GR, Lin Y, Patel R, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis*. 2017;76(5):840-847.
- Burmester GR, Matucci-Cerinic M, Mariette X, et al. Safety and effectiveness of adalimumab in patients with rheumatoid arthritis over 5 years of therapy in a phase 3b and subsequent postmarketing observational study. *Arthritis Res Ther*. 2014b;16(1):R24. doi: 10.1186/ar4452.
- Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term safety in 23,458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis*. 2013[b];72: 517–24.
- Burmester GR, Rubbert-Roth A, Cantagrel A, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab vs intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). *Ann Rheum Dis*. 2014a;73:69-74.
- Burmester GR, Rubbert-Roth A, Cantagrel A, et al. Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA). *Ann Rheum Dis*. 2016;75:68-74.
- Burmester G, Drescher E, Hrycaj P, Chien D, Pan Z, Cohen S. Efficacy and safety results from a randomized double-blind study comparing proposed biosimilar ABP 798 with rituximab reference product in subjects with moderate-to-severe rheumatoid arthritis. *Clin Rheumatol*. 2020;39(11):3341-3352. doi:10.1007/s10067-020-05305-y.
- Busard C, Zweegers J, Limpens J, et al. Combined use of systemic agents for psoriasis: a systematic review. *JAMA Dermatol*. 2014;150(11):1213-1220.
- Calin A, Dijkmans BAC, Emery P, et al. Outcomes of a multicentre randomized clinical trial of etanercept to treat ankylosing spondylitis. *Ann Rheum Dis*. 2004; 63:1594-600.
- Capogrosso Sansone A, Mantarro S, Tuccori M, et al. Safety profile of certolizumab pegol in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis. *Drug Saf*. 2015;38:869-888.
- Chandran V, van der Heijde D, Fleischmann RM, et al. Ixekizumab treatment of biologic-naïve patients with active psoriatic arthritis: 3-year results from a phase III clinical trial (SPIRIT-P1). *Rheumatology (Oxford)*. 2020;59(10):2774-2784. doi:10.1093/rheumatology/kez684.
- Chen C, Zhang X, Xiao L, et al. Comparative effectiveness of biologic therapy regimens for ankylosing spondylitis: a systematic review and a network meta-analysis. Medicine (Baltimore). 2016;95(11):e3060. doi: 10.1097/MD.0000000000003060.
- Choe JY, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis*. 2017;76(1):58-64.
- Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001;344(12):907-16.
- Cimzia prescribing information. UCB, Inc. Smyrna, GA. December 2022.
- Coates LC, Gossec L, Theander E, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: results through one year of a phase IIIb, randomised, controlled study (COSMOS). *Ann Rheum Dis*. 2022[a];81(3):359-369. doi:10.1136/annrheumdis-2021-220991.
- Coates LC, Soriano ER, Corp N, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol.* 2022[b];18:465-479. doi:10.1038/s41584-022-00798-0

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- Cohen SB, Alonso-Ruiz A, Klimiuk PA, et al. Similar efficacy, safety and immunogenicity of adalimumab biosimilar BI 695501 and Humira reference product in patients with moderately to severely active rheumatoid arthritis: results from the phase III randomised VOLTAIRE-RA equivalence study. *Ann Rheum Dis.* 2018;77(6):914-921. doi:10.1136/annrheumdis-2017-212245.
- Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti–tumor necrosis factor therapy results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis* Rheum. 2006;54: 2793-806.
- Cohen S, Genovese MC, Choy E, et al. Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: a randomised, double-blind, phase III equivalence study. *Ann Rheum Dis*. 2017;76:1679-1687. doi:10.1136/annrheumdis-2016-210459
- Cohen AD, Vender R, Naldi L, et al. Biosimilars for the treatment of patients with psoriasis: A consensus statement from the Biosimilar Working Group of the International Psoriasis Council. *JAAD Int*. 2020;1(2):224-230. doi:10.1016/j.jdin.2020.09.006.
- Combe B, Dasgupta B, Louw I, et al. Efficacy and safety of golimumab as add-on therapy to disease-modifying antirheumatic drugs: results of the GO-MORE study. *Ann Rheum Dis*. 2014;73:1477-1486.
- Cosentyx prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. December 2021.
- Crowley J, Thaçi D, Joly P, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol*. 2017;77(2):310-317.e1.
- Cutolo M, Myerson GE, Fleischmann RM, et al. Long-term (52-week) results of a Phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis (PALACE 2). Abstract session presented at: The American College of Rheumatology and Association of Rheumatology Health Professionals Annual Meeting; 2013 October 25-30; San Diego, CA.
- Davis JC, van der Heijde DM, Braun J, et al. Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2008;67:346-52.
- De Benedetti F, Gattorno M, Anton J, et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *N Engl J Med*. 2018;378(20):1908-1919. doi: 10.1056/NEJMoa1706314.
- De Benedetti, Brunner H, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med.* 2012;367:2385-95.
- Deodhar A, Blanco R, Dokoupilová E, et al. Secukinumab improves signs and symptoms of non-radiographic axial spondyloarthritis: primary results of a randomized controlled phase III study. *Arthritis Rheumatol*. 2020[b];10.1002/art.41477. doi:10.1002/art.41477.
- Deodhar A, Braun J, Inman RD, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. *Ann Rheum Dis*. 2015;74:757-61.
- Deodhar A, Gensler LS, Kay J, et al. A fifty-two-week, randomized, placebo-controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2019[a];71(7):1101-1111. doi: 10.1002/art.40866.
- Deodhar A, Helliwell PS, Boehncke WH, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet*. 2020[c];395(10230):1115-1125. doi:10.1016/S0140-6736(20)30265-8.
- Deodhar A, Poddubnyy D, Pacheco-tena C, et al. Efficacy and safety of ixekizumab in the treatment of radiographic axial spondyloarthritis: sixteen-week results from a phase III randomized, double-blind, placebo-controlled trial in patients with prior inadequate response to or intolerance of tumor necrosis factor inhibitors. *Arthritis Rheumatol*. 2019[b];71(4):599-611. doi: 10.1002/art.40753.
- Deodhar A, Sliwinska-Stanczyk P, Xu H, et al. Tofacitinib for the treatment of ankylosing spondylitis: a phase III, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis.* 2021. doi:10.1136/annrheumdis-2020-219601.
- Deodhar A, Van den Bosch F, Poddubnyy D, et al. Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2022[a];400(10349):369-379. doi:10.1016/s0140-6736(22)01212-0
- Deodhar A, van der Heijde D, Gensler LS, et al. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomized, placebo-controlled trial. *Lancet*. 2020[a];395(10217):53-64. doi: 10.1016/S0140-6736(19)32971-X.
- Deodhar AA, Combe B, Accioly AP, et al. Safety of ixekizumab in patients with psoriatic arthritis: data from four clinical trials with over 2000 patient-years of exposure. *Ann Rheum Dis*. 2022[b];81(7):944-950. doi:10.1136/annrheumdis-2021-222027.
- Donahue KE, Jonas DE, Hansen RA, et al. Drug therapy for rheumatoid arthritis in adults: an update [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Apr. (Comparative Effectiveness Reviews, No. 55.) Available from: http://www.ncbi.nlm.nih.gov/books/NBK97388/. Accessed February 6, 2023.
- Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis.* 2017;76(1):88-95. doi: 10.1136/annrheumdis-2016-210094.
- Dougados M, Wei JC, Landewé R, et al. Efficacy and safety of ixekizumab through 52 weeks in two phase 3, randomised, controlled clinical trials in patients with active radiographic axial spondyloarthritis (COAST-V and COAST-W). *Ann Rheum Dis*. 2020;79(2):176-185. doi:10.1136/annrheumdis-2019-216118.
- DRUGS@FDA [database on the internet]. Rockville, MD: Food and Drug Administration (US), Center for Drug Evaluation and Research; 2023. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 6, 2023.
- Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomized, controlled trial (PALACE 3). *Ann Rheum Dis*. 2016;75(6):1065-73.
- Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol.* 2021;84(2):432-470. doi:10.1016/j.jaad.2020.07.087.
- Elmets CA, Lim HW, Stoff B, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. *J Am Acad Dermatol.* 2019;81(3):775-804. doi: 10.1016/j.jaad.2019.04.042.
- Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum*. 2009;60(8):2272-83.

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- Emery P, Keystone E, Tony H, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biological: results from a 24-week multicenter randomized placebo-controlled trial. *Ann Rheum Dis*. 2008;67:1516-23.
- Enbrel prescribing information. Immunex Corporation. Thousand Oaks, CA. June 2022.
- Fénix-Caballero S, Alegre-del Rey EJ, Castano-Lara R, et al. Direct and indirect comparison of the efficacy and safety of adalimumab, etanercept, infliximab and golimumab in psoriatic arthritis. *J Clin Pharm Ther*. 2013;38(4):286-93.
- Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367(6): 495-507.
- Fleischmann R, Pangan AL, Mysler E, et al. A Phase 3, randomized, double-blind study comparing upadacitinib to placebo and to adalimumab, in patients with active rheumatoid arthritis with inadequate response to methotrexate. Poster presented at: 2018 American College of Rheumatology and Association of Rheumatology Health Professionals Annual Meeting; October 21, 2018; Chicago, IL.
- Fleischmann R, van Adelsberg J, Lin Y, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. *Arthritis Rheumatol*. 2017;69(2):277-290.
- Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every four weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis*. 2009; 68:805-11.
- Fleischmann RM, Halland AM, Brzosko M, et al. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. *J Rheumatol*. 2013;40(2):113-26.
- Fleischmann R, Mysler E, Bessette L, et al. Long-term safety and efficacy of upadacitinib or adalimumab in patients with rheumatoid arthritis: results through 3 years from the SELECT-COMPARE study. *RMD Open*. 2022;8(1):e002012. doi:10.1136/rmdopen-2021-002012.
- Food and Drug Administration. Drug Safety Communication: FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. FDA Web site. September 1, 2021. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death?utm_medium=email&utm_source=govdelivery. Accessed February 6, 2023.
- Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. 2021;73(7):1108-1123. doi:10.1002/art.41752.
- Furst DE, Kavanaugh A, Florentinus S, et al. Final 10-year effectiveness and safety results from study DE020: adalimumab treatment in patients with rheumatoid arthritis and an inadequate response to standard therapy. *Rheumatology*. 2015;54:2188-2197.
- Gabay C, Emery P, van Vollenhoven R, et al. ADACTA Study Investigators. Tocilizumab monotherapy vs adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet*. 2013; 381(9877):1541-50.
- Galvao TF, Zimmermann IR, da Mota LM, et al. Withdrawal of biologic agents in rheumatoid arthritis: a systematic review and meta-analysis. *Clin Rheumatol*. 2016;35(7):1659-68.
- Genovese M, McKay J, Nasonov E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum*. 2008;58(10):2968-80.
- Genovese MC, Covarrubias A, Leon G, et al. Subcutaneous abatacept vs intravenous abatacept: A phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum*. 2011;63(10):2854-64.
- Genovese MC, Fleischmann R, Kivitz AJ, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. *Arthritis Rheumatol*. 2015;67(6):1424-1437.
- Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374(13):1243-1252.
- Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet*. 2018;391(10139):2513-2524. doi: 10.1016/S0140-6736(18)31116-4.
- Genovese MC, Mease PJ, Thomson GTD, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheum*. 2007;34:1040-50.
- Genovese MC, Rubbert-Roth A, Smolen JS, et al. Long-term safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. *J Rheumatol*. 2013;40: 768–80. doi:10.3899/jrheum.120687.
- Genovese MC, Sanchez-Burson J, Oh M, et al. Comparative clinical efficacy and safety of the proposed biosimilar ABP 710 with infliximab reference product in patients with rheumatoid arthritis. *Arthritis Res Ther*. 2020;22(1):60. doi:10.1186/s13075-020-2142-1.
- Ghosh S, Gensler LS, Yang Z, et al. Ustekinumab safety in psoriasis, psoriatic arthritis, and Crohn's disease: an integrated analysis of phase II/III clinical development programs. *Drug Saf*. 2019;42(6):751-768. doi: 10.1007/s40264-019-00797-3.
- Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N Engl J Med*. 2017;377(16):1525-1536. doi: 10.1056/NEJMoa1615977.
- Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016;375:345-56.
- Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650-661. doi: 10.1016/S0140-6736(18)31713-6.
- Gorman JD, Sack KE, Davis JC. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor α. *N Engl J Med*. 2002;346(18):1349-56.
- Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020;79(6):700-712. doi:10.1136/annrheumdis-2020-217159.
- Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis*. 2016;75(5):795-810.
- Gottenberg JE, Brocq O, Perdriger A, et al. Non-TNF-targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug: a randomized clinical trial. *JAMA*. 2016;316(11):1172-1180.
- Gottlieb AB, Langley RG, Strober BE, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. *Br J Dermatol*. 2012;167:649-657.

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- Griffiths CEM, Papp KA, Song M, et al. Continuous treatment with guselkumab maintains clinical responses through 4 years in patients with moderate-to-severe psoriasis: results from VOYAGE 1. *J Dermatolog Treat*. 2022;33(2):848-856. doi:10.1080/09546634.2020.1782817.
- Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet*. 2015;386:541-51.
- Griffiths CE, Strober BE, van de Kerkhof P, et al; ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med*. 2010;362(2):118-28.
- Gulliver W, Zouboulis CC, Prens E, et al. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. *Rev Endocr Metab Disord*. 2016;17(3):343-51.
- Haraoui B, Bokarewa M, Kallmeyer I, et al. Safety and effectiveness of rituximab in patients with rheumatoid arthritis following an inadequate response to 1 prior tumor necrosis factor inhibitor: the RESET trial. *J Rheumatol*. 2011;38; 2548-56.
- Hatemi G, Mahr A, Ishigatsubo Y, et al. Trial of apremilast for oral ulcers in Behcet's syndrome. *N Engl J Med*. 2019;381(20):1918-1928. doi: 10.056/NEJMoa1816594.
- Hazlewood GS, Barnabe C, Tomlinson G, et al. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: a network meta-analysis. *Cochrane Database of Systematic Reviews*. 2016, Issue 8. Art. No.: CD010227. doi: 10.1002/14651858.CD010227.pub2.
- Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. 2020;79(1):19-30. doi:10.1136/annrheumdis-2019-215672.
- Ho Lee Y, Gyu Song G. Comparative efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib as monotherapy for active rheumatoid arthritis. *J Clin Pharm Ther*. 2020;45(4):674-681. doi:10.1111/jcpt.13142.
- Hou LQ, Jiang GX, Chen YF, et al. The comparative safety of TNF inhibitors in ankylosing spondylitis – a meta-analysis update of 14 randomized controlled trials. *Clin Rev Allergy Immunol*. 2018;54(2):234-243. doi:10.1007/s12016-017-8623-6.
- Humira prescribing information. AbbVie Inc. North Chicago, IL. February 2021.
- Ilaris prescribing information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. September 2020.
- Ilumya prescribing information. Sun Pharma Global FZE. Cranbury, NJ. December 2022.
- Inflectra prescribing information. Hospira. Lake Forest, IL. March 2022.
- Jabbar-Lopez ZK, Yiu ZZN, Ward V, et al. Quantitative evaluation of biologic therapy options for psoriasis: a systematic review and network meta-analysis. *J Invest Dermatol*. 2017;137(8):1646-1654.
- Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in patients with active noninfectious uveitis. *N Engl J Med*. 2016;375:932-43.
- Janke K, Biester K, Krause D, et al. Comparative effectiveness of biological medicines in rheumatoid arthritis: systematic review and network meta-analysis including aggregate results from reanalysed individual patient data. *BMJ*. 2020;370:m2288. doi:10.1136/bmj.m2288.
- Jeyaratnam J, Simon A, Calvo I, et al. Long-term efficacy and safety of canakinumab in patients with mevalonate kinase deficiency: results from the randomised Phase 3 CLUSTER trial. *Rheumatology (Oxford)*. 2022;61(5):2088-2094. doi:10.1093/rheumatology/keab696.
- Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy vs methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. *Ann Rheum Dis*. 2010;69(1):88-96.
- Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 2017;389(10086):2304-2316.
- Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: Results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *JAMA Dermatol*. 2015;151(9):961-9.
- Kavanaugh A, McInnes I, Mease P, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum*. 2009;60(4):976-86.
- Kavanaugh A, McInnes IB, Mease P, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomized, placebo-controlled trial (the GO-REVEAL study). *Ann Rheum Dis*. 2014[b];73(9):1689-94. doi: 10.1136/annrheumdis-2013-204902.
- Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Long-term (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. *J Rheumatol*. 2015[b];42:479-88.
- Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3, randomized, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis*. 2014[a];73(6):1020-6. doi: 10.1136/annrheumdis-2013-205056.
- Kavanaugh A, Mease PJ, Reimold AM, et al. Secukinumab for long-term treatment of psoriatic arthritis: a two-year follow-up from a phase III, randomized, double-blind placebo-controlled study. *Arthritis Care Res* (Hoboken). 2017;69(3):347-355.
- Kavanaugh A, Puig L, Gottlieb AB, et al; PSUMMIT 1 Study Group. Maintenance of clinical efficacy and radiographic benefit through two years of ustekinumab therapy in patients with active psoriatic arthritis: results from a randomized, placebo-controlled phase III trial. *Arthritis Care Res*. 2015[a];67(12):1739-1749.
- Kavanaugh A, van der Heijde D, Beutler A, et al. Radiographic progression of patients with psoriatic arthritis who achieve minimal disease activity in response to golimumab therapy: results through 5 years of a randomized, placebo-controlled study. *Arthritis Care Res* (Hoboken). 2016;68(2):267-74.
- Kawalect P, Holko P, Mocko P, et al. Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis. *Rheumatol Int*. 2018 Feb;38(2):189-201. doi: 10.1007/s00296-017-3919-7.
- Kay J, Fleischmann R, Keystone E, et al. Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomized, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. *Ann Rheum Dis*. 2015;74(3):538-46. doi: 10.1136/annrheumdis-2013-204195.
- Kay J, Schoels MM, Dorner T, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. *Ann Rheum Dis*. 2018;77(2):165-174. doi: 10.1136/annrheumdis-2017-211937.
- Kedor C, Listing J, Zernicke J, et al. Canakinumab for treatment of adult-onset still's disease to achieve reduction of arthritic manifestation (CONSIDER): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. *Ann Rheum Dis*. 2020;79(8):1090-1097. doi:10.1136/annrheumdis-2020-217155.

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- Kerschbaumer A, Smolen JS, Dougados M, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis*. 2020;79(6):778-786. doi: 10.1136/annrheumdis-2020-217163.
- Kevzara prescribing information. Sanofi-Aventis US, LLC. Bridgewater, NJ. April 2018.
- Keystone E, Landewe R, van Vollenhoven R, et al. Long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the treatment of rheumatoid arthritis: 5-year results from the RAPID 1 trial and open-label extension. *Ann Rheum Dis*. 2014[a];73(12):2094-100. doi: 10.1136/annrheumdis-2013-203695.
- Keystone E, van der Heijde D, Mason D, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis. *Arthritis Rheum*. 2008;58(11):3319-29.
- Keystone EC, Breedveld FC, van der Heijde D, et al. Long-term effect of delaying combination therapy with tumor necrosis factor inhibitor in patients with aggressive early rheumatoid arthritis: 10-year efficacy and safety of adalimumab from the randomized controlled PREMIER trial with open-label extension. *J Rheumatol*. 2014[b];41(1):5-14. doi: 10.3899/jrheum.130543.
- Keystone EC, Genovese MC, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results through 2 years of the GO-FORWARD study extension. *J Rheumatol*. 2013[a];40; 1097-1103.
- Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumor necrosis factor alpha given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis*. 2009;68(6):789-96.
- Keystone ED, van der Heijde D, Kavanaugh A, et al. Clinical, functional, and radiographic benefits of long-term adalimumab plus methotrexate: final 10-year data in longstanding rheumatoid arthritis. *J Rheum*. 2013[b];40(9): 2-11.
- Khanna D, Lin CJF, Furst DE, et al. Long-term safety and efficacy of tocilizumab in early systemic sclerosis-interstitial lung disease: open-label extension of a phase 3 randomized controlled trial. *Am J Respir Crit Care Med*. 2022;205(6):674-684. doi:10.1164/rccm.202103-0714OC.
- Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963-974. doi:10.1016/S2213-2600(20)30318-0.
- Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med*. 2016;375:422-34.
- Kimball AB, Rothman KJ, Kricorian G, et al. OBSERVE-5: Observational postmarketing safety surveillance registry of etanercept for the treatment of psoriasis final 5-year results. *J Am Acad Dermatol*. 2015;72(1):115-22. doi: 10.1016/j.jaad.2014.08.050.
- Kineret prescribing information. Swedish Orphan Biovitrum (SOBI, INC). Stockholm, Sweden. December 2020.
- King B, Ohyama M, Kwon O, et al. Two phase 3 trials of baricitinib for alopecia areata. *N Engl J Med*. 2022;386(18):1687-1699. doi:10.1056/NEJMoa2110343.
- Kivitz A, Olech E, Borofsky M, et al. Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. *Arthritis Care Res*. 2014;66:1653-61.
- Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220-233. doi:10.1002/art.41142.
- Koné-Paut I, Lachmann HJ, Kuemmerle-Deschner JB, et al. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. *Arthritis Res Ther*. 2011;13(1):R34.
- Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017;76(8):1327-1339. doi:10.1136/annrheumdis-2016-209909.
- Kremer J, Ritchlin C, Mendelsohn A, et al. Golimumab, a new human anti–tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis. Forty-eight–week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. *Arthritis Rheum*. 2010;62(4): 917–28.
- Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum*. 2011;63:609-21.
- Kristensen LE, Keiserman M, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. *Ann Rheum Dis*. 2022;81(2):225-231. doi:10.1136/annrheumdis-2021-221019.
- Kristensen LE, Keiserman M, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 52-week results from the KEEPsAKE 1 study. *Rheumatology (Oxford)*. 2022. doi:10.1093/rheumatology/keac607
- Kuemmerle-Deschner JB, Gautam R, George AT, Raza S, Lomax KG, Hur P. A systematic literature review of efficacy, effectiveness and safety of biologic therapies for treatment of familial Mediterranean fever. *Rheumatology (Oxford)*. 2020;59(10):2711-2724. doi:10.1093/rheumatology/keaa205.
- Kuemmerle-Deschner JB, Hachulla E, Cartwright R, et al. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes. *Ann Rheum Dis*. 2011;70:2095-2102.
- Lachmann HJ, Koné-Paut I, Keummerle-Deschner JB, et al. Use of Canakinumab in the Cryopyrin Associated Periodic Syndrome. *N Engl J Med.* 2009;360:2416-25.
- Landells I, Marano C, Hsu MC, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. *J Am Acad Dermatol*. 2015;73:594-603.
- Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24 week results of a double-blind randomized placebo-controlled Phase 3 study. *Ann Rheum Dis*. 2014;73:39-47.
- Langley RG, Blauvelt A, Gooderham M, et al. Efficacy and safety of continuous Q12W risankizumab vs treatment withdrawal: Results from the Phase 3 IMMhance trial. Poster presented at: The American Academy of Dermatology Annual Meeting; March 1 to 5, 2019; Washington, DC.
- Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis – results of two phase 3 trials. *N Engl J Med*. 2014;371:326-38.
- Langley RG, Lebwohl M, Krueger GG, et al for the Phoenix 2 Investigators. Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate to severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. *Br J Dermatol*. 2015;172(5):1371-1383.

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- Langley RG, Tsai TF, Flavin S, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: Results of the randomized, double-blind, Phase 3 NAVIGATE trial. *Br J Dermatol*. 2018;178(1):114-123. doi: 10.1111/bjd.15750.
- Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med*. 2015;373:1318-28.
- Lee EB, Fleischmann R, Hall S, et al for the Oral Start Investigators. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med*. 2014;370:2377-86.
- Lee YH, Song GG. Comparative efficacy and safety of tofacitinib, baricitinib, upadacitinib, and filgotinib in active rheumatoid arthritis refractory to biologic disease-modifying antirheumatic drugs. *Z Rheumatol*. 2021;80(4):379-392. doi:10.1007/s00393-020-00796-1.
- Lee YH. Comparative efficacy and safety of janus kinase inhibitors and secukinumab in patients with active ankylosing spondylitis: a systematic review and meta-analysis. *Pharmacology*. 2022;107(11-12):537-544. doi:10.1159/000525627.
- Lemos LLP, de Oliveira Costa J, Almeida AM, et al. Treatment of psoriatic arthritis with anti‑TNF agents: a systematic review and meta‑analysis of efficacy, effectiveness and safety. *Rheumatol Int*. 2014;34:3145-1360.
- Leonardi C, Kimball A, Papp K, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371:1665-74.
- Lethaby A, Lopez-Olivo MA, Maxwell L, et al. Etanercept for the treatment of rheumatoid arthritis (Review). *The Cochrane Collaboration*. Cochrane Library. 2013;5:1-452.
- Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology*. 2014;121(3):785-96.
- Lopez-Olivio MA, Amezaga Urruela M, McGahan L, et al. Rituximab for rheumatoid arthritis. *Cochrane Database Syst Reviews*. 2015, Issue 1. Art. No.: CD007356. doi: 10.1002/14651858.CD007356.pub2.
- Lovell D, Ruperto N, Goodman S, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med*. 2008; 359(8):810-20.
- Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med*. 2000;342:763-9.
- Lovell DJ, Reiff A, Jones OY, et al. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum*. 2006;54:1987-94.
- Machado MA, Barbaos MM, Almeida AM, et al. Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis. *Rheumatol Int*. 2013;33(9):2199-2213. doi: 10.1007/s00296-013-2772-6.
- Manders SH, Kievit W, Adang E, et al. Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. *Arthritis Research & Therapy*. 2015;17:134.
- Maneiro JR, Souto A, Gomez-Reino JJ. Risks of malignancies related to tofacitinib and biologic drugs in rheumatoid arthritis: Systematic review, meta-analysis, and network meta-analysis. *Semin Arthritis Rheum*. 2017;47(2):149-156. doi: 10.1016/j.semarthrit.2017.02.007.
- Marzo-Ortega H, Sieper J, Kivitz A, et al. Secukinumab and sustained improvement in signs and symptoms of patients with active ankylosing spondylitis through two years: results from a phase III study. *Arthritis Care Res* (Hoboken). 2017 Jul;69(7):1020-1029.
- Maxwell L, Singh JA. Abatacept for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2009;(4):CD007277.
- Maxwell LJ, Zochling J, Boonen A, et al. TNF-alpha inhibitors for ankylosing spondylitis. *Cochrane Database Syst Rev*. 2015, Issue 4. Art. No.: CD005468. doi: 10.1002/14651858.CD005468.pub2.
- Maz M, Chung SA, Abril A, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of giant cell arteritis and takayasu arteritis. *Arthritis Rheumatol*. 2021;73(8):1349-1365. doi:10.1002/art.41774.
- McInnes IB, Anderson JK, Magrey M, et al. Trial of upadacitinib and adalimumab for psoriatic arthritis. *N Engl J Med*. 2021;384(13):1227-1239. doi:10.1056/NEJMoa2022516.
- McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. *Lancet*. 2020;395(10235):1496-1505. doi:10.1016/S0140-6736(20)30564-X.
- McInnes IB, Kavanaugh A, Gottlieb AB, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet*. 2013;382:780-9.
- McInnes IB, Mease PJ, Kirkham B, et al for the FUTURE 2 Study Group. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015;386(9999):1137-46.
- McInnes IB, Rahman P, Gottlieb AB, et al. Long-term efficacy and safety of guselkumab, a monoclonal antibody specific to the p19 subunit of interleukin-23, through two years: results from a phase III, randomized, double-blind, placebo-controlled study conducted in biologic-naive patients with active psoriatic arthritis. *Arthritis Rheumatol*. 2022;74(3):475-485. doi:10.1002/art.42010.
- Mease P, Genovese MC, Gladstein G, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis Rheum*. 2011;63(4):939-948.
- Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med*. 2017[c];377(16):1537-1550. doi: 10.1056/NEJMoa1615975.
- Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis*. 2014;73:48-55.
- Mease PJ, Gladman DD, Collier DH, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase 3 trial. *Arthritis Rheumatol*. 2019;71(7):1112-1124. doi: 10.1002/art.40851.
- Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis. *Arthritis Rheum*. 2005; 52(10):3279-89.
- Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. *Lancet*. 2000;356;385-90.
- Mease PJ, Gottlieb AB, van der Heijde D, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. *Ann Rheum Dis*. 2017[a];76(9):1550-1558.
- Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy and effect on disease progression. *Arthritis Rheum*. 2004;50:2264-72.
- Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. *Ann Rheum Dis*. 2020[a];80(3):312-320. doi:10.1136/annrheumdis-2020-218870.

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- Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N Engl J Med*. 2015;373(14):1329-39.
- Mease PJ, McInnes IB, Tam LS, et al. Comparative effectiveness of guselkumab in psoriatic arthritis: Updates to a systematic literature review and network meta-analysis. *Rheumatology (Oxford)*. 2022. doi:10.1093/rheumatology/keac500
- Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet*. 2020[b];395(10230):1126-1136. doi:10.1016/S0140-6736(20)30263-4.
- Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis*. 2017[b];76(1):79-87. doi: 10.1136/annrheumdis-2016-209709.
- Menter A, McCabe D, Lang B, Schaible J, Eduru SK. 27381 Phase III, randomized trial comparing clinical outcomes between patients with moderate-to-severe chronic plaque psoriasis receiving adalimumab reference product (RP) continuously vs those who switched between BI 695501 and adalimumab RP. *J Am Acad Dermatol.* 2021;85(3):AB140. doi:10.1016/j.jaad.2021.06.574.
- Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *J Am Acad Dermatol*. 2020[b];82(1):161-201. doi:10.1016/j.jaad.2019.08.049.
- Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *J Am Acad Dermatol*. 2020[a];82(6):1445-1486. doi:10.1016/j.jaad.2020.02.044.
- Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072. doi: 10.1016/j.jaad.2018.11.057.
- Mertens M, Singh JA. Anakinra for rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD005121. doi: 10.1002/14651858. CD005121.pub3.
- Minozzi S, Bonovas S, Lytras T, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. *Expert Opin Drug Saf*. 2016;15(sup1):11-34.
- Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet*. 2017;389(10086):2317-2327. doi: 10.1016/S0140-6736(17)31429-0.
- Nast A, Jacobs A, Rosumeck S, Werner RN. Efficacy and safety of systemic long-term treatments for moderate-to-severe psoriasis: a systematic review and meta-analysis. *J Invest Dermatol.* 2015;135(11):2641-8.
- Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, et al. Adalimumab for treating rheumatoid arthritis. *Cochrane Database Syst Rev.* 2005, Issue 3. Art. No.: CD005113. doi: 10.1002/14651858.CD005113.pub2.
- Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet*. 2016;388:1183-92.
- Nguyen T, Churchill M, Levin R, et al. Secukinumab in united states biologic-naïve patients with psoriatic arthritis: results from the randomized, placebo-controlled CHOICE study. *J Rheumatol*. 2022;49(8):894-902. doi:10.3899/jrheum.210912.
- Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumor necrosis factor α and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. *Rheumatology*. 2007;46:1140-7.
- O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med*. 2013;369 (4):307-18.
- Olumiant prescribing information. Eli Lilly and Company. Indianapolis, IN. June 2022.
- Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. *Arthritis Rheumatol*. 2022;74(4):553-569. doi:10.1002/art.42037.
- Orencia prescribing information. Bristol Myers Squibb. Princeton, NJ. December 2021.
- Östör A, Van den Bosch F, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial. *Ann Rheum Dis*. 2022;81(3):351-358. doi:10.1136/annrheumdis-2021-221048.
- Östör A, Van den Bosch F, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 52-week results from the KEEPsAKE 2 study. *Rheumatology (Oxford)*. 2022. doi:10.1093/rheumatology/keac605
- Otezla prescribing information. Amgen Inc. Thousand Oaks, CA. December 2021.
- Ozen S, Demirkaya E, Erer B, et al. EULAR recommendations for the management of familial Mediterranean fever. *Ann Rheum Dis*. 2016;75:644-51.
- Paller AS, Seyger MMB, Alejandro Magariños G, et al. Efficacy and safety of ixekizumab in a phase III, randomized, double-blind, placebo-controlled study in paediatric patients with moderate-to-severe plaque psoriasis (IXORA-PEDS). *Br J Dermatol*. 2020;183(2):231-241. doi:10.1111/bjd.19147.
- Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med*. 2008;358:241-51.
- Paller AS, Siegfried EC, Pariser DM, et al. Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis. *J Am Acad Dermatol.* 2016;74:280-7.
- Paller AS, Seyger MMB, Magariños GA, et al. Long-term efficacy and safety of up to 108 weeks of ixekizumab in pediatric patients with moderate to severe plaque psoriasis: the IXORA-PEDS randomized clinical trial. *JAMA Dermatol.* 2022;158(5):533-541. doi:10.1001/jamadermatol.2022.0655.
- Papp K, Langley R, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371:1675-84.
- Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE 4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol.* 2015;73(1):37-49.
- Papp KA, Griffiths CEM, Gordon K, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *Br J Derm*. 2013;168: 844–54.
- Papp KA, Reich K, Paul C, et al. A prospective, phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol.* 2016;175:273-86.

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- Papp K, Bachelez H, Costanzo A, et al. Clinical similarity of the biosimilar ABP 501 compared with adalimumab after single transition: long-term results from a randomized controlled, double-blind, 52-week, phase III trial in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol.* 2017[b];177(6):1562-1574. doi:10.1111/bjd.15857
- Papp K, Bachelez H, Costanzo A, et al. Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study. *J Am Acad Dermatol.* 2017[a];76(6):1093-1102. doi:10.1016/j.jaad.2016.12.014
- Park W, Božić-Majstorović L, Milakovic D, et al. Comparison of biosimilar CT-P10 and innovator rituximab in patients with rheumatoid arthritis: a randomized controlled Phase 3 trial. *MAbs*. 2018;10(6):934-943. doi:10.1080/19420862.2018.1487912.
- Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis*. 2013;72:1605-1612.
- Park W, Yoo DH, Jaworski J, et al. Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. *Arthritis Res Ther*. 2016;18:25. doi: 10.1186/s13075-016-0930-4.
- Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. *Ann Rheum Dis*. 2017;76(2):346-54.
- Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe psoriasis over 52 weeks: a phase III randomized, controlled trial (ESTEEM 2). *Br J Dermatol.* 2015[a];173:1355-56.
- Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). *J Eur Acad Dermatol Venereol*. 2015[b];29(6):1082-90. doi: 10.1111/jdv.12751.
- Philipp S, Menter A, Nikkels AF, et al. Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in paediatric patients (≥ 6 to < 12 years of age): efficacy, safety, pharmacokinetic and biomarker results from the open-label CADMUS Jr study. *Br J Dermatol*. 2020;10.1111/bjd.19018. doi:10.1111/bjd.19018.
- Porter D, van Melckebeke J, Dale J, et al. Tumor necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. *Lancet*. 2016;388:239-47.
- Puig L, Lebwohl M, Bachelez H, Sobell J, Jacobson AA. Long-term efficacy and safety of brodalumab in the treatment of psoriasis: 120-week results from the randomized, double-blind, placebo- and active comparator-controlled phase 3 AMAGINE-2 trial. *J Am Acad Dermatol*. 2020;82(2):352-359. doi:10.1016/j.jaad.2019.05.095.
- Purple Book: Database of Licensed Biological Products [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2023. Available at: https://purplebooksearch.fda.gov/. Accessed February 6, 2023.
- Qiu M, Xu Z, Gao W, et al. Fourteen small molecule and biological agents for psoriatic arthritis: A network meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2020;99(31):e21447. doi:10.1097/MD.0000000000021447.
- Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *N Engl J Med*. 20177;376(17):1637-1646. doi: 10.1056/NEJMoa1614160.
- Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis*. 2023;82:19-34. doi:10.1136/ard-2022-223296
- Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol*. 2017[a];76(3):418-431.
- Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomized controlled trial. *Lancet.* 2019[a];394(10201):831-839. doi: 10.1016/S0140-6736(19)31773-8.
- Reich K, Gooderham M, Thaci D, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomized, double-blind, active-comparator-controlled phase 3 trial. *Lancet*. 2019[b];394(10198):576-586. doi: 10.1016/S0140-6736(19)30952-3.
- Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE1 and reSURFACE2): results from two randomized controlled, phase 3 trials. *Lancet*. 2017;390(10091):276-288.
- Reich K, Pinter A, Lacour JP, et al; IXORA-S investigators. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol*. 2017[b];77(4):1014-1023. doi:10.1111/bjd.15666.
- Remicade prescribing information. Janssen Biotech. Horsham, PA. October 2021.
- Renflexis prescribing information. Merck Sharpe & Dohme Corp. Kenilworth, NJ. January 2022.
- Riabni prescribing information. Amgen. Thousand Oaks, CA. June 2022.
- Rich P, Gooderham M, Bachelez H, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). *J Am Acad Dermatol*. 2016;74(1):134-42.
- Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Care Res (Hoboken)*. 2019;71(6):717-734. doi: 10.1002/acr.23870.
- Rinvoq prescribing information. AbbVie Inc, North Chicago, IL. October 2022.
- Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis*. 2014;73:990-999.
- Rituxan prescribing information. Genentech, Inc. South San Francisco, CA. December 2021.
- Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. *Ann Rheum Dis*. 2022;81(7):907-921. doi:10.1136/annrheumdis-2021-221801.
- Rubbert-Roth A, Enejosa J, Pangan AL, et al. Trial of upadacitinib or abatacept in rheumatoid arthritis. *N Engl J Med*. 2020;383(16):1511-1521. doi:10.1056/NEJMoa2008250.

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- Ruperto N, Brunner HI, Pacheco-Tena C, et al. Open-label phase 3 study of intravenous golimumab in patients with polyarticular juvenile idiopathic arthritis. *Rheumatology (Oxford).* 2021[a];keab021. doi:10.1093/rheumatology/keab021.
- Ruperto N, Brunner HI, Quartier P, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med.* 2012;367: 2396-406. doi: 10.1056/NEJMoa1205099.
- Ruperto N, Brunner HI, Quartier P, et al. Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: results from the 5-year long-term extension of the phase III pivotal trials. *Ann Rheum Dis*. 2018;77(12):1710-1719. doi: 10.1136/annrheumdis-2018-213150.
- Ruperto N, Brunner HI, Synoverska O, et al. Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomised trial. *Lancet.* 2021[b];398(10315):1984-1996. doi:10.1016/s0140-6736(21)01255-1.
- Ruperto N, Foeldvari I, Alexeeva E, et al. Efficacy and safety of secukinumab in enthesitis-related arthritis and juvenile psoriatic arthritis: Primary results from a randomised, double-blind, placebo controlled, treatment withdrawal, phase 3 study (junipera). *Ann Rheum Dis.* 2021[c];80(Suppl 1):201-202. doi:10.1136/annrheumdis-2021-eular.5038.
- Ruperto N, Lovell DJ, Quartier P, et al; Pediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Abatacept in children with juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled withdrawal trial. *Lancet.* 2008;372(9636):383-91.
- Ruxience. Pfizer Inc. New York, NY. November 2021.
- Ryan C, Menter A, Guenther L, et al. Efficacy and safety of ixekizumab in a randomized, double-blinded, placebo-controlled phase IIIb study of patients with moderate-to-severe genital psoriasis. *Br J Dermatol*. 2018;179(4):844-852. doi: 10.1111/bjd.16736.
- Ryoo JY, Yang HJ, Ji E, Yoo BK. Meta-analysis of the efficacy and safety of secukinumab for the treatment of plaque psoriasis. *Ann Pharmacother.* 2016;50(5):341-51.
- Saurat JH, Stingl G, Dubertret L, et al; CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). *Br J Dermatol.* 2008;158(3):558-66.
- Sbidian E, Chaimani A, Garcia-Doval I, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev*. 2022;5(5):CD011535. doi:10.1002/14651858.CD011535.pub5.
- Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis.* 2008;67:1096-1103.
- Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept vs adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Ann Rheum Dis*. 2014;73:86-94.
- Schmitt J, Zhang Z, Wozel, G, et al. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *Br J Derm*. 2008;159:513-26.
- Shim SC, Božić-Majstorović L, Berrocal Kasay A, et al. Efficacy and safety of switching from rituximab to biosimilar CT-P10 in rheumatoid arthritis: 72-week data from a randomized Phase 3 trial. *Rheumatology (Oxford)*. 2019;58(12):2193-2202. doi:10.1093/rheumatology/kez152.
- Shin D, Kim Y, Kim YS, Körnicke T, Fuhr R. A randomized, phase I pharmacokinetic study comparing SB2 and infliximab reference product (Remicade(®)) in healthy subjects. *BioDrugs*. 2015;29(6):381-388.
- Sibley CH, Plass N, Snow J, et al. Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra. A cohort study to determine 3- and 5-year outcomes. *Arthritis Rheum*. 2012;64(7): 2375-86.
- Sieper J, Kivitz A, van Tubergen A, et al. Impact of certolizumab pegol on patient-reported outcomes in patients with axial spondyloarthritis. *Arthritis Care Res*. 2015[a];67(10):1475-1480.
- Sieper J, Landewe R, Rudwaleit M, et al. Effects of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis. *Arthritis & Rheumatology*. 2015[b];67(3):668-677.
- Siliq prescribing information. Valeant Pharmaceuticals. Bridgewater, NJ. April 2020.
- Simponi Aria prescribing information. Janssen Biotech, Inc. Horsham, PA. February 2021.
- Simponi prescribing information. Janssen Biotech, Inc. Horsham, PA. September 2019.
- Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Arthritis Rheumatol*. 2019;71(1):5-32. doi: 10.1002/art.40726.
- Singh JA, Hossain A, Mudano AS, et al. Biologics or tofacitinib for people with rheumatoid arthritis naive to methotrexate: a systematic review and network meta-analysis. *Cochrane Database of Systematic Reviews* 2017[b], Issue 5. Art. No.: CD012657.
- Singh JA, Hossain A, Tanjong Ghogomu E, et al. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug failure: a Cochrane systematic review and network meta-analysis. *Cochrane Database of Systematic Reviews*. 2016[b], Issue 11. Art. No.: CD012437. doi: 10.1002/14651858.CD012437.
- Singh JA, Hossain A, Tanjong Ghogomu E, et al. Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics; a systematic review and network meta-analysis. *Cochrane Database of Systematic Reviews*. 2017[a], Issue 3. Art. No.: CD012591. doi: 10.1002/14651858.CD012591.
- Singh JA, Hossain A, Tanjong Ghogomu E, et al. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis. *Cochrane Database of Systematic Reviews.* 2016[a], Issue 5. Art. No.: CD012183. doi: 10.1002/14651858.CD012183.
- Skyrizi prescribing information. AbbVie Inc, North Chicago, IL. December 2022.
- Smolen J, Landewe R, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomized controlled trial. *Ann Rheum Dis*. 2009[a];68:797-804.
- Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. *Lancet*. 2008;371(9617):987-97.
- Smolen JS, Emery P, Ferraccioli GF, et al. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomized, placebo-controlled trial. *Ann Rheum Dis*. 2015[a];74:843-850. doi:10.1136/annrheumdis-2013-204632.
- Smolen JS, Kay J, Doyle M, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor inhibitors: findings with up to 5 years of treatment in the multicenter, randomized, double-blind, placebo-controlled, phase 3 GO-AFTER study. *Arthritis Res Ther.* 2015[b];17(1):14. doi: 10.1186/s13075-015-0516-6.

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- Smolen JS, Kay J, Doyle MK, et al; GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomized, double-blind, placebo-controlled, phase III trial. *Lancet*. 2009[b];374(9685):210-21.
- Smolen JS, Landewe RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis*. 2023;82:3-18. doi:10.1136/ard-2022-223356
- Smolen JS, Mease P, Tahir H, et al. Multicentre, randomised, open-label, parallel-group study evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naïve to biological disease-modifying antirheumatic drug: final results by week 52. *Ann Rheum Dis*. 2020[b];79(10):1310-1319. doi:10.1136/annrheumdis-2020-217372.
- Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet*. 2019;393(10188):2303-2311. doi: 10.1016/S0140-6736(19)30419-2.
- Smolen JS, Xie L, Jia B, et al. Efficacy of baricitinib in patients with moderate-to-severe rheumatoid arthritis with 3 years of treatment: results from a long-term study. *Rheumatology (Oxford)*. 2021;60(5):2256-2266. doi:10.1093/rheumatology/keaa576.
- Song GG, Lee YH. Comparative efficacy and safety of 15 and 30 mg upadacitinib administered to patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Z Rheumatol*. 2020;79(1):103-111. doi:10.1007/s00393-019-0601-3.
- Song GG, Lee YH. Comparison of the efficacy and safety of tofacitinib and apremilast in patients with active psoriatic arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Clin Drug Investig*. 2019;39(5):421-428. doi: 10.1007/s40261-019-00765-w.
- Sotyktu prescribing information. Bristol-Myers Squibb, Princeton, NJ. September 2022.
- Stein Gold L, Papp K, Pariser D, et al. Efficacy and safety of apremilast in patients with mild-to-moderate plaque psoriasis: Results of a phase 3, multicenter, randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol*. 2022;86(1):77-85. doi:10.1016/j.jaad.2021.07.040.
- Stelara prescribing information. Janssen Biotech. Horsham, PA. August 2022.
- Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med*. 2017 Jul 27;377(4):317-328.
- Strand V, Ahadieh S, French J, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. *Arthritis Res Ther*. 2015[b];17:362. doi 10.1186/s13075-015-0880-2.
- Strand V, Burmester GR, Zerbini CAF, et al. Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. *Arthritis Care Res*. 2015[a];67(4):475-483.
- Strober B, Thaçi D, Sofen H, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 Program fOr Evaluation of TYK2 inhibitor psoriasis second trial. *J Am Acad Dermatol*. 2023;88(1):40-51. doi:10.1016/j.jaad.2022.08.061
- Suh CH, Yoo DH, Berrocal Kasay A, et al. Long-term efficacy and safety of biosimilar CT-P10 versus innovator rituximab in rheumatoid arthritis: 48-week results from a randomized phase III trial. *BioDrugs*. 2019;33(1):79-91. doi:10.1007/s40259-018-00331-4.
- Tada Y, Watanabe R, Noma H, Kanai Y, Nomura T, Kaneko K. Short-term effectiveness of biologics in patients with moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis. *J Dermatol Sci*. 2020;99(1):53-61. doi:10.1016/j.jdermsci.2020.06.003.
- Taltz prescribing information. Eli Lilly and Company, Indianapolis, IN. July 2022.
- Tarp S, Amarilyo G, Foeldvari I, et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. *Rheumatology*. 2016;55:669-79.
- Taylor PC, Weinblatt ME, Burmester GR, et al. Cardiovascular safety during treatment with baricitinib in rheumatoid arthritis. *Arthritis Rheumatol*. 2019;71(7):1042-1055. doi: 10.1002/art.40841.
- Taylor PC, Takeuchi T, Burmester GR, et al. Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. *Ann Rheum Dis*. 2022;81(3):335-343. doi:10.1136/annrheumdis-2021-221276.
- Thaçi D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol*. 2015;73(3):400-9.
- Thaçi D, Kimball A, Foley P, et al. Apremilast, an oral phosphodiesterase inhibitor, improves patient-reported outcomes in the treatment of moderate to severe psoriasis: results of two phase III randomized, controlled trials. *J Eur Acad Dermatol Venereol*. 2017;31(3):498-506.
- Torres T, Barcelos A, Filipe P, Fonseca JE. A Systematic review with network meta-analysis of the available biologic therapies for psoriatic disease domains. *Front Med (Lausanne)*. 2021;7:618163. doi:10.3389/fmed.2020.618163.
- Tremfya prescribing information. Janssen Biotech, Inc. Horsham, PA. July 2020.
- Truxima prescribing information. Teva Pharmaceuticals, Inc. North Wales, PA. November 2022.
- Tysabri prescribing information. Biogen Idec Inc., Cambridge, MA. December 2021.
- Ungprasert P, Thongprayoon C, Davis JM. Indirect comparisons of the efficacy of biological agents in patients with psoriatic arthritis with an inadequate response to traditional disease-modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: a meta-analysis. *Semin Arthritis Rheum*. 2016[a];45(4):428-38.
- Ungprasert P, Thongprayoon C, Davis JM. Indirect comparisons of the efficacy of subsequent biological agents in patients with psoriatic arthritis with an inadequate response to tumor necrosis factor inhibitors: a meta-analysis. *Clin Rheumatol*. 2016;35:1795-1803.
- van der Heijde D, Cheng-chung wei J, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. *Lancet*. 2018[a];392(10163):2441-2451.
- van der Heijde D, Dijkmans B, Geusens P, et al; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum*. 2005;52(2):582-91.
- van der Heijde D, Gladman DD, Kishimoto M, et al. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: 52-week results from a phase III study (SPIRIT-P1). *J Rheumatol*. 2018[b];45(3):367-377. doi: 10.3899/jrheum.170429.
- van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis. *Arthritis Rheum*. 2006;54(7):2136-46.

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- van der Heijde D, Strand V, Tanaka Y, et al. Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: clinical efficacy, radiographic and safety outcomes from a 24-month phase 3 study. *Arthritis Rheumatol*. 2019[a]; 71(6):878-891. doi: 10.1002/art.40803.
- van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving MTX. Twelve-month data from a twenty-four–month Phase III randomized radiographic study. *Arthritis Rheum*. 2013;65(3): 559-70.
- van der Heijde D, Song IH, Pangan AL, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. *Lancet*. 2019[b];394(10214):2108-2117. doi:10.1016/S0140-6736(19)32534-6.
- van der Heijde D, Gensler LS, Maksymowych WP, et al. Long-term safety and clinical outcomes of certolizumab pegol treatment in patients with active non-radiographic axial spondyloarthritis: 3-year results from the phase 3 C-axSpAnd study. *RMD Open*. 2022;8(1):e002138. doi:10.1136/rmdopen-2021-002138.
- van der Heijde D, Baraliakos X, Sieper J, et al. Efficacy and safety of upadacitinib for active ankylosing spondylitis refractory to biological therapy: a double-blind, randomised, placebo-controlled phase 3 trial. *Ann Rheum Dis*. 2022[b];81(11):1515-1523. doi:10.1136/ard-2022-222608.
- van der Heijde D, Deodhar A, Maksymowych WP, et al. Upadacitinib in active ankylosing spondylitis: results of the 2-year, double-blind, placebo-controlled SELECT-AXIS 1 study and open-label extension. *RMD Open*. 2022[c];8(2):e002280. doi:10.1136/rmdopen-2022-002280.
- Van Vollenhoven R, Takeuchi T, Pangan AL, et al. A Phase 3, randomized, controlled trial comparing upadacitinib monotherapy to MTX monotherapy in mtx-naïve patients with active rheumatoid arthritis. Poster presented at: 2018 American College of Rheumatology and Association of Rheumatology Health Professionals Annual Meeting; October 21, 2018; Chicago, IL.
- van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012;367(6):508-519.
- Van Voorhees AS, Stein Gold L, Lebwohl M, et al. Efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp: results of a phase 3b, multicenter, randomized, placebo-controlled, double-blind study. *J Am Acad Dermatol*. 2020;83(1):96-103. doi:10.1016/j.jaad.2020.01.072.
- Wang F, Sun L, Wang S, et al. Efficacy and safety of tofacitinib, baricitinib, and upadacitinib for rheumatoid arthritis: a systematic review and meta-analysis. *Mayo Clin Proc*. 2020;95(7):1404-1419. doi:10.1016/j.mayocp.2020.01.039.
- Wang S, He Q, Shuai Z. Risk of serious infections in biologic treatments of patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. *Clin Rheumatol*. 2018;37(2);439-450. doi:10.1007/s10067-017-3966-1.
- Wang SH, Yu CL, Wang TY, Yang CH, Chi CC. Biologic disease-modifying antirheumatic drugs for preventing radiographic progression in psoriatic arthritis: a systematic review and network meta-analysis. *Pharmaceutics*. 2022;14(10). doi:10.3390/pharmaceutics14102140
- Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Care Res (Hoboken)*. 2019;71(10):1285-1299. doi: 10.1002/acr.24025.
- Warren RB, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab vs secukinumab in patients with moderate-to-severe plaque psoriasis (IMMerge): results from a phase III, randomized, open-label, efficacy-assessor-blinded clinical trial. *Br J Dermatol*. 2021;184(1):50-59. doi:10.1111/bjd.19341.
- Watkins B, Qayed M, McCracken C, et al. Phase II trial of costimulation blockade with abatacept for prevention of acute GVHD. *J Clin Oncol*. 2021;39(17):1865-1877. doi:10.1200/JCO.20.01086.
- Weinblatt ME, Bingham CO, Mendelsohn AM, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. *Ann Rheum Dis*. 2013;72: 381-89.
- Wells AF, Edwards CJ, Kivitz AJ, et al. Apremilast monotherapy in DMARD-naive psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial. *Rheumatology (Oxford)*. 2018;57(7):1253-1263. doi:10.1093/rheumatology/key032.
- Wells AF, Edwards CJ, Kivitz AJ, et al. Apremilast monotherapy for long-term treatment of active psoriatic arthritis in DMARD-naïve patients. *Rheumatology (Oxford)*. 2022;61(3):1035-1043. doi:10.1093/rheumatology/keab449.
- Westhovens R, Kremer JM, Emery P, et al. Long-term safety and efficacy of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: a 7-year extended study. *Clin Exp Rheumatol*. 2014;32(4):553-62.
- Wiens A, Correr CJ, Venson R, et al. A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. *Clin Rheumatol*. 2009 Dec;28(12):1365-73.
- Wu D, Li C, Zhang S, et al. Effect of biologics on radiographic progression of peripheral joint in patients with psoriatic arthritis: meta-analysis. *Rheumatology (Oxford)*. 2020;59(11):3172-3180. doi:10.1093/rheumatology/keaa313.
- Wu D, Yue J, Tam LS. Efficacy and safety of biologics targeting interleukin-6, -12/23, and -17 pathways for peripheral psoriatic arthritis: a network meta-analysis. *Rheumatology*. 2018;57(3):563-571 doi: 10.1093/rheumatology/kex452.
- Xeljanz / Xeljanz XR/Xeljanz oral solution prescribing information. Pfizer, Inc. New York, NY. January 2022.
- Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis*. 2013;72:1613-1620.
- Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. *Ann Rheum Dis*. 2017;76(2):355-63.
- Yoo DH, Racewicz A, Brzezicki J, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. *Arthritis Res Ther*. 2016;18:82. doi: 10.1186/s13075-016-0981-6.
- Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med*. 2022;386(4):316-326. doi:10.1056/NEJMoa2109927.
- Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurative/acne inversa. *J Eur Acad Dermatol Venereol*. 2015;29(4):619-44.

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