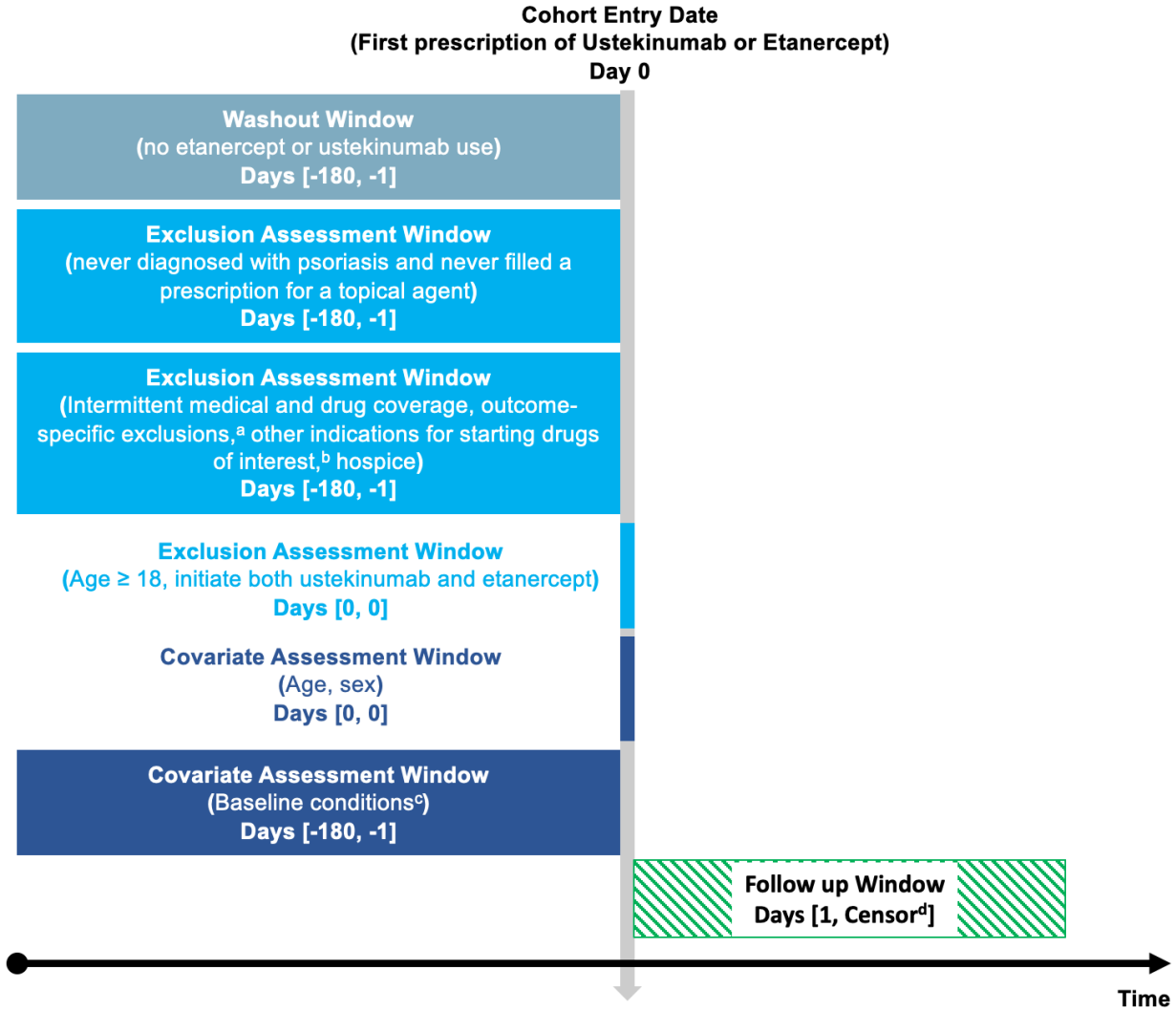
Supplementary Online Content

Schneeweiss MC, Savage TJ, Wyss R, et al. Risk of infection in children with psoriasis receiving treatment with ustekinumab, etanercept, or methotrexate before and after labeling expansion. *JAMA Dermatol.* Published online February 8, 2023. doi:10.1001/jamadermatol.2022.6325

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Study Design Diagram[1]



[a] Outcome specific exclusions: use of non-dermatologic systemic immunomodulating agents (rituximab, tocilizumab, anakinra, cyclophosphamide, mercaptopurine, baricitinib, upadacitinib, tofacitinib, vedolizumab), malignancy except non-melanoma skin cancer, chemotherapy, organ transplant, HIV/AIDs diagnosis or medication use, congenital immune deficiency, cystic fibrosis, chronic infection, hospice.
[b] Other indications for starting methotrexate, ustekinumab or etanercept: ankylosing spondylitis, inflammatory bowel disease, dermatomyositis, rheumatoid arthritis or juvenile idiopathic arthritis.
[c] Baseline conditions included: race, history of past infections that required an office visit or hospitalization, prior use of antibiotic/antifungal/antiviral medication, history of surgery, number of prior and recent non-biologic or biologic immunomodulatory agents, systemic glucocorticoid use, cumulative dose of systemic glucocorticoids in prednisone mg equivalences, and healthcare utilization, i.e., number of outpatient physician visits, number of unique medications, number of dermatologist visits.
[d] Earliest of: outcome of interest (infection), death, disenrollment, 180 days of follow-up, end of the study period

eTable 1. Inpatient Infections Included in Analysis

Outcome	Diagnosis
Inpatient or emergency department infection	
Serious bacterial	Cellulitis and abscess
	necrotizing fasciitis
	skin and soft tissue infection
	septicemia or bacteremia
	bacterial pneumonia
	osteomyelitis
	pyelonephritis
	bacterial meningitis
	bacterial encephalitis
	Endocarditis
	septic arthritis
	Endocarditis
	bacterial pneumonia (incl. Legionella) or pyotharax
	Pyelonephritis or UTI
	Septic arthritis
	Osteomyelitis, acute
	Bacteremia or septicemia or toxic shock syndrome
	Pharyngeal abscess (peritonsillar, retropharyngeal, and parapharyngeal)
	Pyothorax
	Mastoiditis
	Pyomyositis
	Acute rheumatic fever
	Clostridioides difficile
	Sinusitis, acute
Opportunistic	pneumocystis jiroveci pneumonia
	EBV
	CMV
	Aspergillus
	Candidiasis
	Mucormycosis
	Mycobacterium tuberculosis (any site)
	Mycobacterium abscessus
	Mycobacterium avium intracellular complex
	Mycobacterium chelonae
	Mycobacterium fortuitum
	Mycobacterium kansasii
	Mycobacterium marinum
	cryptococcus
	histoplasmosis

Opportunistic cont.	Blastomycosis
	Coccidiodomycosis
	Paracoccidiodomycosis
	Toxoplasma
	Nocardia
	Actinomyces
	Listeria
Viral	Viral Pneumonia, incl COVID
	RSV
	Influenza
	Herpes simplex virus
	Herpes zoster virus
	Encephalitis, viral
	Meningitis, viral
	West Nile virus

eTable 2. Outpatient Infections Included in Analysis

Outcome	Diagnosis
Outpatient infection	
Bacterial	Skin and soft tissue infection Streptococcal pharyngitis and tonsillitis Pneumonia Otitis media, acute Otitis externa, acute Urinary tract infection Bone and joint infection Sinusitis, acute
Mycobacterial infection	Mycobacterium tuberculosis (any site) Mycobacterium abscessus Mycobacterium avium intracellular complex Mycobacterium chelonae Mycobacterium fortuitum Mycobacterium kansasii Mycobacterium marinum
Viral	Herpes simplex virus Herpes zoster virus
Treatment class	
Antibiotics	Trimethoprim-sulfamethoxazole, doxycycline, minocycline, linezolid, dicloxacillin, penicillin, amoxicillin, amoxicillin-clavulanate, delafloxacin, ciprofloxacin, moxifloxacin, levofloxacin, delafloxacin, cephalexin, cefadroxil, cefdinir, cefpodoxime, cefuroxime, cefixime, ceftibuten, clindamycin, azithromycin, clarithromycin, metronidazole, nitrofurantoin, fosfomycin, acetic acid otic solution, ciprofloxacin and dexamethasone otic solution (Ciprodex), ciprofloxacin otic solution, ofloxacin otic solution
Mycobacterium-specific antibiotics	Isoniazid, rifampin, rifabutin, rifapentin, pyrazinamide, ethambutol, bedaquiline, levofloxacin, moxifloxacin, linezolid, azithromycin
Antivirals	aciclovir, valacylcovir, famciclovir

eTable 3. Pediatric Comorbidity Score* [2]

Component	Weight
Alcohol abuse	1
Anemia	2
Anxiety	1
Any malignancy	5
Asthma	1
Chromosomal abnormalities	2
Cardiovascular abnormalities	2
Conduct disorder	1
Congenital malformations	2
Depression	4
Developmental delays	1
Diabetes	4
Drug abuse	3
Eating disorder	1
Epilepsy or convulsions	4
Gastrointestinal conditions	1
Joint disorders	1
Menstrual disorders	2
Nausea vomiting	1
Pain Conditions	1
Psychotic disorders	3
Sleep disorder	1
Smoking	2
Weight loss	2

* Scores range from 0 to 5, with 0 being the lowest risk of hospitalization and 5 being the highest risk of hospitalization

eTable 4. Pooled CONSORT Table

	Ustekinumab (exposure) **vs. etanercept** (referent)		**Ustekinumab** (exposure) **vs. methotrexate** (referent)		**Etanercept** (exposure) **vs. methotrexate** (referent)	
Inclusion and Exclusion criteria	**Excluded**	**Remaining**	**Excluded**	**Remaining**	**Excluded**	**Remaining**
Patients in MarketScan and Optum		**584,525,414**		**584,525,414**		**584,525,414**
Excluded due to age >/= 18	-351,851,914		-351,851,914		-351,851,914	
Excluded due to insufficient enrollment	-77,064,674		-77,064,674		-77,064,674	
Pediatric cohort: Total		**155,608,826**		**155,608,826**		**155,608,826**
Did not meet cohort entry criteria, *i.e.*, did not start a drug of interest	-155,592,351		-155,560,442		-155,556,686	
Insufficient enrollment (180 days) [a]	-4,297		-13,243		-15,097	
Prior use of referent	-1,941		-5,362		-5,187	
Prior use of exposure	-201		-202		-1,765	
Patient qualified in >1 exposure category	0		0		-40	
Age >/= 18 [b]	-4,788		-10,520		-9,952	
Did not have a physician-recorded diagnosis of psoriasis [c]	-3,723		-16,929		-17,866	
Did not fill a prescription for a topical agent [d]	-160		-216		-241	
Comorbid conditions that have an indication for starting the drugs of interest [e]	-149		-245		-245	
Used a non-derm related systemic immunomodulatory agent [f]	-7		-17		-17	
Comorbid malignant neoplasm or chemotherapy procedure	-10		-23		-17	
Organ transplant [g]	0		0		0	
Comorbid HIV/AIDS (diagnosis or medication)	0		-1		-1	
Comorbid congenital immunodeficiency	-1		-5		-4	
Hospice	-11		-12		-10	
Comorbid cystic fibrosis	0		0		0	
Chronic infection	-6		-11		-11	
Dropped as incomplete case or did not begin follow-up	-1		-3		-3	
Total children meeting criteria in each pair-wise comparison		**1,180**		**1,595**		**1,725**
After trimming[h] - total children meeting criteria in each pair-wise comparison	-22	**1,158**	-21	**1,574**	-28	**1,697**

[a] Patients were excluded if they did not have continuous enrollment in their healthplan during the 180 days before initiating the systemic immunomodulatory agent.

[b] While we start with a pediatric cohort, some children and adolescents may have aged 18 years or older by the time they meet our cohort entry criteria, i.e., start ustekinumab, etanercept or methotrexate.
[c] We excluded patients who did not have a physician-recorded diagnosis of psoriasis, within 180 days prior to starting drug.
[d] We further excluded patients who did fill a prescription for either a topical corticosteroid or topical vitamin D derivative, within 180 days prior to starting drug.
[e] Co-occurring conditions that have an indication for starting the drugs of interest, included ankylosing spondylitis, rheumatoid arthritis or juvenile idiopathic arthritis, dermatomyositis, Crohn's disease or ulcerative colitis.
[f] Organ transplant (other than corneal), including bone narrow transplant.
[g] Use of non-dermatologic systemic immunomodulating agents, included rituximab, tocilizumab, anakinra, cyclophosphamide, mercaptopurine, baricitinib, upadacitinib, tofacitinib, vedolizumab.
[h] We conducted PS-decile stratification with symmetric trimming of the extremes of the PS distribution by 2.5%. This is the cohort count after conducting symmetric trimming.

eTable 5. Pooled Patient Characteristics With Standardized Differences for Ustekinumab vs Etanercept, Before and After Propensity-Score Matching

	Unadjusted			Adjusted by PS-matching		
Patient Characteristics	**Ustekinumab***	**Etanercept**	**Standardized difference**	**Ustekinumab***	**etanercept**	**Standardized difference**
Number of patients	394	786	--	206	206	--
Demographics, n (%)						
Sex						
...Male	162 (41.1%)	312 (39.7%)	0.03	78 (37.9%)	81 (39.3%)	-0.03
...Female	232 (58.9%)	474 (60.3%)	-0.03	128 (62.1%)	125 (60.7%)	0.03
Age categories (years)						
...0-5	1 (0.3%)	14 (1.8%)	-0.15	0 (0.0%)	0 (0.0%)	-
...6 – 11	16 (4.1%)	187 (23.8%)	-0.59	13 (6.3%)	13 (6.3%)	0.00
...12-17	377 (95.7%)	585 (74.4%)	0.62	193 (93.7%)	193 (93.7%)	0.00
Healthcare utilization						
Number of office visit (180 days); mean (sd)	5.87 (6.66)	6.82 (6.58)	-0.14	6.21 (7.08)	6.14 (6.02)	0.01
Number of unique medications, topical (180 days); mean (sd)	2.49 (2.45)	2.87 (2.77)	-0.14	2.54 (2.59)	2.58 (2.27)	-0.01
Number of unique medications, non-topical (180 days); mean (sd)	3.87 (4.53)	4.26 (4.84)	-0.08	3.61 (4.52)	3.10 (3.61)	0.12
Hospitalization; n (%)	11 (2.8%)	20 (2.5%)	0.02	2 (1.0%)	2 (1.0%)	0.00
Number of dermatologist visits, (180 days); mean (sd)	2.18 (3.43)	2.85 (4.66)	-0.16	2.41 (3.98)	2.51 (3.57)	-0.03
Infection risk factors, n (%)						
History of any invasive procedures or surgery	1 (0.3%)	1 (0.1%)	0.03	0 (0.0%)	0 (0.0%)	-
Physician administered IV antifungal, antibiotic or antiviral	6 (1.5%)	22 (2.8%)	-0.09	2 (1.0%)	3 (1.5%)	-0.04
Use of antibiotics, antivirals, antifungals, or TB medication	145 (36.8%)	319 (40.6%)	-0.08	79 (38.3%)	74 (35.9%)	0.05
Prior infection – bacterial or viral (inpatient or outpatient)	62 (15.7%)	126 (16.0%)	-0.01	27 (13.1%)	31 (15.0%)	-0.06
Prior infection - opportunistic (inpatient or outpatient)	0 (0.0%)	5 (0.6%)	-0.11	0 (0.0%)	0 (0.0%)	-
Type 1 diabetes	1 (0.3%)	8 (1.0%)	-0.10	0 (0.0%)	0 (0.0%)	-
Sickle cell disease	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Pediatric comorbidity score ...mean (sd)	1.11 (2.15)	0.93 (1.69)	0.09	0.84 (1.75)	0.66 (1.27)	0.12
Comorbid conditions; n (%)						
Acne	59 (15.0%)	70 (8.9%)	0.19	29 (14.1%)	26 (12.6%)	0.04
Hidradenitis suppurativa	2 (0.5%)	1 (0.1%)	0.07	0 (0.0%)	0 (0.0%)	-
Psoriatic arthritis	18 (4.6%)	124 (15.8%)	-0.38	15 (7.3%)	8 (3.9%)	0.15
Uveitis	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-

eTable 5 continued	Ustekinumab (n=394)	Etanercept (n=786)	Unadjusted Standardized difference	Ustekinumab (n=206)	Etanercept (n=206)	Adjusted Standardized difference
Systemic steroid use; n (%)						
Prior use of Glucocorticoids (systemic)	39 (9.9%)	99 (12.6%)	-0.09	20 (9.7%)	14 (6.8%)	0.11
Cumulative sum of daily dose of oral steroids, in oral prednisone mg equivalents, mean (sd)	15.58 (85.46)	13.53 (88.42)	0.02	18.13 (96.58)	8.67 (51.09)	0.12
Prior use of immunomoduatory treatments, n (%)[a]						
Use of prior non-biologic[b] immunomodulators [-30, -1]	23 (5.8%)	94 (12.0%)	-0.22	15 (7.3%)	14 (6.8%)	0.02
Use of prior non-biologic immunomodulators [-60, -31]	30 (7.6%)	107 (13.6%)	-0.20	17 (8.3%)	14 (6.8%)	0.06
Use of prior biologic[c] immunomodulators [-30, -1]	16 (4.1%)	13 (1.7%)	0.14	2 (1.0%)	1 (0.5%)	0.06
Use of prior biologic immunomodulators [-60, -31]	35 (8.9%)	12 (1.5%)	0.34	5 (2.4%)	2 (1.0%)	0.11
Prior use of immunomoduatory treatments, n (%)[a]						
Number of prior non-biologic immunomodulators						
...0; n (%)	337 (85.5%)	582 (74.0%)	0.29	172 (83.5%)	175 (85.0%)	-0.04
...1; n (%)	56 (14.2%)	197 (25.1%)	-0.28	34 (16.5%)	31 (15.0%)	0.04
...2+; n (%)	1 (0.3%)	7 (0.9%)	-0.08	0 (0.0%)	0 (0.0%)	-
Number of prior biologic immunomodulators						
...0; n (%)	335 (85.0%)	749 (95.3%)	-0.35	192 (93.2%)	200 (97.1%)	-0.18
...1; n (%)	56 (14.2%)	37 (4.7%)	0.33	14 (6.8%)	6 (2.9%)	0.18
...2+; n (%)	3 (0.8%)	0 (0.0%)	0.12	0 (0.0%)	0 (0.0%)	-

[a] Due to the new-user requirement we have excluded prior use of the referent drug and the drug of interest, i.e., patients were new-users (180-day washout) of both the referent agent, etanercept, and the exposure agent, ustekinumab.
[b] Non-biologics: methotrexate, cyclosporine, mycophenolate, leflunamide.
[c] Biologics: apremilast, risankizumab, tildrakizumab, guselkumab, brodalumab, golimumab, infliximab, certolizumab, adalimumab, ixekizumab, secukinumab.

eTable 6. Pooled Incidence Rate and Rate Ratio of Infections (2009-2021), Unadjusted

	Ustekinumab[a] vs. Etanercept		Ustekinumab[a] vs. Methotrexate		Etanercept vs. Methotrexate	
	Ustekinumab[a]	Etanercept	Ustekinumab[a]	Methotrexate	Etanercept	Methotrexate
Serious infection						
Number of patients	394	786	406	1189	586	1139
Number of person-years	170	354	178	539	264	516
Number of events	3	9	3	8	9 (1.54%)	8 (0.70%)
Rate per 1000 person-years	17.65	25.42	16.85	14.84	34.09	15.50
Rate Ratio (95% CI)	0.69 (0.19, 2.56)	Referent	1.14 (0.30, 4.28)	Referent	2.20 (0.85, 5.70)	Referent
Rate Difference per 1000 person-years (95% CI)	-7.78 (-33.75, 18.20)	Referent	2.01 (-19.66, 23.68)	Referent	18.59 (-6.14, 43.32)	Referent
Outpatient infection						
Number of patients	394	786	406	1189	586	1139
Number of person-years	158	321	166	484	240	463
Number of events	45	141	48	212	102	202
Rate per 1000 person-years	284.81	439.25	289.16	438.02	425.00	436.29
Rate Ratio (95% CI)	0.65 (0.46, 0.91)	Referent	0.66 (0.48. 0.90)	Referent	0.97 (0.77, 1.24)	Referent
Rate Difference per 1000 person-years (95% CI)	-154.44 (-264.81, -44.07)	Referent	-148.86 (-249.70, -48.02)	Referent	-11.29 (-113.38, 90.81)	Referent

Abbreviations: *CI*, confidence interval; *PS*, propensity-score. [a] Included ustekinumab users who contributed to one or more pairwise comparisons. *Serious infections were defined as infections requiring and emergency room visit or hospitalization.

eTable 7. Pooled Incidence Rate of Serious Infections Stratified by Years, After PS-Decile Stratification

	Ustekinumab[a] vs. Etanercept		**Ustekinumab[a] vs. Methotrexate**		**Etanercept vs. Methotrexate**	
	Ustekinumab[a]	Etanercept	Ustekinumab[a]	Methotrexate	Etanercept	Methotrexate
Serious infection, 2009-2015						
Number of patients	50	443	53	724	313	685
Number of person-years	22	202	24	331	143	312
Number of events	0	5	0	7	4	7
Rate per 1000 person-years	0.00	24.75	0.00	21.15	27.97	22.44
Rate Ratio (95% CI)	n/a	Referent	n/a	Referent	1.25 (1.02, 1.52)	Referent
Rate Difference per 1000 person-years (95% CI)	-24.75 (0.00, 0.00)	Referent	-21.15 (0.00, 0.00)	Referent	5.54 (0.00, 0.00)	Referent
Serious infection, 2016-2021						
Number of patients	329	336	341	456	358	636
Number of person-years	141	150	147	205	158	284
Number of events	3	4	3	1	8	2
Rate per 1000 person-years	21.28	26.67	20.41	4.89	50.63	7.04
Rate Ratio (95% CI)	0.80 (0.63, 1.00)	Referent	4.18 (3.39, 5.17)	Referent	7.19 (5.92, 8.73)	Referent
Rate Difference per 1000 person-years (95% CI)	-5.39 (0.00, 0.00)	Referent	15.53 (0.00, 0.00)	Referent	43.59 (0.00, 0.00)	Referent

Abbreviations: *CI*, confidence interval; *PS*, propensity-score. [a] Included ustekinumab users who contributed to one or more pairwise comparisons. *Serious infections were defined as infections requiring and emergency room visit or hospitalization.

eReferences

1. Schneeweiss S, Rassen JA, Brown JS, et al. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. *Ann Intern Med.* 2019;170(6):398-406.
2. Sun JW, Bourgeois FT, Haneuse S, et al. Development and Validation of a Pediatric Comorbidity Index. *Am J Epidemiol.* 2021;190(5):918-927.