Targeted Immune Modulators for Rheumatoid Arthritis and Axial Spondyloarthritis

Topic Brief

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Presented by Jennifer Lyon, MS, MLIS, MEd

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Background

- Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease of the peripheral joints
  - Progressive erosion of the bone and destruction of the joints
  - Functional disability
- Axial spondyloarthritis (AS) is a chronic inflammatory arthritis of the axial skeleton
  - Severe back pain, particularly involving the spine and sacroiliac joints.
- Adult-Onset Still Disease (AOSD) is an inflammatory disorder
  - Polyarthritis, fluctuating daily fever, and a transient pink rash
- Targeted immune modulators (TIMs) are biologic drugs used to treat RA and AS by selectively blocking mechanisms involved in the inflammatory and immune responses
  - One of these TIMs (canakinumab) is approved by the US Food and Drug Administration (FDA)-approved for AOSD.
  - First TIM (infliximab) became FDA approved for RA in 1998
  - First TIM (etanercept) became FDA approved for AS in 2003
  - Multiple additional agents, including biosimilars, have since been approved for both conditions

Targeted Immune Modulators for RA and AS

TNF-α INHIBITOR

- Adalimumab and biosimilars
- Certolizumab pegol
- Etanercept and biosimilars
- Golimumab[a] and biosimilars
- Infliximab and biosimilars

T-CELL MODULATOR

- Abatacept

IL-1 INHIBITOR

- Anakinra
- Canakinumab

IL-17A RECEPTOR INHIBITOR

- Ixekizumab
- Secukinumab

IL-17A AND IL-17F RECEPTOR INHIBITOR

- Bimekizumab

IL-6 RECEPTOR INHIBITOR

- Sarilumab
- Tocilizumab and biosimilars

B-CELL DEPLETION

- Rituximab and biosimilars

JAK INHIBITOR

- Baricitinib
- Tofacitinib
- Upadacitinib

Note. a Golimumab is the only pipeline agent.
Abbreviations. IL: interleukin; JAK: janus kinase; TNF-α: tumor necrosis factor alpha.

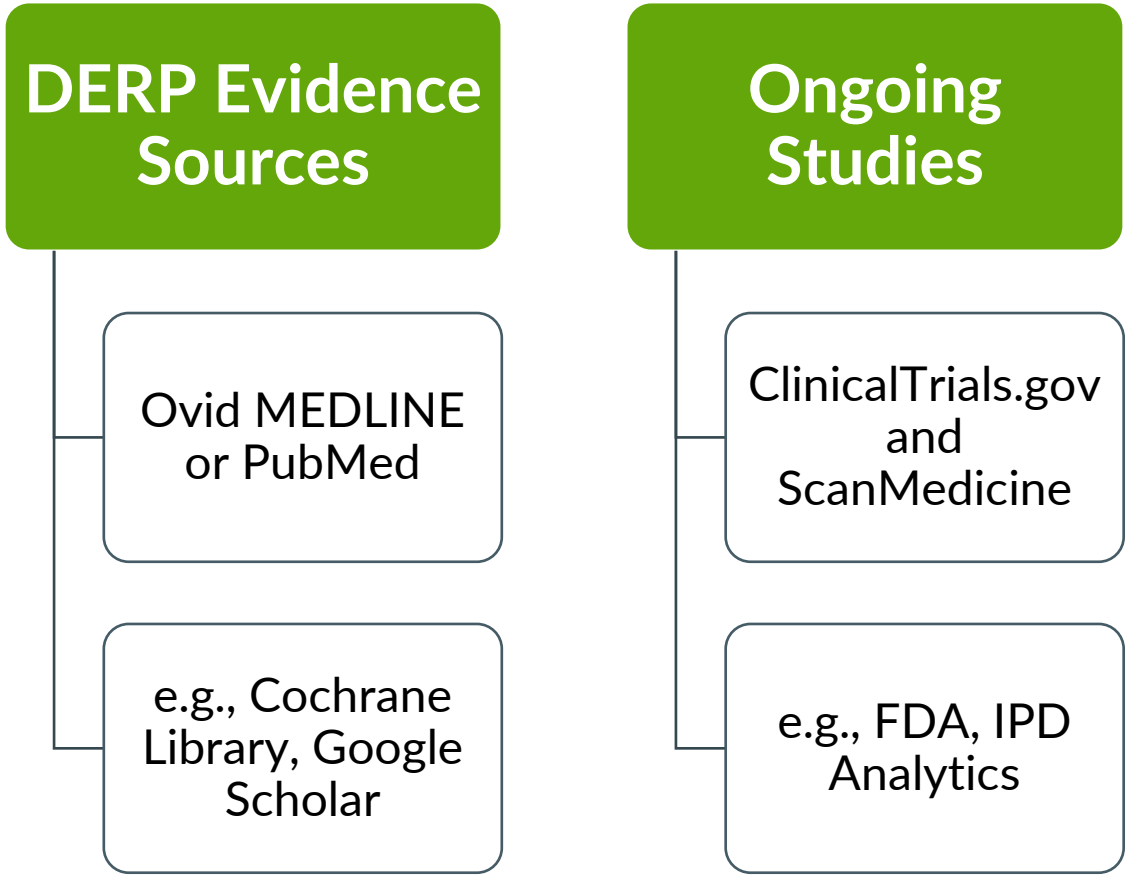
PICOS

- Populations:
  - Adults with moderate-to-severe RA
  - Adults with AS
- Interventions:
  - FDA-approved TIMs and biosimilars
  - Pipeline agents with Prescription Drug User Fee Act (PDUFA) dates
- Comparators:
  - Another eligible intervention
  - Standard of care or placebo (for newly approved or pipeline agents only)
- Outcomes:
  - Measures of clinical improvement and disease remission, quality of life, pain levels, swollen joint counts, adverse events, serious adverse events, and other health outcomes
- Study Designs:
  - Randomized controlled trials (RCTs) with ≥ 12 weeks' duration
  - In countries "very high" on the United Nations Human Development Index

Key Questions

1. Effectiveness of listed interventions for RA and AS
2. Potential harms of the listed interventions for RA and AS
3. Variation based on patients or disease characteristics
4. Characteristics of ongoing studies for the listed interventions for RA and AS

Methods

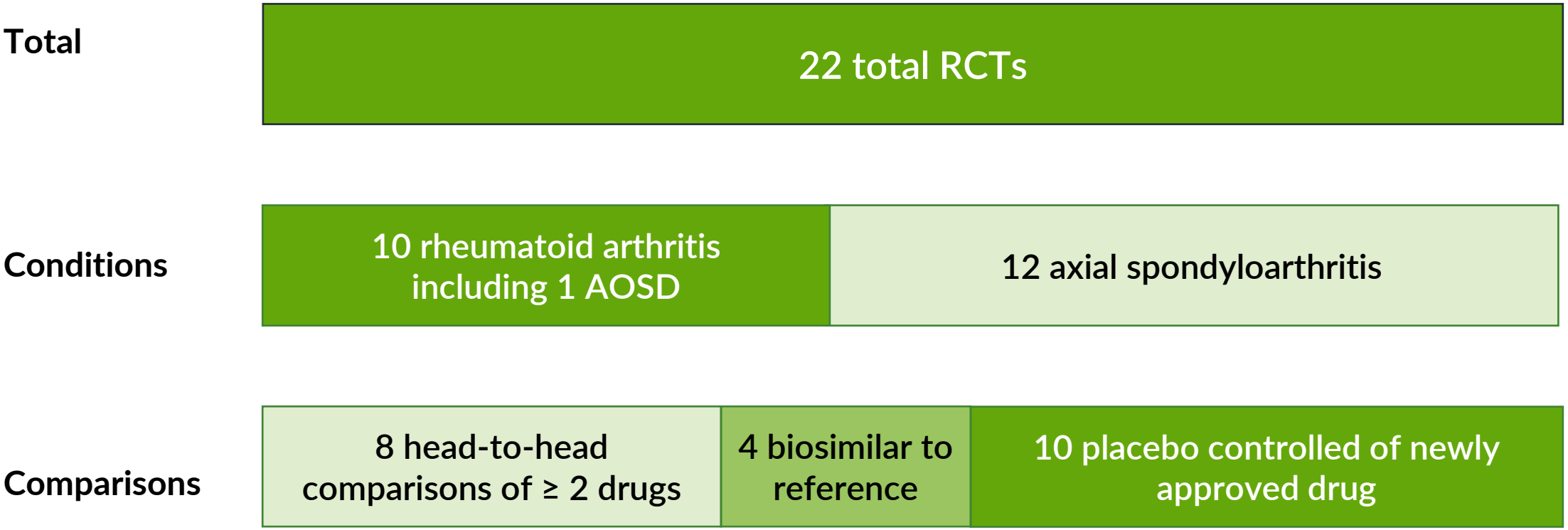


We included only studies conducted in countries categorized as *very high* on the United Nations Human Development Index

Findings

Overall

Overall Study Characteristics of TIMs for RA and AS



Findings

Rheumatoid Arthritis Including AOSD

RCTs: TIMs for RA (Including AOSD)

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- 9 RCTs identified for RA and 1 for AOSD
  - 5 head-to-head studies of 2 or more drugs
  - 4 studies comparing a biosimilar to a reference drug
  - 1 placebo-controlled study of a recently approved drug

NUMBER OF STUDIES BY DRUG

- Abatacept: 2
- Adalimumab: 4
- Adalimumab biosimilar: 1
- Baricitinib: 1
- Canakinumab: 1
- Etanercept: 1
- Rituximab: 1
- TNF inhibitors (grouped): 1
- Tocilizumab: 4
- Tocilizumab biosimilar: 1

COMMON OUTCOMES

- Clinical improvement
- Disease remission
- Adverse events (AEs)
- Pain levels

SAMPLE SIZES

25 to 4,362

STUDY DURATIONS

12 weeks to 4 years

Abbreviation. TNF: tumor necrosis factor.

Characteristics of 9 Head-to-Head[a] RCTs for RA (1 of 3)

Report Pages 7–8

Author (Year)	Setting	Interventions	Demographics Sample Sizes	Study Duration
Ahmed (2024)	UK (single center)	• Abatacept • Adalimumab	Adults with moderate-to-severe RA N = 25	12 months
Kay (2021)	International with US	• Yuflyma (biosimilar) 40 mg SC, Q2W • Adalimumab (reference) 40 mg SC, Q2W	Adults with moderate-to-severe RA N = 648	24 weeks
Leng (2024)	International	• Tofidence (biosimilar) 8 mg/kg IV up to max 800 mg, Q4W • Tocilizumab (reference) 8 mg/kg IV up to max 800 mg, Q4W	Adults with moderate-to-severe RA N = 621	24 weeks
Rigby (2021)	Canada, Mexico, US	• Abatacept 125 mg SC, weekly • Adalimumab 40 mg SC, Q2W	Adults with moderate-to-severe RA who are autoantibody positive for ACCP-2 and RF N = 80	24 weeks

Note. a Includes biosimilars in comparison to reference drugs.
Abbreviations. RCT: randomized controlled trial; RA: rheumatoid arthritis; N: number; UK: United Kingdom; mg: milligrams; kg: kilogram; IV: intravenous; SC: subcutaneous; Q2W: every two weeks; Q4W: every four weeks; ACCP-2: Anti-Cyclic Citrullinated Peptide 2; RF: rheumatoid factor.

Characteristics of 9 Head-to-Head[a] RCTs for RA (2 of 3)

Report Pages 7–8

Author (year)	Setting	Interventions	Demographics Sample Sizes	Study Duration
Rivallese (2023)	International with US	• Rituximab 1000 mg IV at weeks 0 and 2 • Tocilizumab 162 mg SC weekly • Etanercept 50 mg SC weekly	Adults with moderate-to-severe RA characterized by B cell level (B cell rich or poor) N = 226	16 weeks
Smolen (2024)	Poland (multisite)	• Avtozma (biosimilar) 8 mg/kg IV, Q4W • Tocilizumab (reference) 8 mg/kg IV, Q4W	Adults with moderate-to-severe RA N = 471	48 weeks
Van de Laar (2024)	Belgium and Netherlands	• Baricitinib • TNF-α inhibitors (grouped)	Adults with moderate-to-severe RA N = 201	48 weeks
Ytterberg (2022)	International with US	• Tofacitinib citrate 5 mg or 10 mg oral, twice daily • Adalimumab 40 mg SC (US, PR, CA), 50 mg SC (rest of world), Q2W	Adults aged ≥ 50 years with moderate-to-severe RA N = 4,362	24 weeks

Note. a Includes biosimilars in comparison to reference drugs.
Abbreviations. RCT: randomized controlled trial; RA: rheumatoid arthritis; N: number; mg: milligrams; kg: kilogram; IV: intravenous; TNF: tumor necrosis factor; PR: Puerto Rico; CA: Canada; SC: subcutaneous; Q2W: every two weeks; Q4W: every four weeks.

Characteristics of 9 Head-to-Head[a] RCTs for RA *(3 of 3)*

Report Pages 7–8

Author (year)	Setting	Interventions	Demographics Sample Sizes	Study Duration
Zubrzyck-Sienkiewicz (2024)	International not including US	• Tocilizumab-aazg (biosimilar Tyenne) 162 mg SC, weekly • Tocilizumab (reference) 162 mg SC, weekly	Adults with moderate-to-severe RA N = 604	24 weeks

Note. a Includes biosimilars in comparison to reference drugs.
Abbreviations. RCT: randomized controlled trial; RA: rheumatoid arthritis; N: number; mg: milligrams; SC: subcutaneous.

1 Placebo-Controlled RCT for TIMs for AOSD

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- Kedor (2020)
  - Condition: adults with AOSD and active joint involvement (tender and swollen joint counts of ≥ 4 each)
  - Comparison:
    - Canakinumab 4 mg/kg SC, max 300 mg, every four weeks
    - Placebo
  - Setting: Germany (multisite)
  - Sample size: N = 36
  - Duration: 12 weeks

Abbreviations. mg: milligrams; kg: kilograms; SC: subcutaneous; N: number.

Findings

Axial Spondyloarthritis

RCTs: TIMs for AS

Report Pages 9–11

- 12 RCTs identified
  - 3 head-to-head studies of 2 or more drugs
  - 9 placebo-controlled studies of a recently approved drug

NUMBER OF STUDIES BY DRUG

- Abatacept: 2
- Bimekizumab: 2
- Certolizumab pegol: 1
- Ixekizumab: 4
- Secukinumab: 1
- Tofacitinib: 2
- Upadacitinib: 3

COMMON OUTCOMES

- Clinical improvement
- Disease remission
- Adverse events (AEs)
- Pain levels

SAMPLE SIZES

76 to 859

STUDY DURATIONS

12 weeks to 104 weeks

Characteristics of Head-to-Head RCTs for AS

Report Pages 7–11

Author (year)	Setting	Interventions	Demographics Sample Sizes	Study Duration
Baraliakos (2024)	International with US	• Bimekizumab 160 mg SC Q2W for weeks 0–10 and 320 mg SC Q4W for weeks 12–44 • Certolizumab pegol 400-mg-SC loading dose Q2W for weeks 0–4, 200 mg SC Q2W for weeks 6–10, 400 mg SC Q4W for weeks 12–44	Adults with AS N = 76	44 weeks
Baraliakos (2024)	International with US	• Secukinumab 150 mg or 300 mg SC for weeks 1–4 and then Q4W • Adalimumab (Sandoz biosimilar) 40 mg SC, Q2W	Adults with AS N = 859	104 weeks
Van der Heijde (2018)	International with US	• Ixekizumab 80 mg SC, Q2W or Q4W • Adalimumab 40 mg SC, Q2W • Placebo	Adults with AS N = 341	16 weeks

Abbreviations. RCT: randomized controlled trial; AS: axial spondyloarthritis; N: number; mg: milligrams; SC: subcutaneous; Q2W: every two weeks; Q4W: every four weeks.

Placebo-Controlled RCTs for TIMs for AS

Drug	Number of RCTs	Study Size Range	Total N	Study Duration, (weeks)
Bimekizumab	1	254 to 332	586	16
Ixekizumab	3	155 to 316	774	16 to 40
Tofacitinib	2	208 to 269	477	12 to 16
Upadacitinib	3	187 to 420	921	14 to 52
Total	9	**155 to 420**	**2,758**	12 to 52

Abbreviations. RCT: randomized controlled trial; TIMs: targeted immune modulators; AS: axial spondyloarthritis; N: number.

Comparison of Head-to-Head Studies Between 2022 Report and New Studies

Rheumatoid Arthritis: Head-to-Head Comparisons

	Abatacept	Adalimumab	Anakinra	Baricitinib	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Rituximab	Sarilumab	Tocilizumab	Tofacitinib	Upadacitinib	TNF-α Inhibitors (class)	Non-TNF-α Inhibitors (class)
Abatacept		X √√			X			X	XX		XX		X	XX	
Adalimumab		√*		X	X	XX				X	XX	XXX √	X		
Anakinra															X
Baricitinib														√	
Certolizumab pegol											X				
Etanercept								X			X √§				
Golimumab															
Infliximab															
Rituximab						√§					X √§				
Sarilumab															
Tocilizumab										X	√*√*√*				
Tofacitinib															
Upadacitinib															
TNF-α Inhibitors (class)															X
Combination Therapies	X					XX			X						

In 2022 Report: X

New in Topic Brief: √

* Biosimilar to Reference

§ 3 or More Drug Arms

Abbreviation. TNF-α: tumor necrosis factor alpha.

Axial Spondyloarthritis: Head-to-Head Comparisons

	Adalimumab	Bimekizumab	Certolizumab pegol	Etanercept	Infliximab	Ixekizumab	Secukinumab	Tofacitinib	Upadacitinib	TNF-α Inhibitors (class)
Adalimumab										
Bimekizumab			√							
Certolizumab pegol										
Etanercept					X					
Infliximab										
Ixekizumab	√									
Secukinumab	√									
Tofacitinib										
Upadacitinib										
TNF-α Inhibitors (class)										

In 2022 Report: X

New in Topic Brief: √

Abbreviation. TNF-α: tumor necrosis factor alpha.

Ongoing Studies

Ongoing RCTs for TIMs for RA

Report Pages 12–15

- 12 RCTs identified
  - All are for RA (no ongoing studies for AS or AOSD)
  - All are head-to-head studies of 2 or more drugs

NUMBER OF STUDIES BY DRUG

- Abatacept: 4
- Adalimumab: 6
- Baricitinib: 5
- Certolizumab pegol: 1
- Etanercept: 7
- Golimumab: 1
- Rituximab: 1
- Sarilumab: 3
- TNF[a] inhibitors (grouped): 1
- Tocilizumab: 3
- Tofacitinib: 4
- Upadacitinib: 3

COMMON OUTCOMES

- Clinical improvement
- Disease remission
- Adverse events (AEs)
- Pain levels

SAMPLE SIZES

75 to 2,600

COMPLETION DATES

March 2024 to December 2028

Note. [a] *TNF: tumor necrosis factor.*

Characteristics of Ongoing RCTs *(1 of 3)*

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Study ID	Interventions	Demographics Sample Size	Completion Date
ISRCTN44988547	• Sarilumab 200 mg SC, Q2W • Etanercept 50 mg SC, weekly	Adults aged ≥ 18 years with RA N = 240 (estimated)	September 2026 (estimated)
NCT03227419	• Abatacept 125 mg SC Q1W • Tocilizumab 162 mg SQ Q2W	Adults aged ≥ 18 years with RA and inadequate response to TNFi N = 224 (estimated)	November 2024
NCT03915964	• Baricitinib oral low dose • Baricitinib oral high dose • Adalimumab SC per SOC • Etanercept SC per SOC	Adults aged ≥ 18 years with RA, venous thromboembolism, and inadequate response or intolerance to ≥ 1 DMARD N = 2,600 (estimated)	February 2026 (estimated)
NCT03976245	• Etanercept 50 mg SC Q1W • Tofacitinib 5 mg oral daily	Adults aged ≥ 18 years with RA N = 144 (estimated)	March 2025 (estimated)
NCT04086745	• Baricitinib oral low dose • Baricitinib oral high dose • Adalimumab SC per SOC • Etanercept SC per SOC	Adults aged ≥ 18 years with RA, venous thromboembolism, and inadequate response or intolerance to ≥ 1 DMARD N = 1,300 (estimated)	April 2026 (estimated)

Abbreviations. RCT: randomized controlled trial; RA: rheumatoid arthritis; ID: identification; N: number; mg: milligrams; SC: subcutaneous; Q1W: every week; Q2W: every two weeks; SOC: standard of care; TNFi: tumor necrosis factor inhibitor; DMARD: disease-modifying antirheumatic drug.

Characteristics of Ongoing RCTs *(2 of 3)*

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Study ID	Interventions	Demographics Sample Size	Completion Date
NCT04485325	• Tofacitinib 5 mg oral, BID • Etanercept 50 mg SC, weekly	Adults aged 18–65 years with RA, and an inadequate response to 1 to 2 DMARDs N = 92 (actual)	March 2024
NCT04692493	• Baricitinib, tofacitinib, or upadacitinib • Abatacept, rituximab, sarilumab, or tocilizumab	Adults aged ≥ 18 years with RA N = 924 (estimated)	December 2028 (estimated)
NCT04870203	• Baricitinib 4 mg daily with anti-TNF (adalimumab 40 mg Q2W or etanercept 50 mg Q1W) • Baricitinib 4 mg daily with placebo	Adults aged 18–65 years with RA and an inadequate response to ≥ 1 DMARD N = 178 (estimated)	December 2026 (estimated)
NCT04909801	• Abatacept 125 mg SC Q1W with methotrexate • Abatacept 125 mg SC Q1W with MTX followed by adalimumab 40 mg Q2W with Methotrexate	Adults aged ≥ 18 years with RA (epitope-positive) and inadequate response to MTX N = 338 (actual)	September 2027 (estimated)

Abbreviations. RCT: randomized controlled trial; ID: identification; RA: rheumatoid arthritis; BID: bis in die (twice a day); N: number; mg: milligrams; SC: subcutaneous; Q1W: every week; Q2W: every two weeks; DMARD: disease-modifying antirheumatic drug; TNFi: tumor necrosis factor inhibitor.

Characteristics of Ongoing RCTs *(3 of 3)*

Report Pages 12–15

Study ID	Interventions	Demographics Sample Size	Completion Date
NCT05305066	• Adalimumab, certolizumab, etanercept, or golimumab • Sarilumab or tocilizumab • Baricitinib, tofacitinib, or upadacitinib	Adults aged ≥ 18 years with RA and failure to respond to standard conventional synthetic DMARDs N = 75 (estimated)	December 2026 (estimated)
NCT05428488	• TNFi then switched to abatacept 125 mg weekly • TNFi then switched to another TNFi	Adults aged ≥ 18 years with RA, targeted DMARDs naïve N = 220 (estimated)	November 2027 (estimated)
NCT05814627	• Adalimumab SC • Upadacitinib oral	Adults aged ≥ 18 years with RA, treated with a TNFi but either continued to exhibit active disease or had to discontinue due to intolerability or toxicity, and on MTX N = 480 (estimated)	August 2026 (estimated)

Abbreviations. RCT: randomized controlled trial; ID: identification; RA: rheumatoid arthritis; N: number; mg: milligrams; SC: subcutaneous; MTX: methotrexate; DMARD: disease-modifying antirheumatic drug; TNFi: tumor necrosis factor inhibitor.

Questions?


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