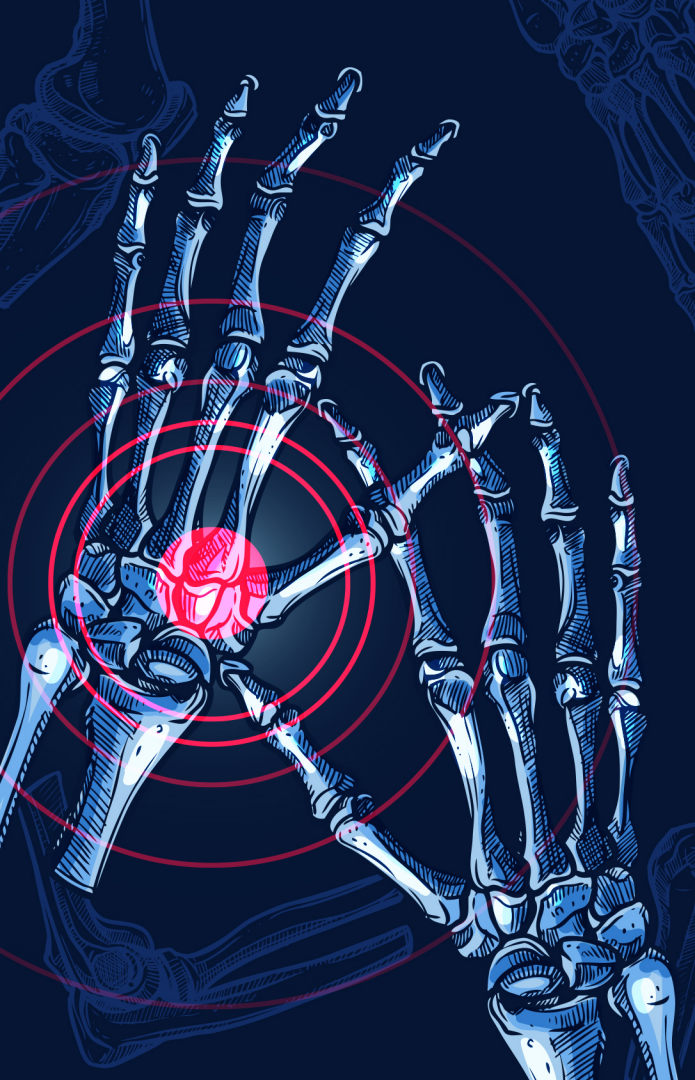
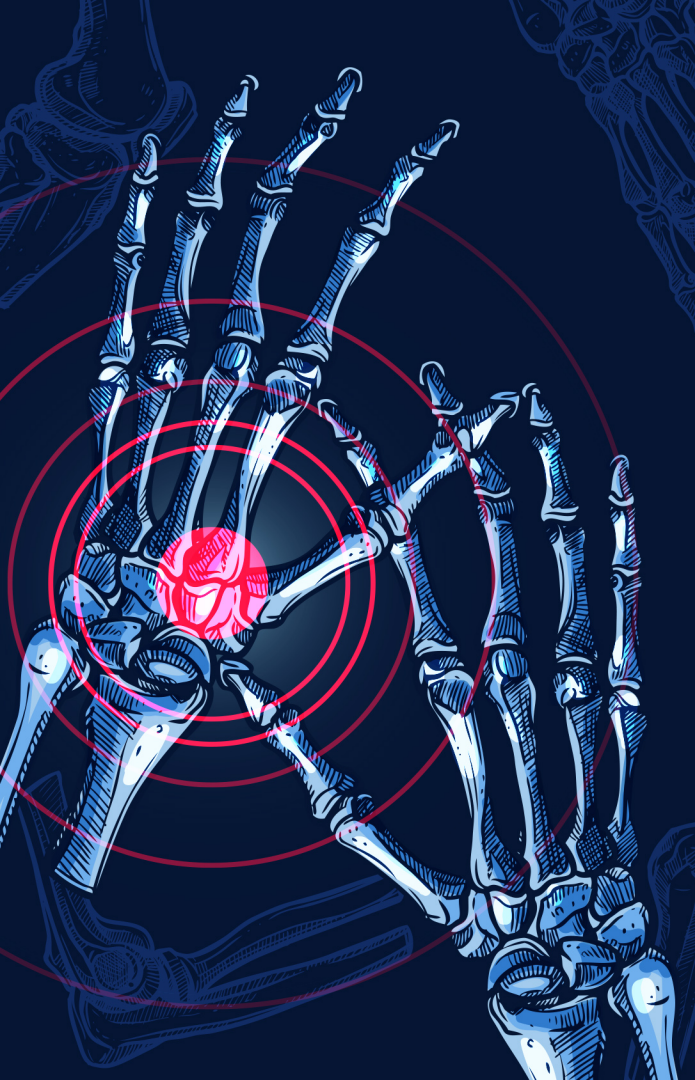


FROM PATHWAYS TO PROs

Translating the Latest Evidence for Current and Emerging JAK Inhibitors to Clinical Practice

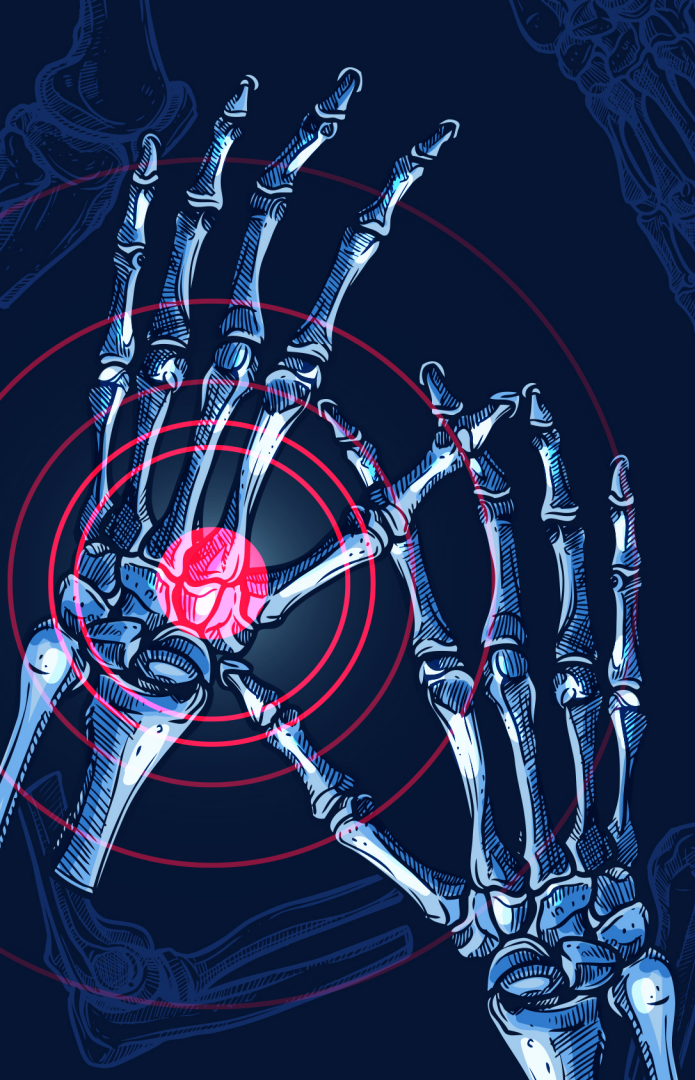
Supported by an educational grant from Gilead Sciences, Inc.

Provided by: CME Outfitters



Stanley B. Cohen, MD

University of Texas Southwestern
Medical School
Presbyterian Hospital
Metroplex Clinical Research Center
Dallas, TX
Past President of the American
College of Rheumatology
Atlanta, GA

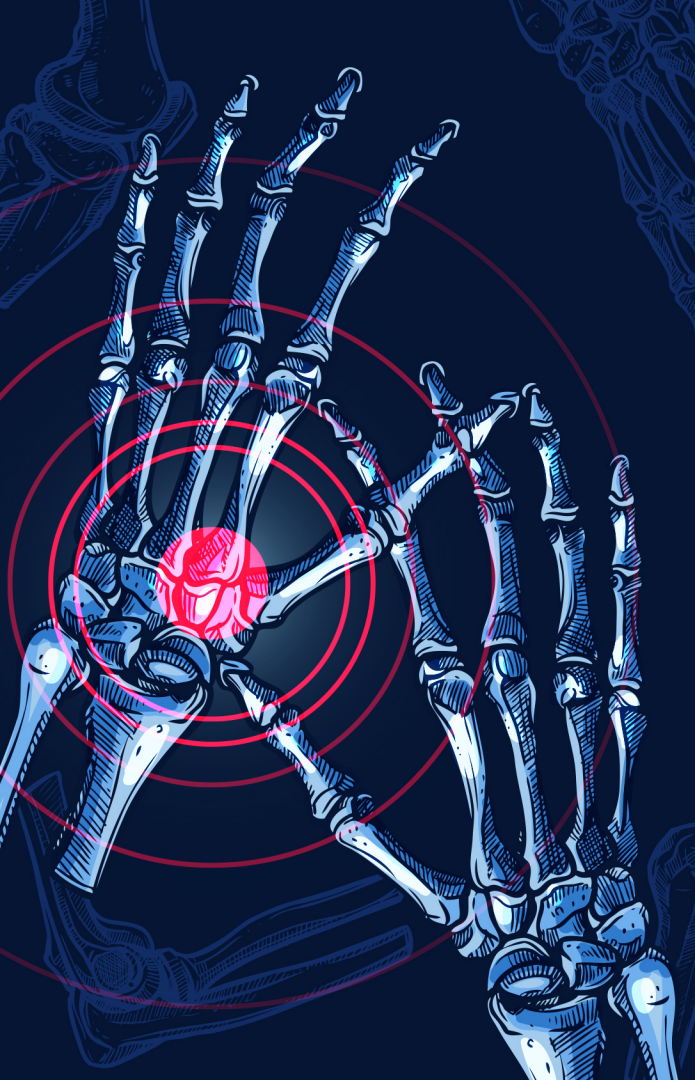


Leonard H. Calabrese, DO

Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Cleveland Clinic Foundation
Cleveland, OH

Real World Translation

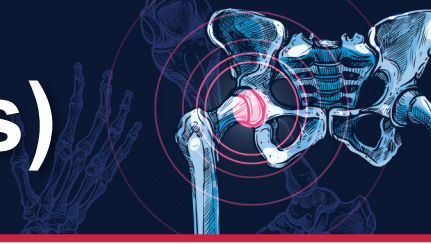
How Does What We Know About Mechanism Of Action Of JAK Inhibitors Impact Clinical Decision Making?



Learning Objective 1

Translate basic clinical immunology to current evidence for the pathophysiology and MOA for current and emerging JAK inhibitors

Protein Tyrosine Kinases (PTKs)

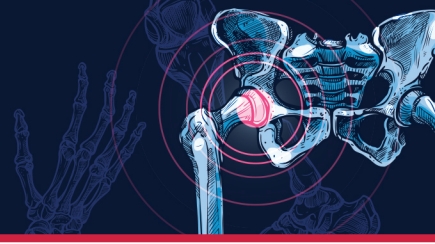


- 90 PTKs identified
  - Receptor (PDGF-R/EGFR)
  - Non-receptor PTKs: 32 cytoplasmic, including JAK and SYK — integral in signal transduction
- Significant experience with PTK inhibitors in oncology
  - Multiple approved therapies

PDGF-R = platelet-derived growth factor receptor; EGFR = epidermal growth factor receptor.

Ghoreschi K, et al. *Immunol Rev.* 2009;228:273-287.

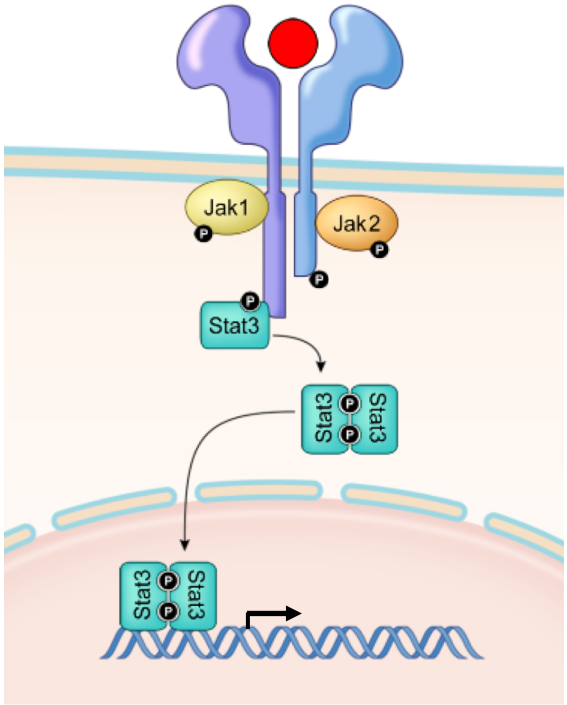
FDA-Approved PTK Inhibitors



Indication	Agents
Oncology	Acalabrutinib, afatinib, alectinib, axitinib, bosutinib, brigatinib, cabozantinib, ceritinib, crizotinib, erlotinib, gefitinib, ibrutinib, imatinib, lapatinib, lenvatinib, midostaurin, neratinib, nilotinib, osimertinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, vandetanib, vemurafenib
Hematology	Ruxolitinib, fostamatinib
Pulmonology	Nintedanib
Inflammatory disease/immunology	Tofacitinib, baricitinib

Roskoski R. http://www.brimr.org/PKI/PKIs.htm. Last updated June 30, 2018.

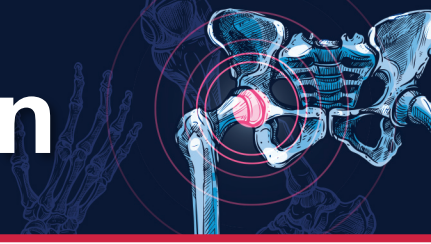
Type I/Type II Cytokine Signaling[1,2]



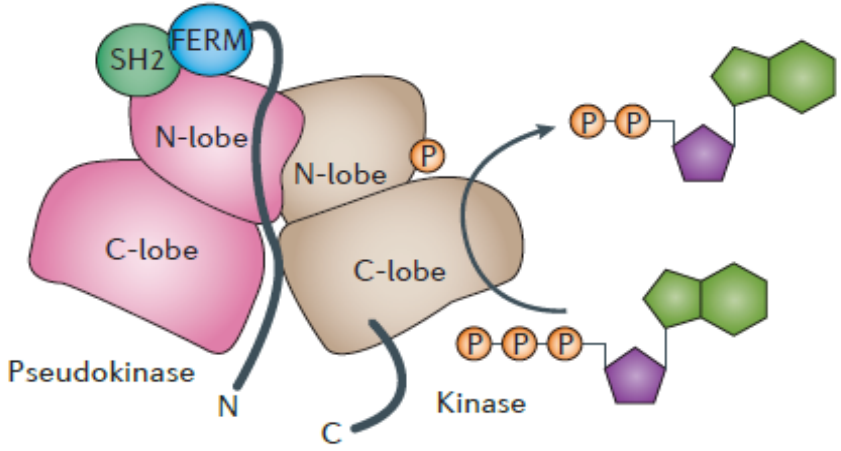
- Rapid membrane to nucleus signaling
  1. Cytokines bind transmembrane receptors that are associated with JAKs
  2. Binding activates JAKs
  3. JAKs phosphorylate receptors
  4. STATs bind receptors
  5. JAKs phosphorylate STATs
  6. STATs translocate to the nucleus
  7. STATs bind DNA and regulate transcription
- Simple and essential pathways

1. FDA Advisory Committee Meeting. Tofacitinib for the Treatment of Rheumatoid Arthritis. NDA 203214 Briefing Document. May 9, 2012.
2. Schwartz DM, et al. *Nat Rev Rheumatol*. 2016;12(1):25-36.

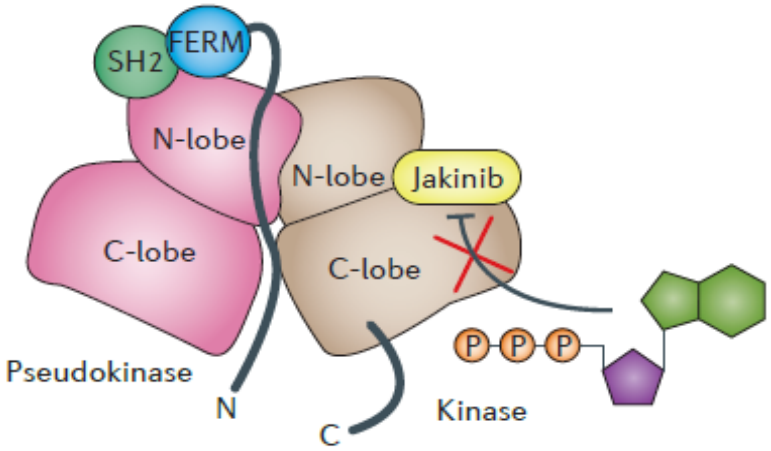
JAK Protein Phosphorylation



JAKs use ATP to phosphorylate substrates

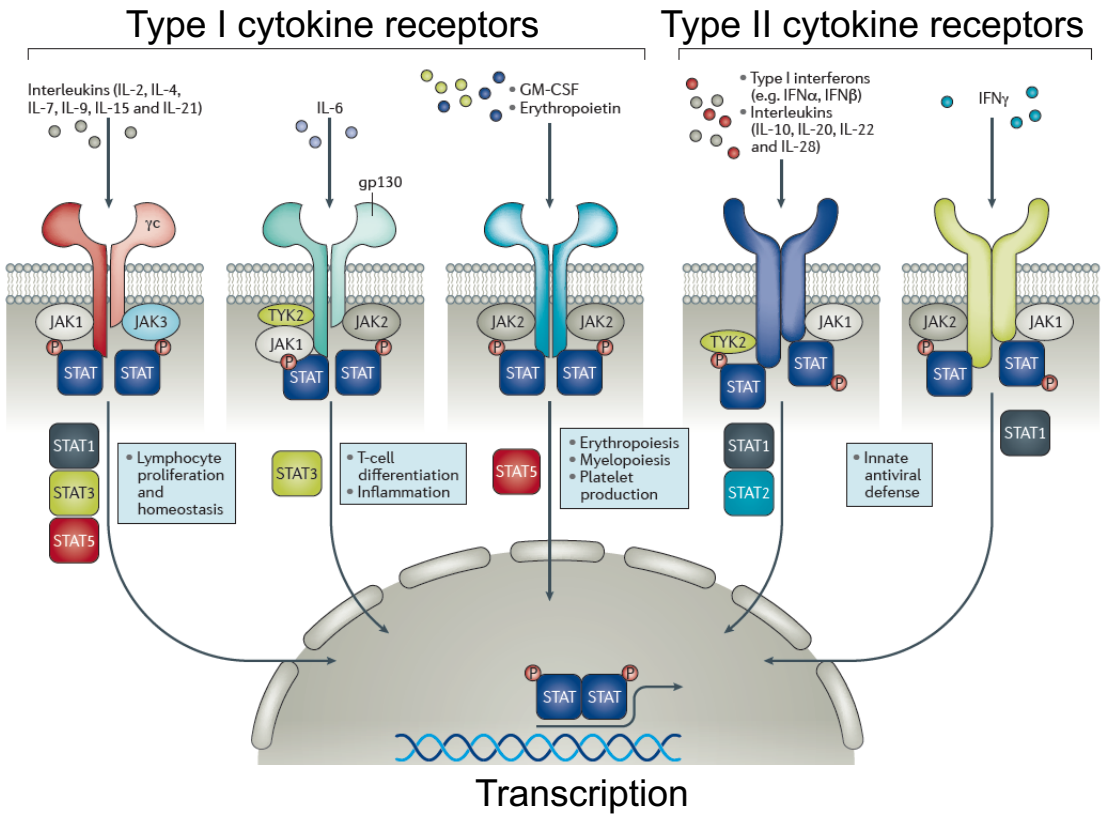


Jakinibs block ATP binding to JAKs



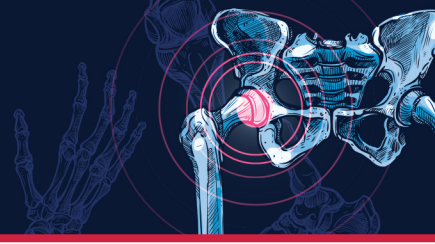
Schwartz DM, et al. *Nat Rev Rheumatol.* 2016;12:25-36.

JAK-STAT Pathways for TypeI/II Cytokine Receptors



Winthrop K. *Nature Rev Rheum*. 2017;13:234-243.

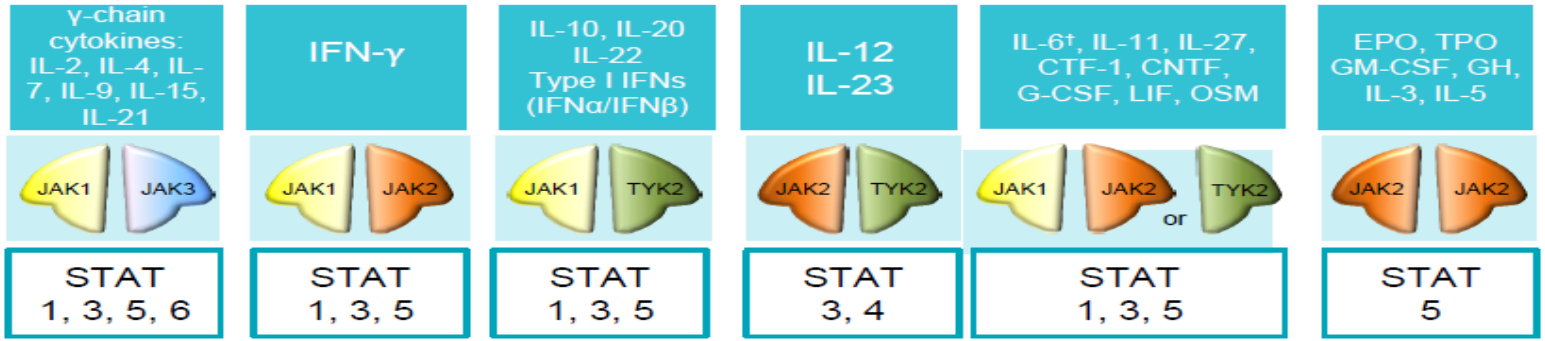
Type I/II Cytokine Signal Transduction Pathways



Cytokines Signal Through Different JAK Pairs

- Four JAK family members: JAK1, JAK2, JAK3, and TYK2[1]
- Seven STAT family members: STAT1, 2, 3, 4, 5a, 5b, and 6 activate transcription[1,2]

Example of Cytokines that Signal through JAK/STAT Combinations



1. O'Sullivan LA, et al. *Mol Immunol*. 2007;44:2497-2506. 2. Ghoreschi K, et al. *Immunol Rev*. 2009;228:273-287.

JAK Inhibitors for RA

Agent	Selectivity	Status in RA	Other Indications[a]
Tofacitinib[1-3]	JAK3/1	Approved	**Approved**: PsA, UC **Investigational:** AS, alopecia areata, JIA, lupus
Baricitinib[2-4]	JAK1/2	Approved	AD, alopecia areata, SLE, diabetic nephropathy
Upadacitinib[2,3]	JAK1	Phase 3	AD, CD, UC, PsA, axSpA
Filgotinib[2,3]	JAK1	Phase 3	CD, UC, PsA, lupus, uveitis, Sjogren syndrome
Peficitinib[3,5]	JAK3/1	Under development in Asia	N/A
Decernotinib[3,6]	JAK3	Discontinued	N/A

[a]Not a comprehensive list. AD = atopic dermatitis; AS = ankylosing spondylitis; CD = Crohn's disease; GCA = giant cell arteritis; UC = ulcerative colitis. 1. PI for tofacitinib. http://labeling.pfizer.com/showlabeling.aspx?id=959 2018. 2. https://www.clinicaltrials.gov/. 3. Winthrop K. *Nat Rev Rheumatol*. 2017;13:234-243. 4. PI for baricitinib. pi.lilly.com/us/olumiant-uspi.pdf. 2018. 5. https://www.thepharmaletter.com/in-brief/brief-after-japan-filing-of-ra-drug-astellas-sets-sights-on-other-asian-countries. 6. https://rheumatology.medicinematters.com/rheumatoid-arthritis-/jak-inhibitors/jak-inhibitors-the-next-generation-of-drugs-for-treating-rheumat/12336972.

Jakinibs: JAK Isotype Specificity

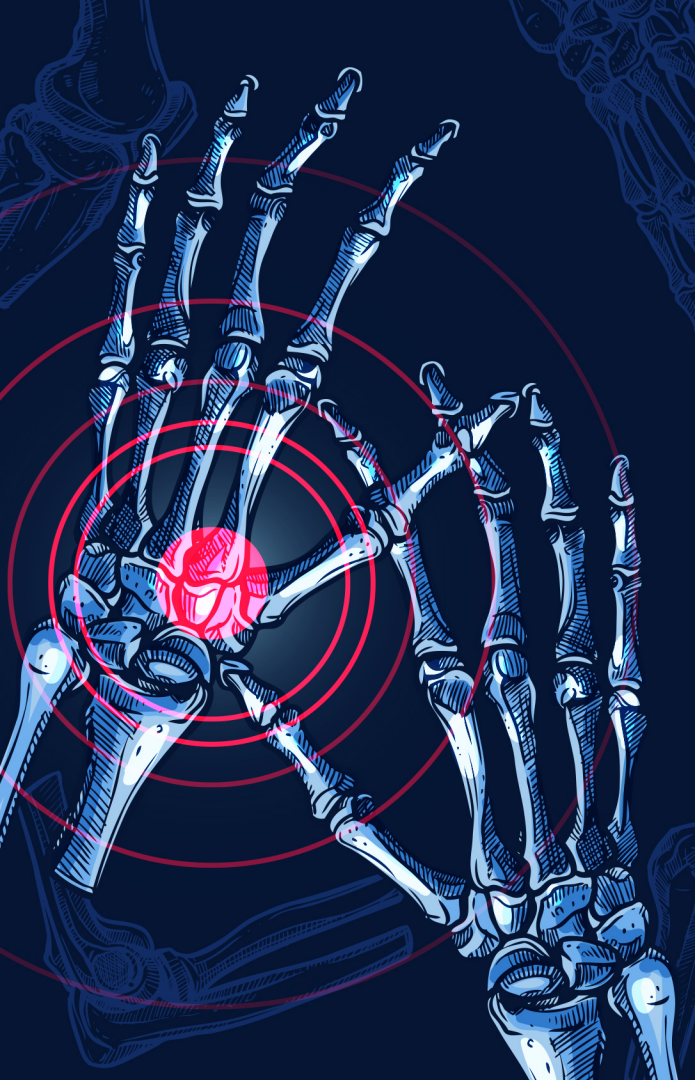
Compound	Enzyme assay IC_{50} (nM)				Human whole blood IC_{50} (nM)					
	JAK1	JAK2	JAK3	TYK2	IL-15 pSTAT 5	IL-6 pSTAT 1	IL-12 pSTAT 4	IFN-alpha pSTAT 3	IL-23 pSTAT 5	CD34+ cells EPO pSTAT 5
Tofacitinib	15.1	77.4	55.0	489	55.8	75.4	409	35.0	229	302
Baricitinib	4.0	6.6	787.0	61.0	259	21.1	149	28.7	81.9	87.8
Filgotinib	363	2,400	>10,000	2,600	2,140	918	13,362	1,500	10,123	13,200
Ruxolitinib	6.4	8.8	487.0	30.1	1,850	298	1.090	194	818	677

EPO = erythropoietin.

Winthrop K. *Nat Rev Rheumatol*. 2017;13:234-243.

Diving Into the Data

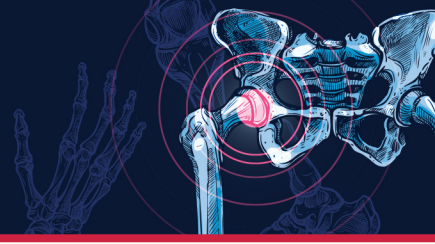
Efficacy and Safety of Current and Emerging Small Molecule JAK Inhibitors



Learning Objective 2

Evaluate clinical trial data for current and emerging small molecule/intracellular signaling targets in the management of patients with RA

Audience Response

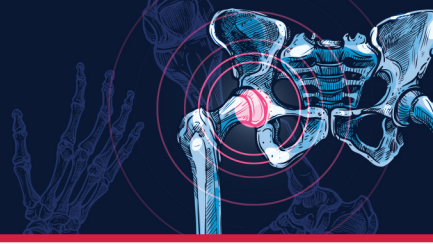


Please rate your level of familiarity with efficacy and safety data for emerging JAK inhibitors in RA.

A. Minimally familiar
B. Somewhat familiar
C. Familiar
D. Very familiar

Tofacitinib: Phase 3 RA Program[1,2]

2211 Patient-Years



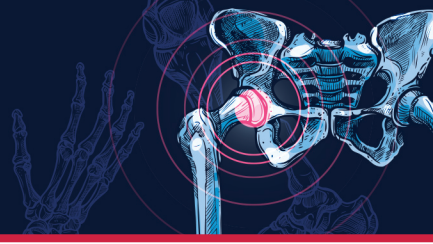
Tofacitinib: Phase 3 Study Designs–DMARD-IRs

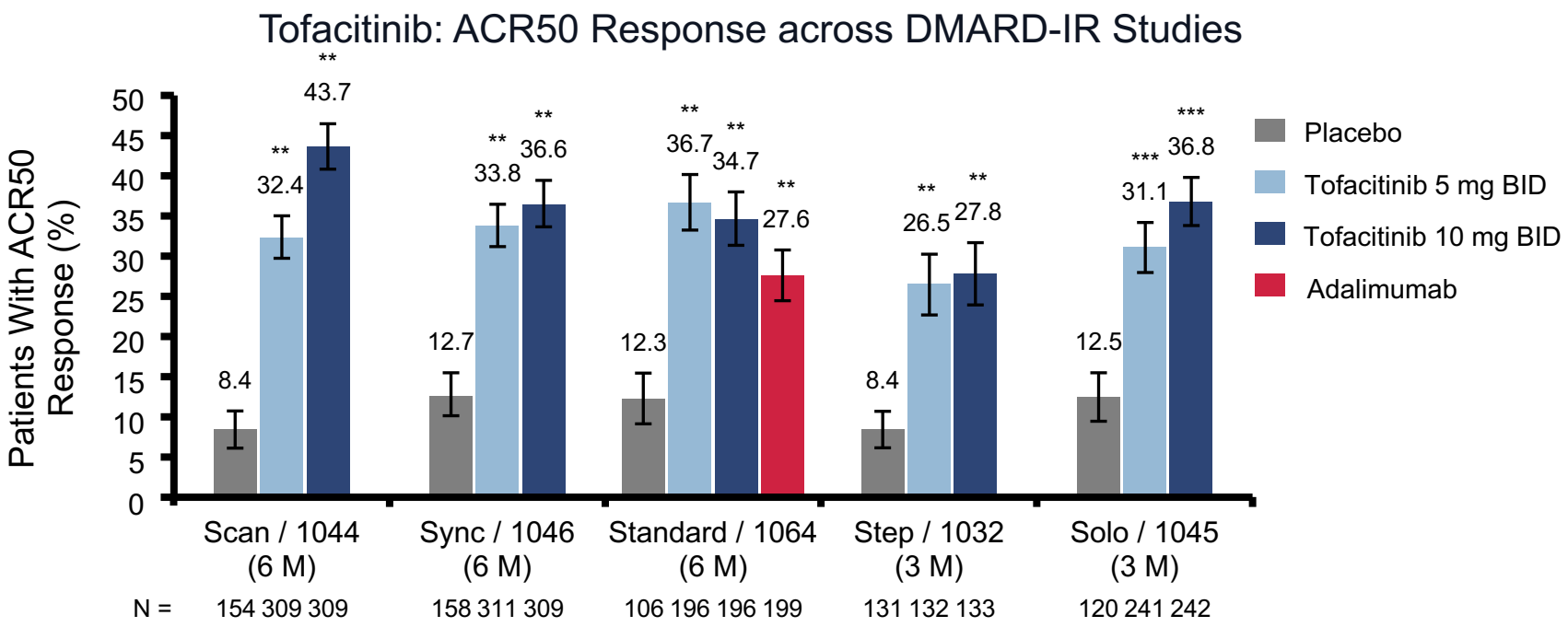
	Duration ≥ 1 Year			Duration of 6 Months	
Study N	**Study 1044 N = 797**	**Study 1046 N = 792**	**Study 1064 N = 717**	**Study 1032 N = 399**	**Study 1045 N = 610**
Population	MTX-IR	DMARD-IR	MTX-IR	TNF-IR	DMARD-IR
Background treatment	MTX	DMARDs	MTX	MTX	None
Distinguishing feature	X-ray	Background DMARDs	Active control (adalimumab)	TNF failures	Monotherapy
	↓	↓	↓	↓	↓
	"SCAN"	**"SYNC"**	**"STANDARD"**	**"STEP"**	**"SOLO"**

1. Lundquist LM, et al. *World J Orthop.* 2014;5:504-511. 2. Bird P, et al. *J Clin Rheumatol.* 2018;1-12.

Tofacitinib: Phase 3 Registration[a]

RCTs and ACR50 Responses

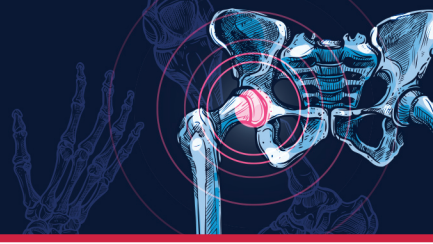


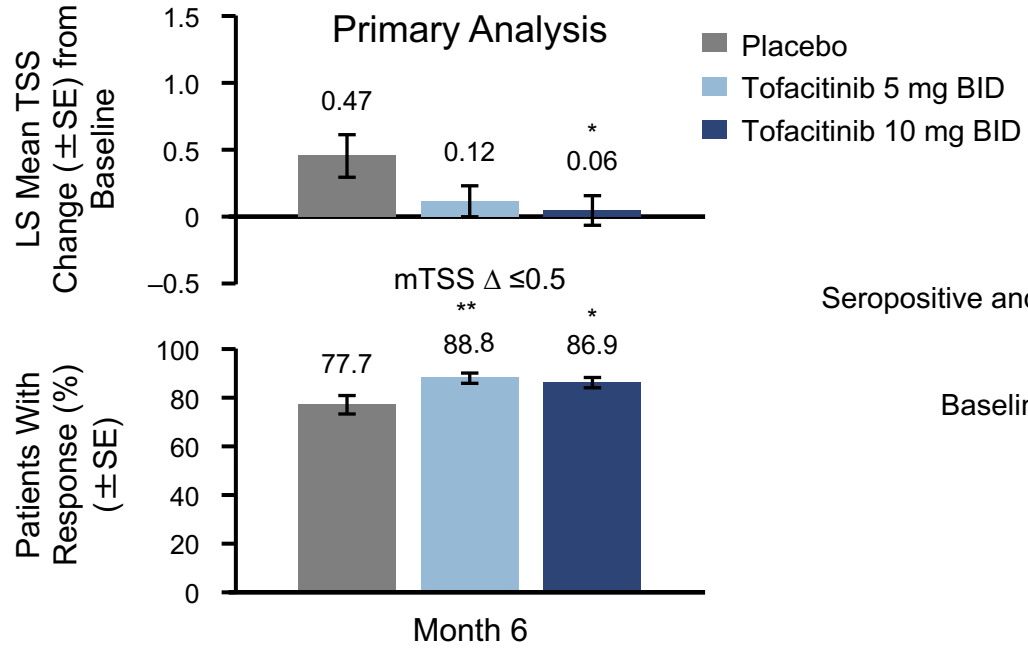


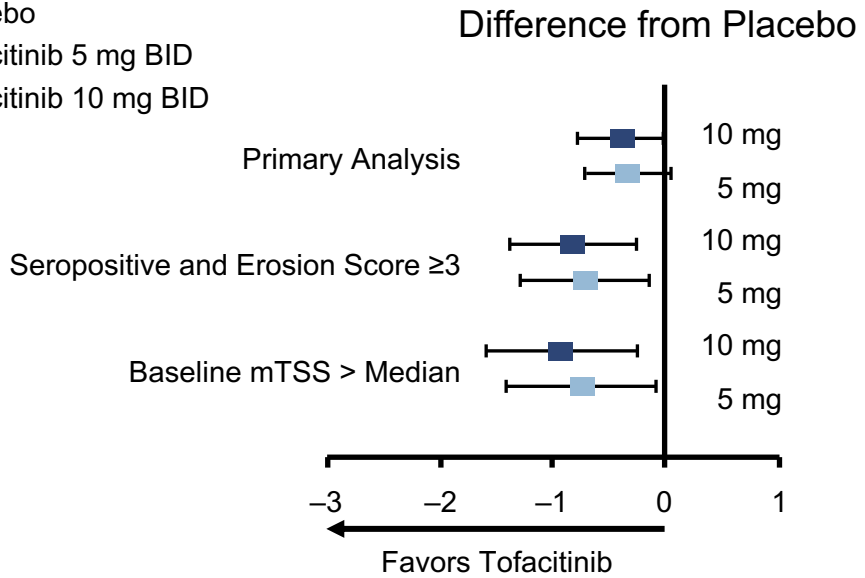
[a]**FDA-approved dose is 5 mg BID or 11 mg XR QD.** ***p* < .001. ****p* < .0001.

FDA Advisory Committee Meeting. Tofacitinib for the Treatment of Rheumatoid Arthritis. NDA 203214 Briefing Document. May 9, 2012.

Tofacitinib: Radiographic Outcomes[a,1,2]





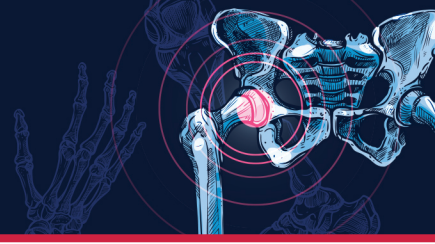


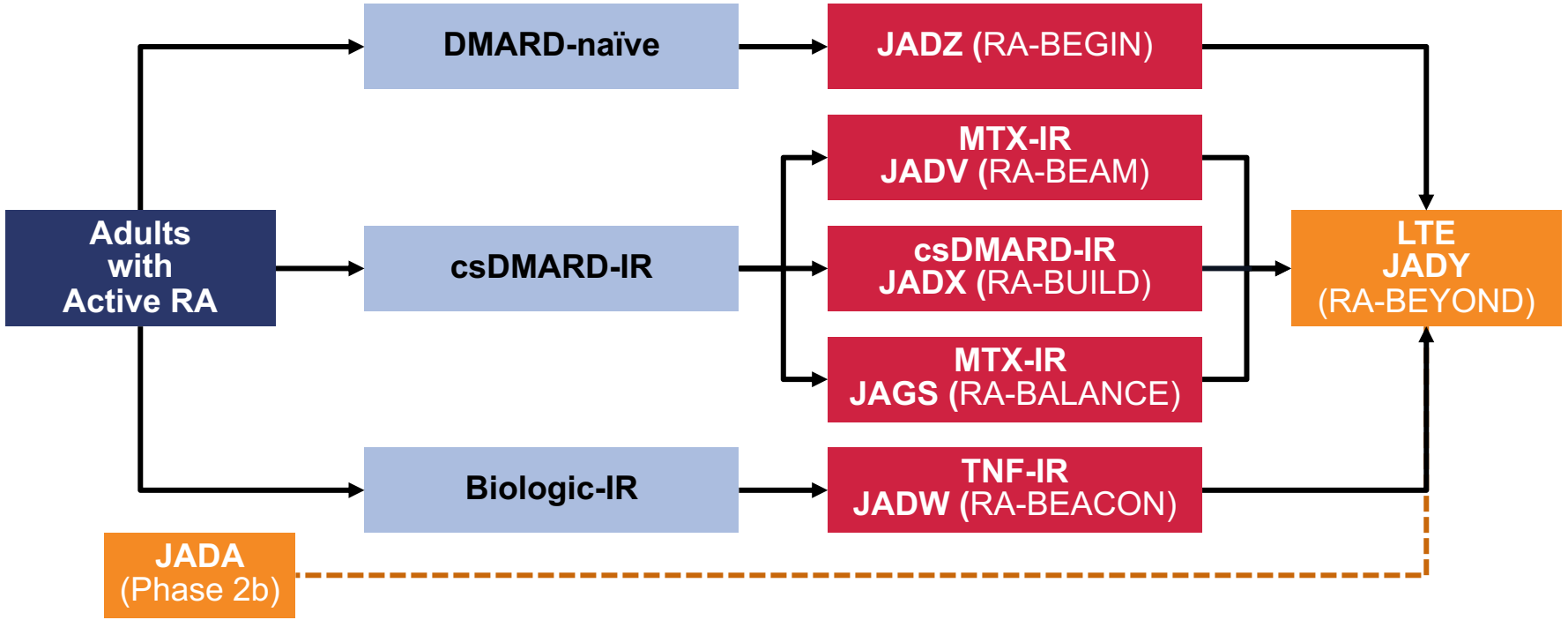
[a]**FDA-approved dose is 5 mg BID or 11 mg XR QD.** *$p \leq .05$. **$p \leq .01$.
SE = standard error; LS = least square; mTSS = modified total Sharp score.

1. van der Heijde D, et al. *Arthritis Rheum.* 2012;65:559-570. 2. Landewé R, et al. *Arthritis Res Ther.* 2016;18:212.

Baricitinib Phase 3 RA Program:[1-4]

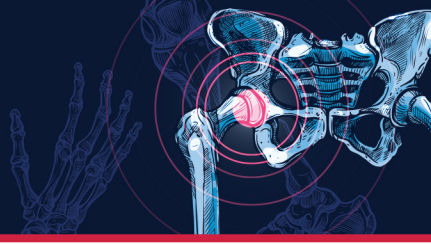
4214 Patient-Years

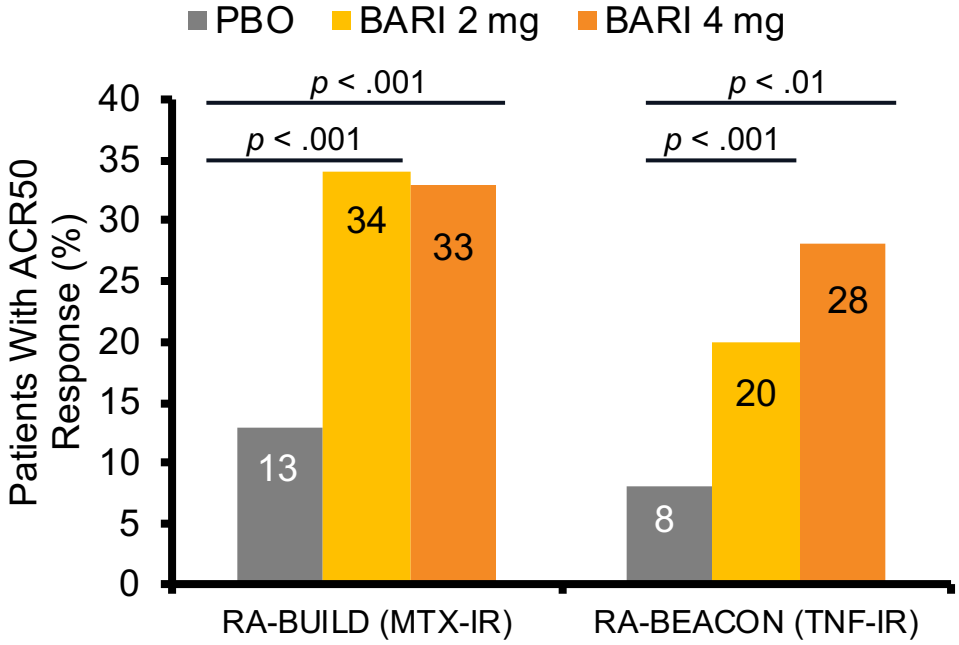


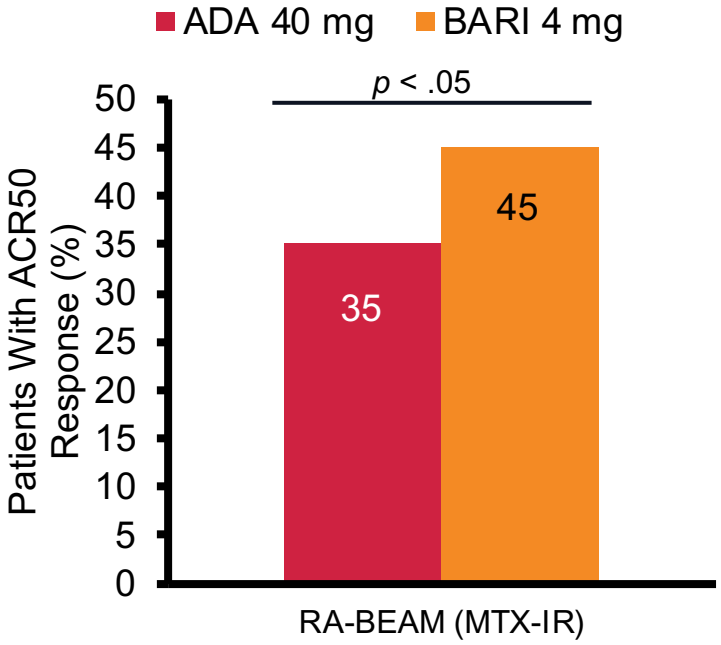


LTE = long-term extension. 1. Kuriya B, et al. *Ther Adv Musculoskeletal Dis.* 2017;9(2):37-44. 2. Dougados M, et al. *Ann Rheum Dis.* 2017;76:88-95. 3. Li Z, et al. Presented at: EULAR; 2018. Abstract No. SAT0218. 3. Kubo S, et al. *Exp Rev Clin Immunol.* 2016;12:911-919. 4. https://clinicaltrials.gov/ct2/show/NCT01885078.

Baricitinib: ACR50 Responses Across DMARD-IR Studies[a,1,2]



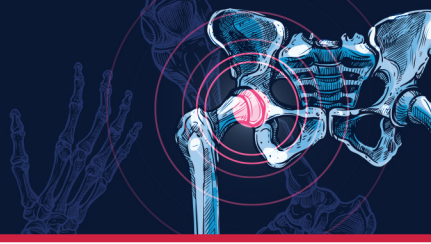




[a]FDA-approved dose is 2 mg QD.

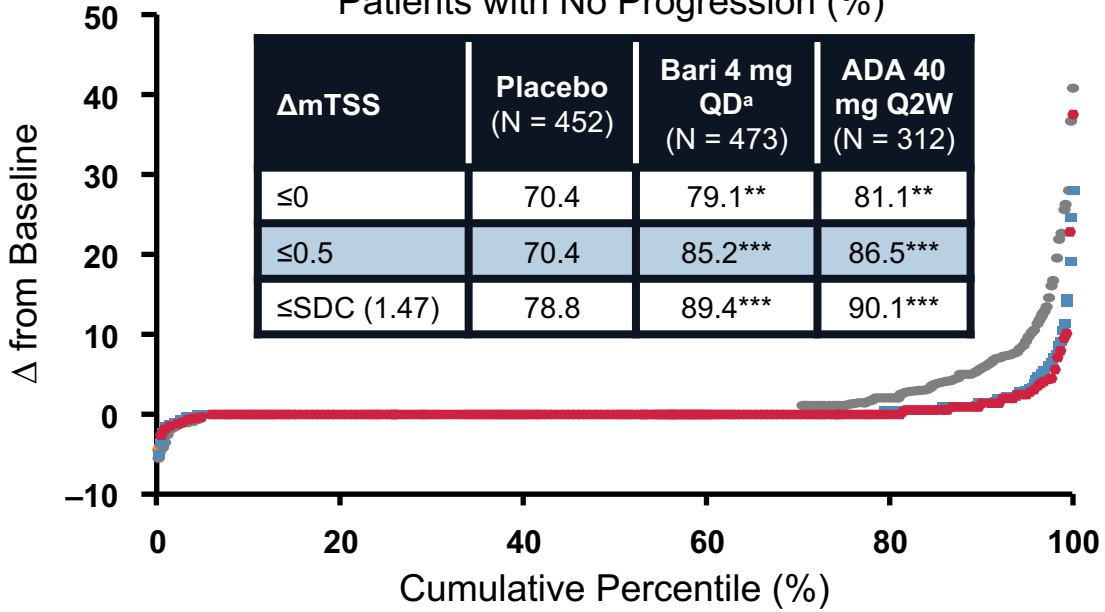
1. Kuriya B, et al. *Ther Adv Musculoskelet Dis.* 2017;9(2):37-44. 2. Taylor PC, et al. *N Engl J Med.* 2017;376:652-662.

Baricitinib: 52-Week Radiographic Change in MTX-IR Patients



Patients with No Progression (%)

ΔmTSS	Placebo (N = 452)	Bari 4 mg QD[a] (N = 473)	ADA 40 mg Q2W (N = 312)
≤0	70.4	79.1**	81.1**
≤0.5	70.4	85.2***	86.5***
≤SDC (1.47)	78.8	89.4***	90.1***



vs. Placebo:
***$p \leq .001$
**$p \leq .01$

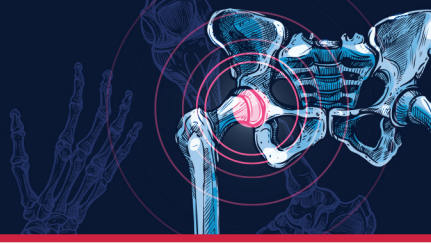
- Placebo
- Baricitinib 4 mg
- Adalimumab 40 mg

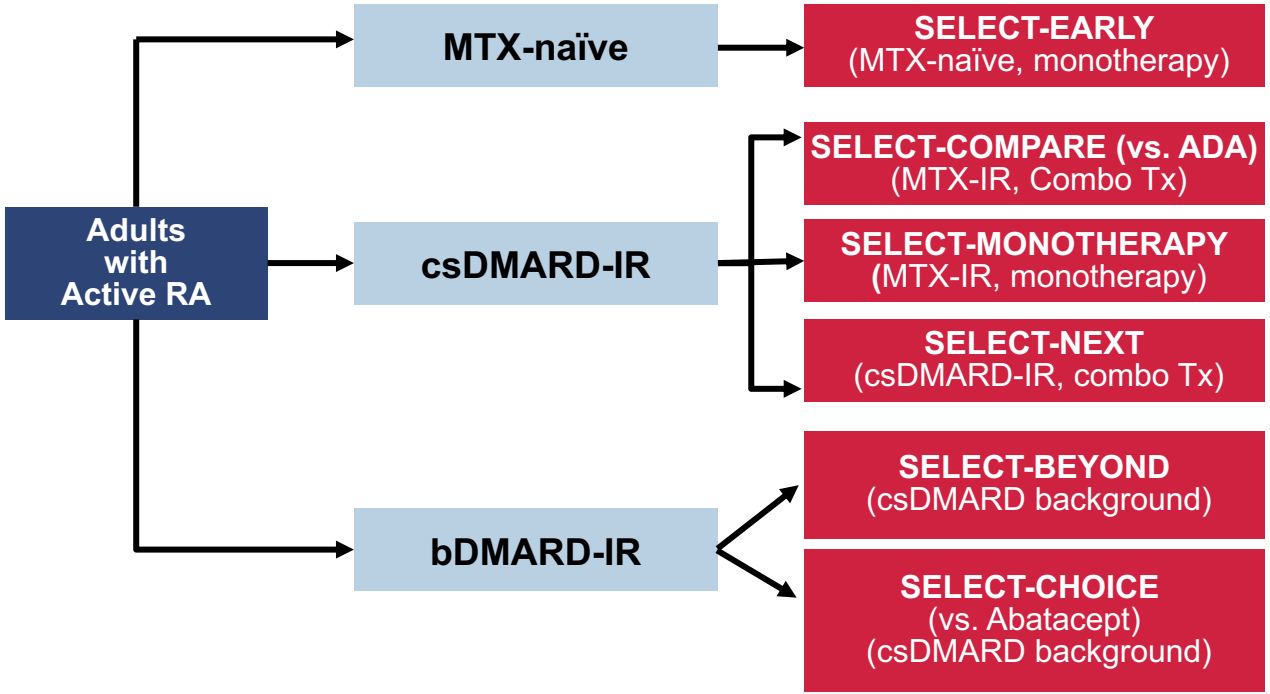
[a]**FDA-approved dose is 2 mg QD**. SDC = smallest detectable change.

Taylor PC, et al. *N Engl J Med.* 2017;376:652-662.

Upadacitinib Phase 3 RA Program[a]

≅5000 Patients[1-6]

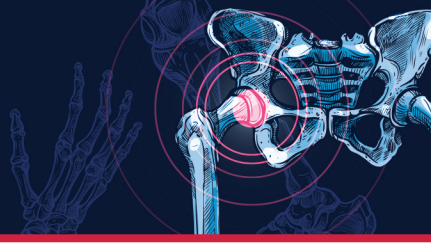


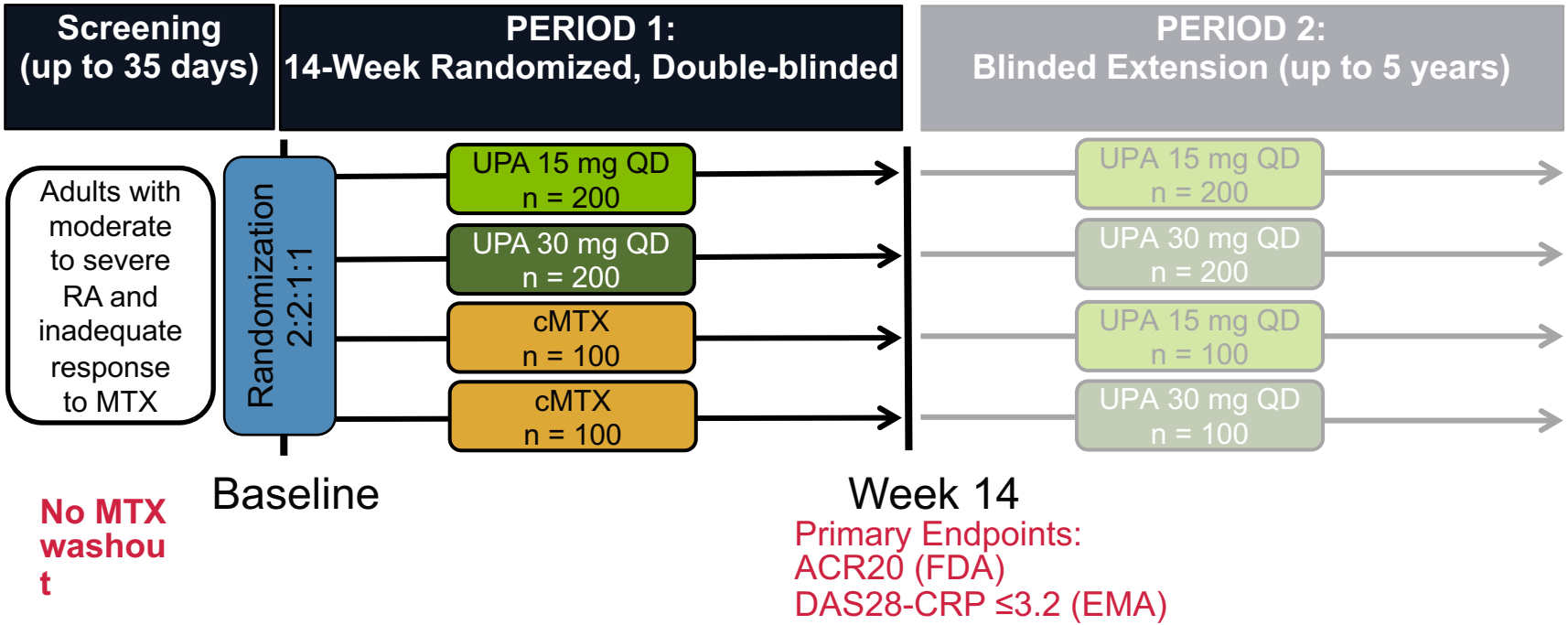


[a]**Investigational agent.** 1. https://clinicaltrials.gov/ct2/show/NCT02706873. 2. https://clinicaltrials.gov/ct2/show/NCT02629159. 3. https://clinicaltrials.gov/ct2/show/NCT027069515. 4. https://clinicaltrials.gov/ct2/show/NCT02675426. 5. https://clinicaltrials.gov/ct2/show/NCT02706847. 6. https://clinicaltrials.gov/ct2/show/NCT03086343.

SELECT-MONOTHERAPY[a]

Study Design



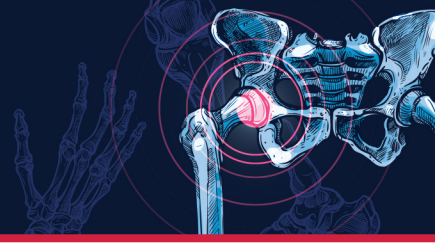


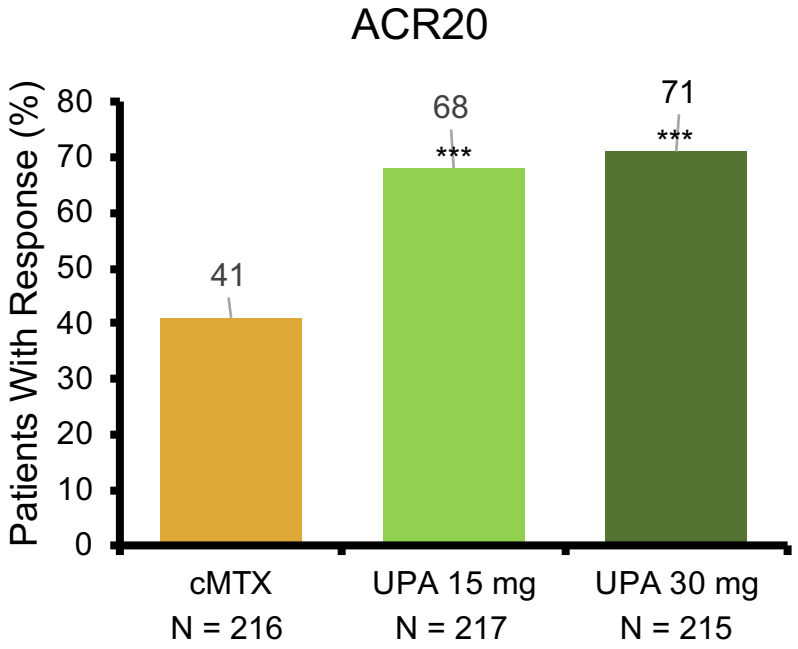
[a]**Investigational agent.**

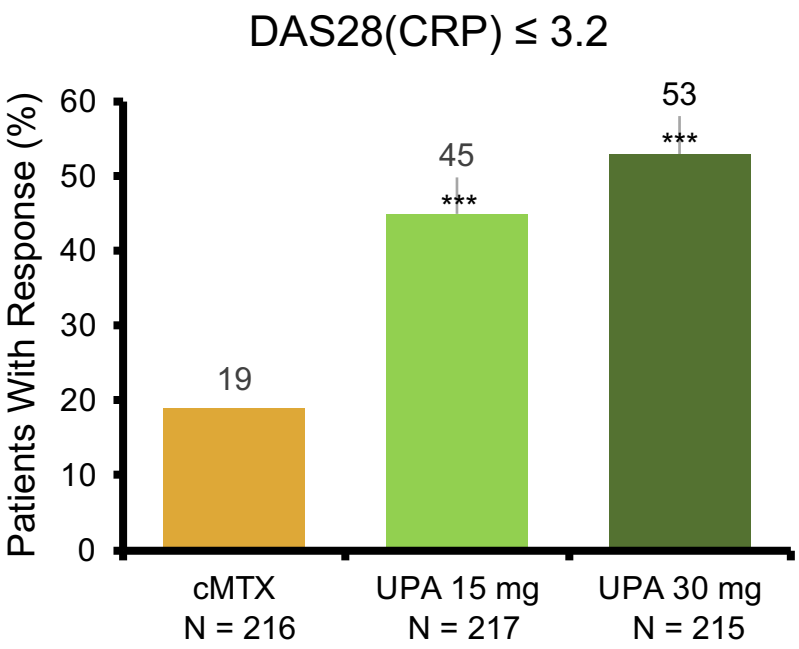
cMTX = continuing MTX as blinded study drug. Smolen J, et al. Presented at: EULAR; 2018. Abstract No. OP0035.

SELECT-MONOTHERAPY[a]

Primary Endpoints at Week 14 (NRI)



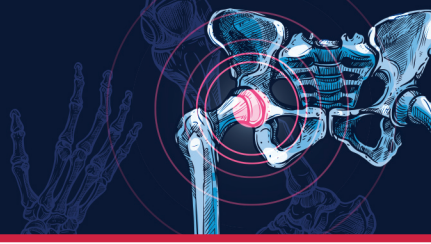


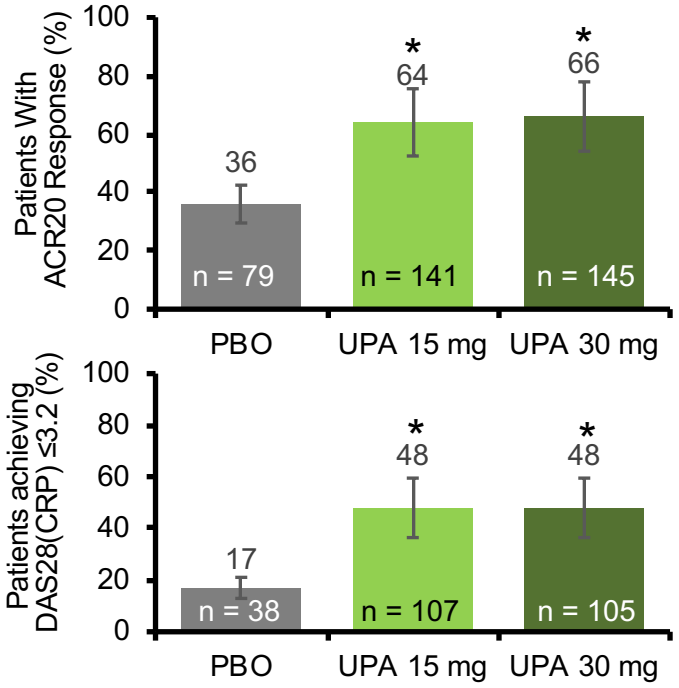


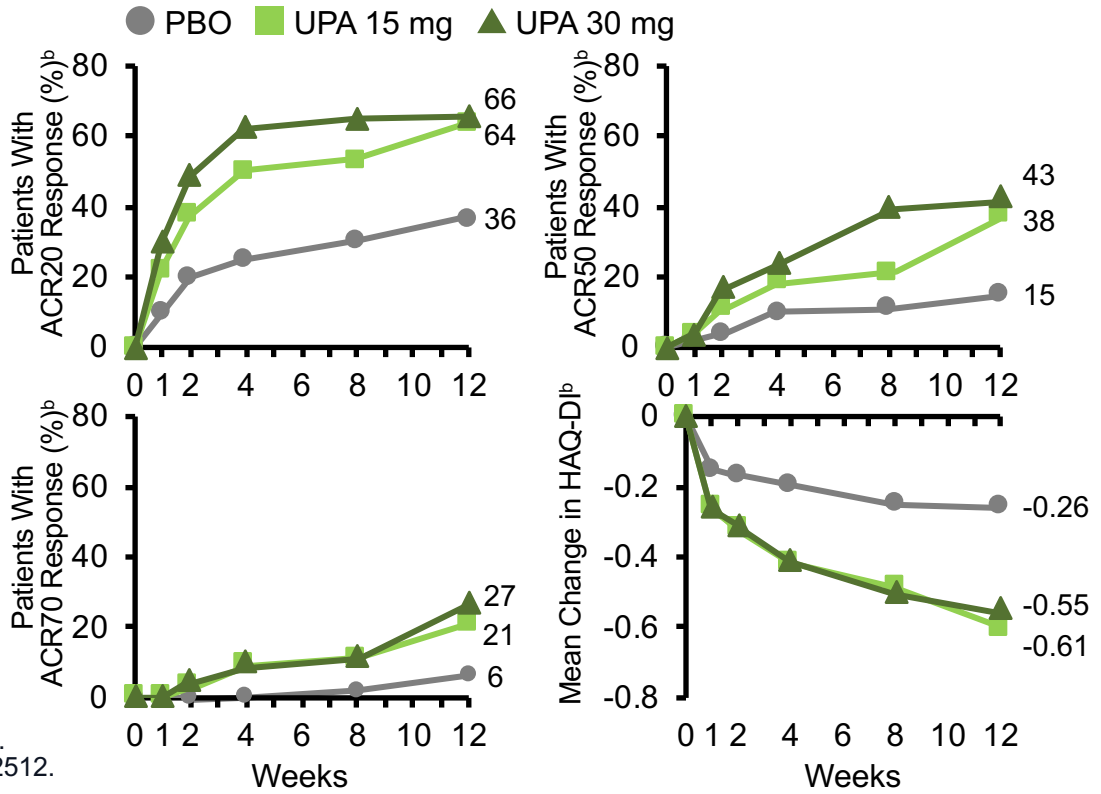
[a]**Investigational agent.** *** $p < .001$ vs. cMTX.

Smolen J, et al. Presented at: EULAR; 2018. Abstract No. OP0035.

Upadacitinib: csDMARD-IR (SELECT-NEXT)[a]

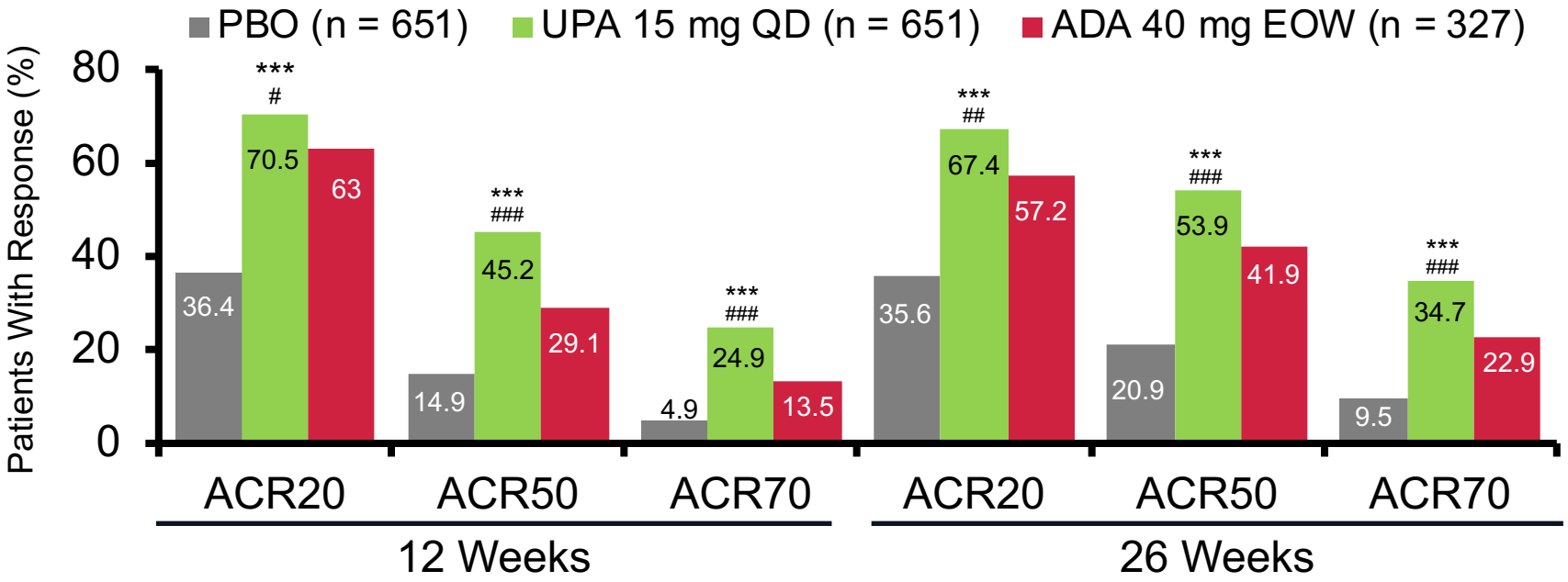






[a]**Investigational agent.** * $p \leq .0001$.
[b]Significant difference at all timepoints for both UPA doses.
Adapted from Burmester G, et al. *Lancet.* 2018;391:2503-2512.

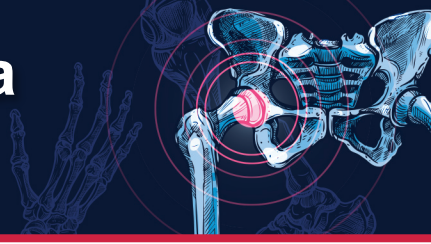
Upadacitinib: SELECT-COMPARE[a]

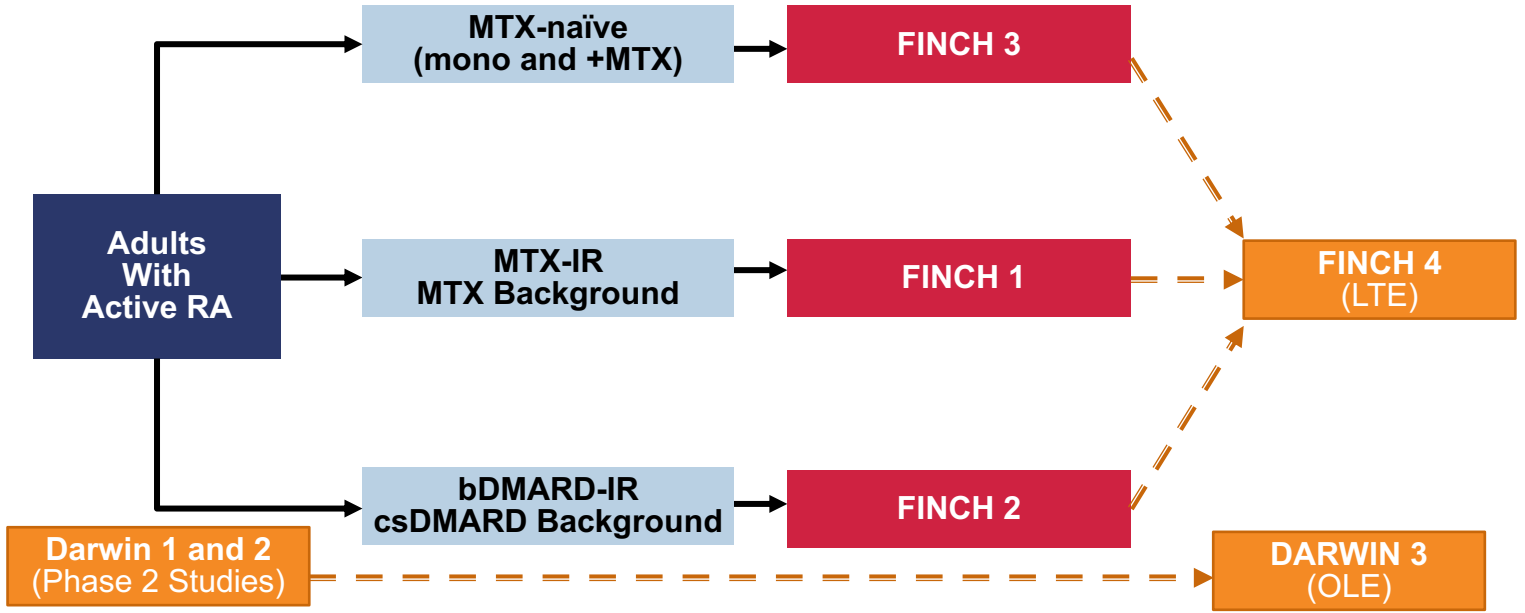


[a]**Investigational agent.** EOW = every other week. ***$p < .001$ for UPA vs. PBO; #$p < .05$, ##$p < .01$, ###$p < .001$ for UPA vs. ADA
Fleischmann R, et al. Presented at: ACR/ARHP; 2018. Abstract No. 890.

Filgotinib RA Phase 3 Program[a]

3460 Patients[1-5]

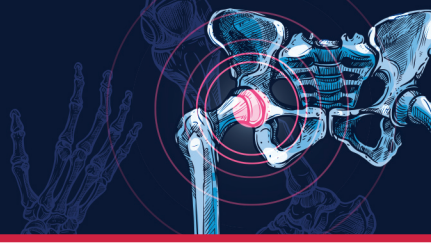


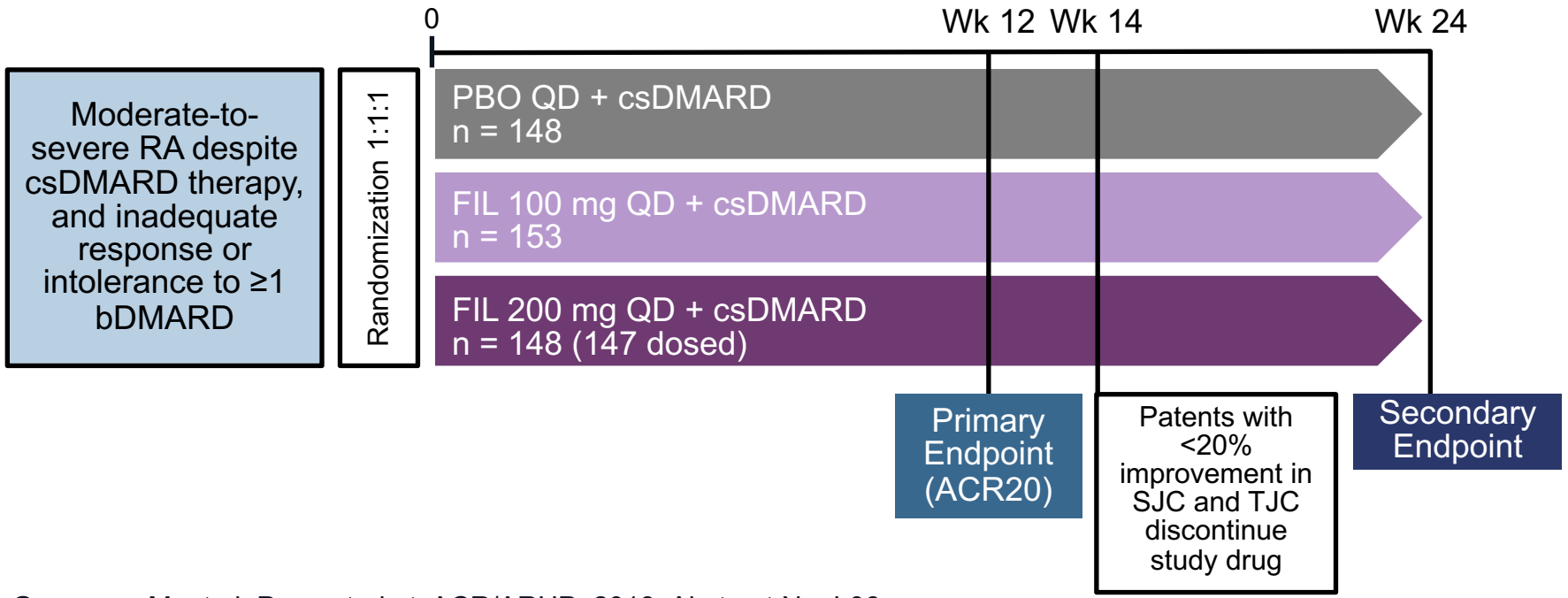


[a]Investigational agent.

1. https://www.clinicaltrials.gov/ct2/show/NCT02889796?term=filgotinib&cond=Rheumatoid+Arthritis&rank=5.
2. https://www.clinicaltrials.gov/ct2/show/NCT02873936?term=filgotinib&cond=Rheumatoid+Arthritis&rank=3.
3. https://www.clinicaltrials.gov/ct2/show/NCT02886728?term=filgotinib&cond=Rheumatoid+Arthritis&rank=4.
4. https://www.clinicaltrials.gov/ct2/show/NCT03025308?term=filgotinib&cond=Rheumatoid+Arthritis&rank=2.
5. Westhovens R, et al. *EULAR*; 2018. Abstract No. SAT0200.

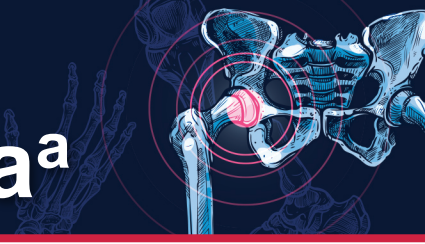
FINCH 2: Study Design

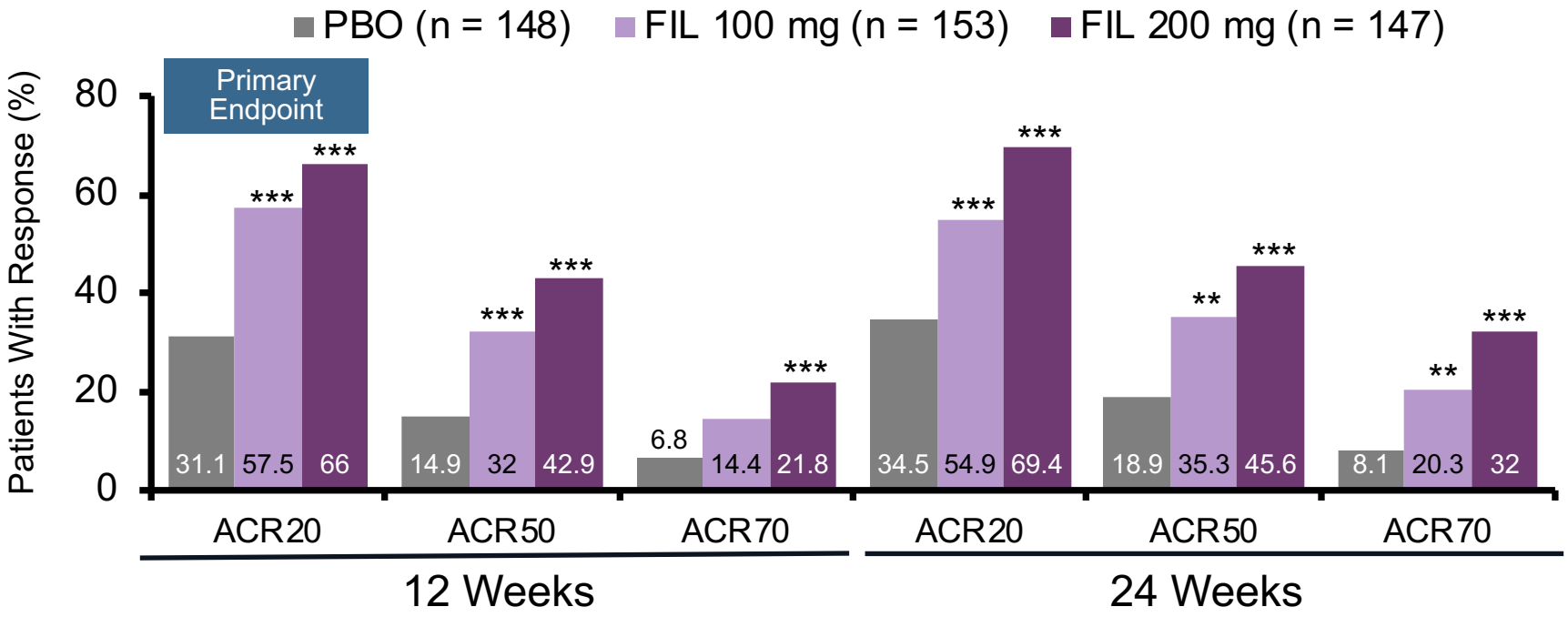




Genovese M, et al. Presented at: ACR/ARHP; 2018. Abstract No. L06.

Filgotinib: FINCH 2
12-Week and 24-Week ACR Data[a]

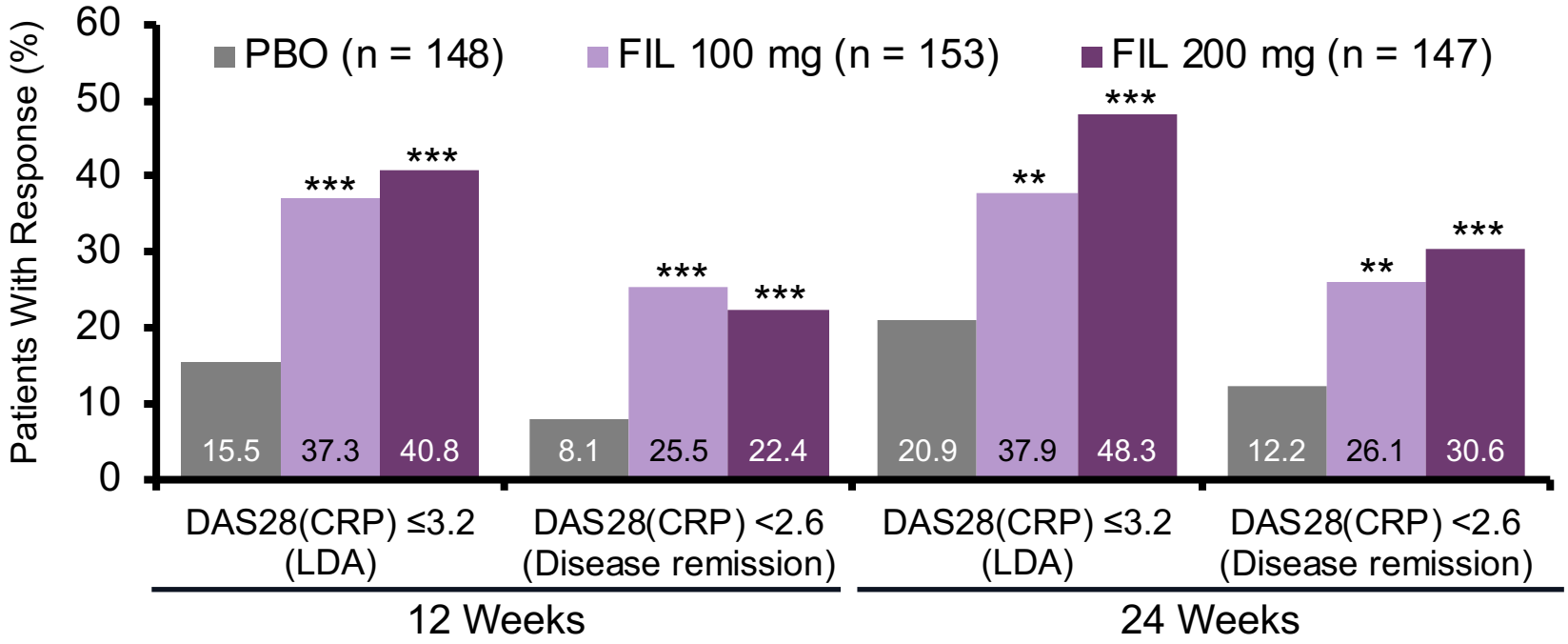




[a]**Investigational agent.** $^{**}p < .01$, $^{***}p < .001$ vs. placebo.

Genovese M, et al. Presented at: ACR/ARHP; 2018. Abstract No. L06.

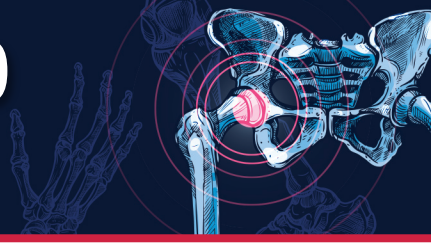
Filgotinib: FINCH 2
12-Week and 24-Week DAS Scores[a]

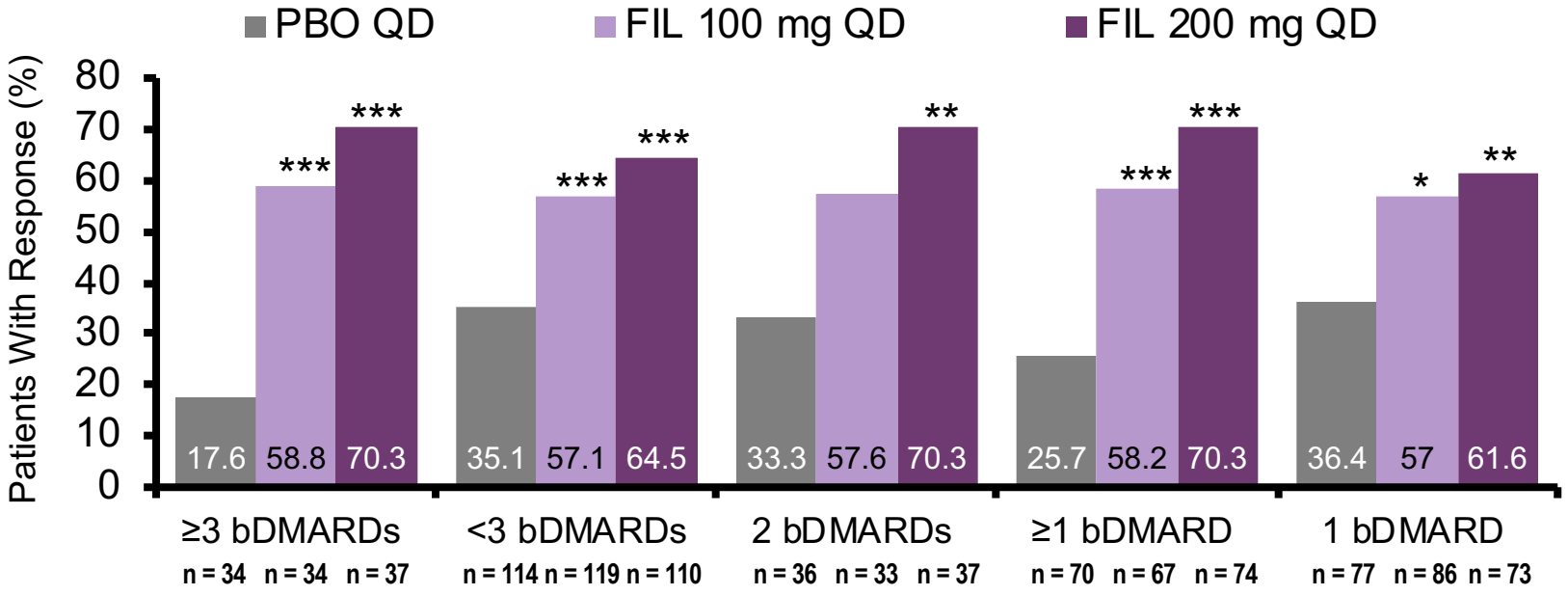


[a]**Investigational agent.** ***p* < .01. ****p* < .001 vs. placebo.

Genovese M, et al. Presented at: ACR/ARHP; 2018. Abstract No. L06.

Filgotinib: FINCH 2 12-Week ACR20 Responses by Prior bDMARD Use[a]

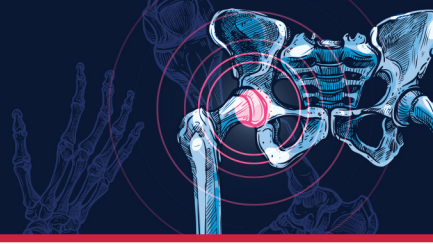




[a]**Investigational agent.** *$p < .05$. **$p < .01$. ***$p < .001$ vs. placebo.

Genovese M, et al. Presented at: ACR/ARHP; 2018. Abstract No. L06.

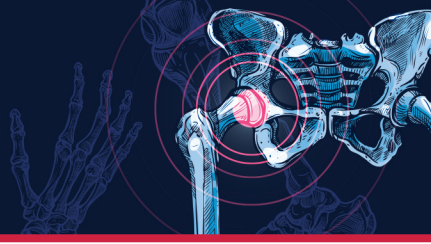
Jakinib Safety

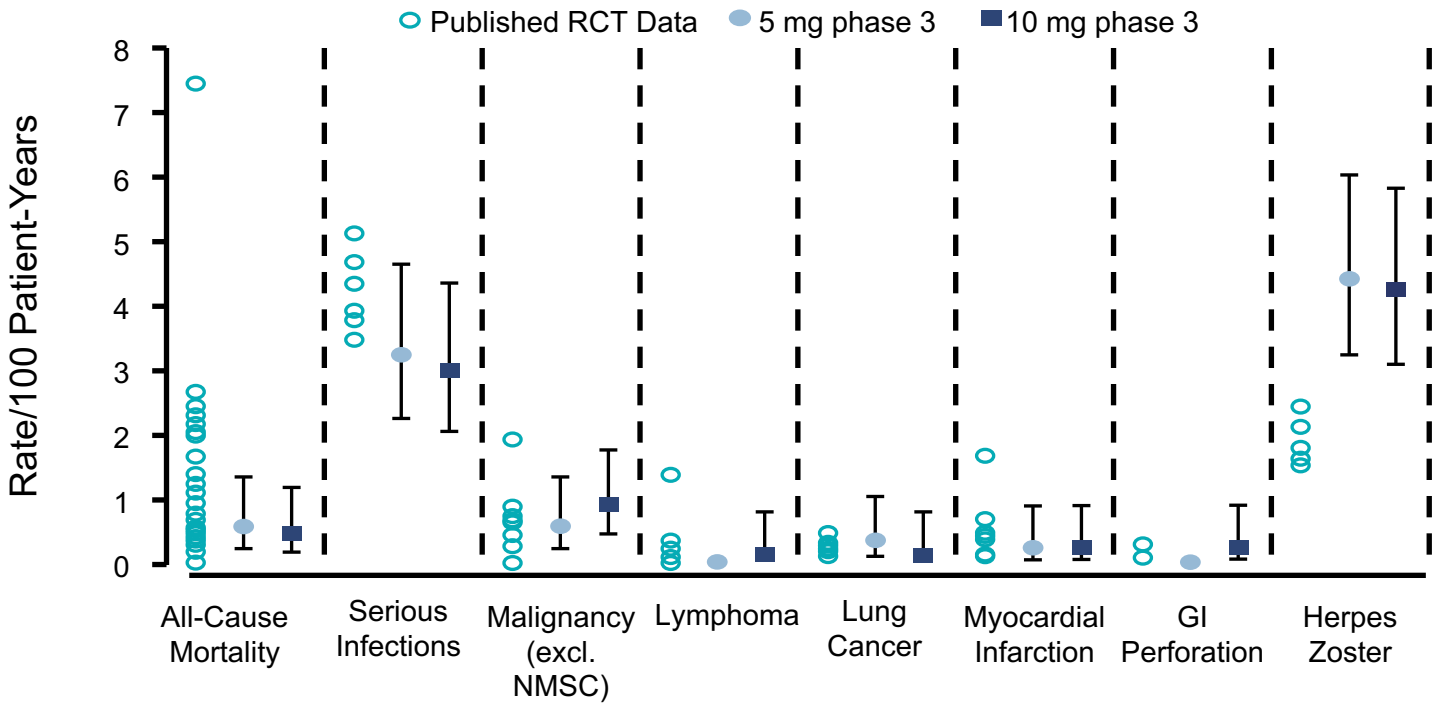


- Serious infectious episodes
- Viral/opportunistic infections: herpes zoster
- Tuberculosis
- Lipids and cardiovascular risk
- Hepatic safety
- GI perforations
- Increased risk of thromboembolic disease?

Winthrop K. *Nature Rev Rheum*. 2017.13:234-243.

Safety Profile of Tofacitinib in Phase 3 Studies vs. Clinical Trial Data of TNF Inhibitors and Other Biologic DMARDs[a]

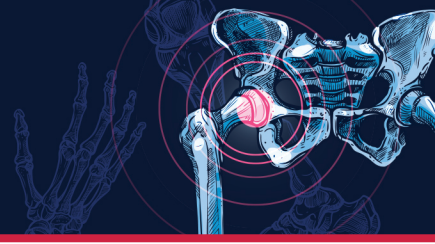




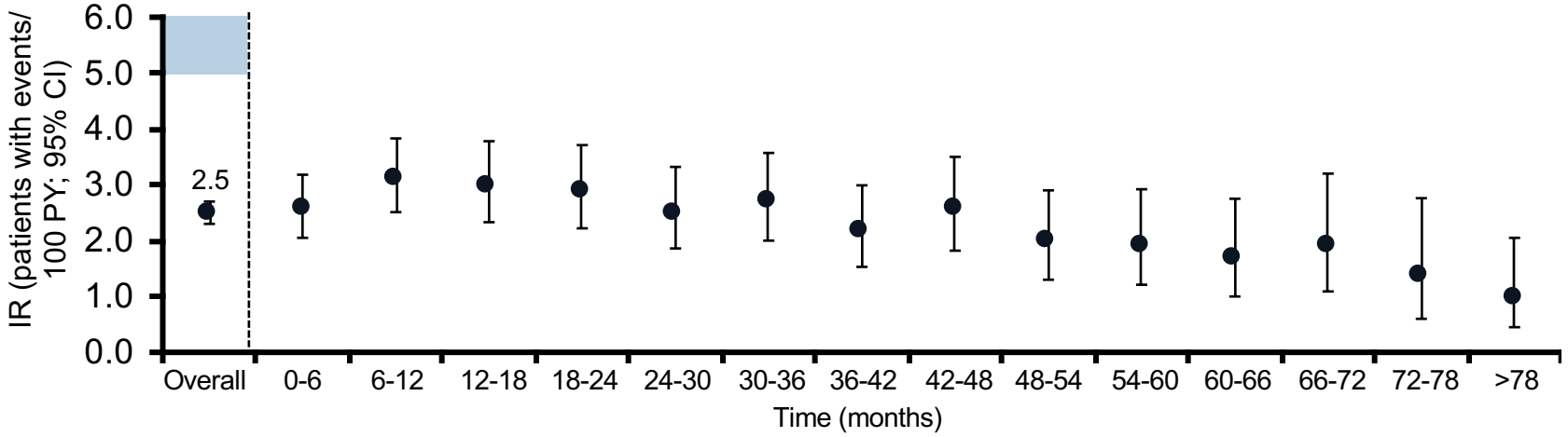
[a]**FDA-approved dose is 5 mg BID or 11 mg XR QD.** NMSC = non-melanoma skin cancer.

FDA Advisory Committee Meeting. Tofacitinib for the Treatment of Rheumatoid Arthritis. NDA 203214 Briefing Document. May 9, 2012.

IRs of SIEs Remained Stable Over Time With Tofacitinib[a]



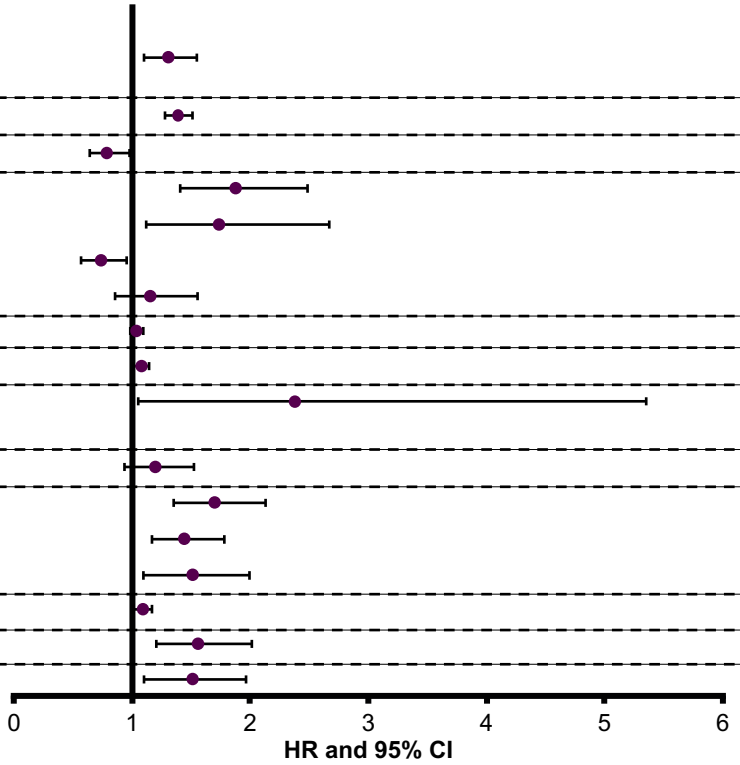
IR, patients with events/ 100 PY (95% CI)	Overall	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66	66-72	72-78	>78
	2.5 (2.3, 2.7)	2.6 (2.1, 3.2)	3.1 (2.5, 3.8)	3.0 (2.3, 3.8)	2.9 (2.2, 3.7)	2.5 (1.9, 3.3)	2.7 (2.0, 3.6)	2.2 (1.5, 3.0)	2.6 (1.8, 3.5)	2.0 (1.3, 2.9)	1.9 (1.2, 2.9)	1.7 (1.0, 2.8)	1.9 (1.1, 3.2)	1.4 (0.6, 2.8)	1.0 (0.5, 2.1)



	Overall	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66	66-72	72-78	>78
Patients, n	7061	7061	6218	5565	4516	4177	3808	3574	3330	2865	2481	2197	1811	1354	940
Patients with SIE*, n	576	84	90	70	62	49	49	37	39	26	22	17	15	8	8
Total PY exposure for event	23,194.0	3274.3	2887.6	2341.9	2140.8	1948.7	1816.3	1705.7	1524.9	1311.5	1142	988.1	772	571.2	769.2

[a]**FDA-approved dose is 5 mg BID or 11 mg XR QD.** *Requiring hospitalization, or parenteral antimicrobial therapy use, or meeting other SAE criteria. Cohen S, et al. Presented at: ACR/ARHP; 2018. Abstract No. 963.

Potential Risk Factors for SIEs



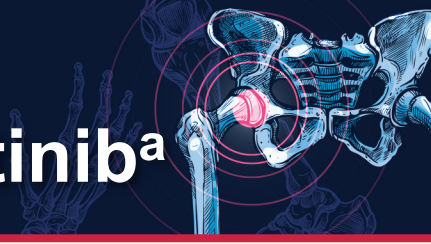
Factors	Comparisons	HR	95% CI	Overall p value
Time-varying tofacitinib dose, mg BID*	Unit=5†	**1.3**	**1.1, 1.5**	**0.0021**
Baseline age, years	Unit=10†	**1.4**	**1.3, 1.5**	**<0.0001**
Gender	Female vs Male	**0.8**	**0.6, 1.0**	**0.0309**
Geographic region	Asia vs US/Canada	**1.9**	**1.4, 2.5**	**<0.0001**
	Aus/NZ/ROW vs US/Canada	**1.7**	**1.1, 2.7**	
	Europe vs US/Canada	**0.7**	**0.6, 1.0**	
	Latin America vs US/Canada	1.2	0.9, 1.6	
RA disease duration, years	Unit=5†	1.0	1.0, 1.1	0.1149
Baseline HAQ-DI score	Unit=0.5†	**1.1**	**1.0, 1.1**	**0.0240**
Prior confirmed post-baseline lymphopenia <500 cells/uL‡	Unit=1†	**2.4**	**1.1, 5.4**	**0.0365**
Line of therapy	3rd line vs 2nd line	1.2	0.9, 1.5	0.1420
Baseline GC use	[≥7.5 mg/day] vs [0 mg/day]	**1.7**	**1.4, 2.1**	**<0.0001**
	[0-<7.5 mg/day] vs [0 mg/day]	**1.4**	**1.2, 1.8**	
	Unknown Dose vs [0 mg/day]	**1.5**	**1.1, 2.0**	
Baseline BMI, kg/m²	Unit=5†	**1.1**	**1.0, 1.2**	**0.0185**
Baseline diabetes	Yes vs No	**1.6**	**1.2, 2.0**	**0.0008**
Baseline COPD§	Yes vs No	**1.5**	**1.1, 2.0**	**0.0082**

All-level comparison of a factor is boxed if significant; and 2-level comparison is bolded if significant.

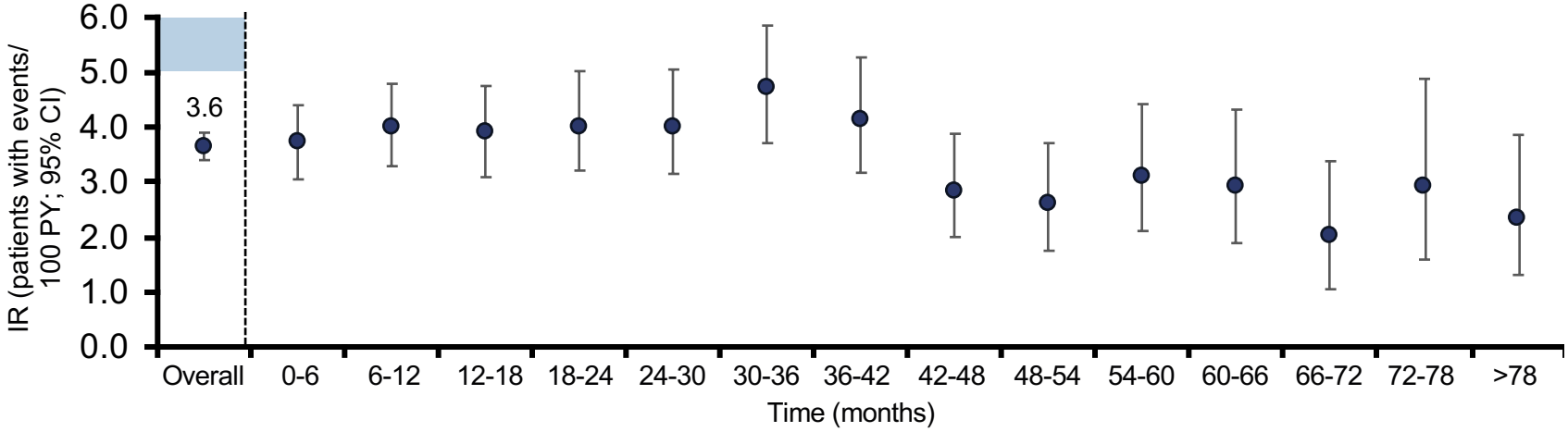
*Determined by the time of first onset of event. If the first onset of event occurred during the index study, the randomized dose in the index study was used. If the first onset of event occurred during the LTE study, average tofacitinib dose (5 or 10 mg BID) was used. †In Unit=x, 'x' is the change in the continuous variable corresponding to which the change in hazards is observed. ‡Based on exposure period before lymphopenia <500 cells/μL vs exposure period after lymphopenia <500 cells/μL. §Medical history and/or complication of COPD

Aus, Australia; HR, hazard ratio; NZ, New Zealand; ROW, rest of world

IRs of HZ (Serious and Non-serious) Remained Stable Over Time With Tofacitinib[a]



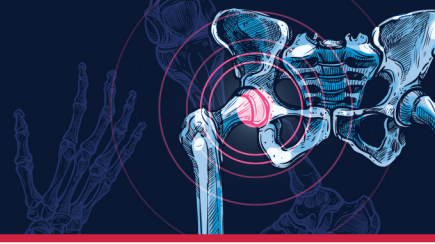
IR, patients with events/ 100 PY (95% CI)	Overall	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66	66-72	72-78	>78
	3.6 (3.4, 3.9)	3.7 (3.1, 4.4)	4.0 (3.3, 4.8)	3.9 (3.1, 4.8)	4.0 (3.2, 5.0)	4.0 (3.2, 5.1)	4.7 (3.7, 5.9)	4.1 (3.2, 5.3)	2.8 (2.0, 3.9)	2.6 (1.8, 3.7)	3.1 (2.1, 4.4)	2.9 (1.9, 4.3)	2.0 (1.1, 3.4)	2.9 (1.6, 4.9)	2.3 (1.3, 3.9)



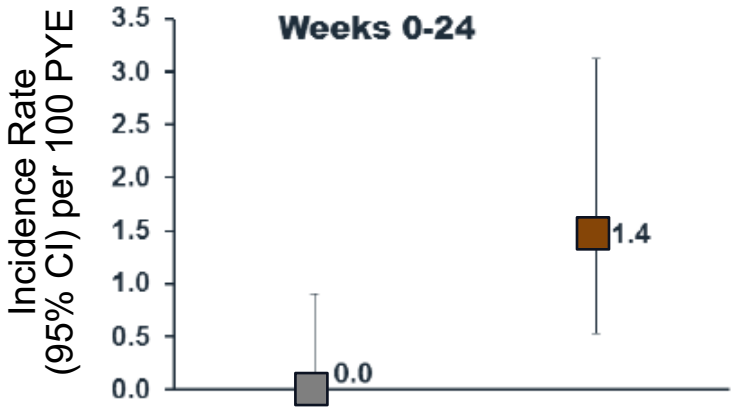
	Overall	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66	66-72	72-78	>78
Patients, n	7061	7061	6150	5417	4318	3931	3520	3234	2950	2525	2171	1906	1552	1147	793
Patients with HZ, n	782	120	113	87	82	73	78	63	38	30	31	25	13	14	15
Total PY exposure for event	21,519.0	3260.1	2833.9	2258.7	2028.6	1816.7	1662.7	1528.6	1345.7	1153.7	996.1	854.2	657.6	481.6	640.7

[a]**FDA-approved dose is 5 mg BID or 11 mg XR QD.** Cohen S, et al. Presented at: ACR/ARHP; 2018. Abstract No. 963.

Baricitinib Placebo-Controlled RA RCTs
Venous Thromboembolic Events (VTE)



Imbalance in Venous Thromboembolic Events, Placebo-Controlled Period, Weeks 0-24



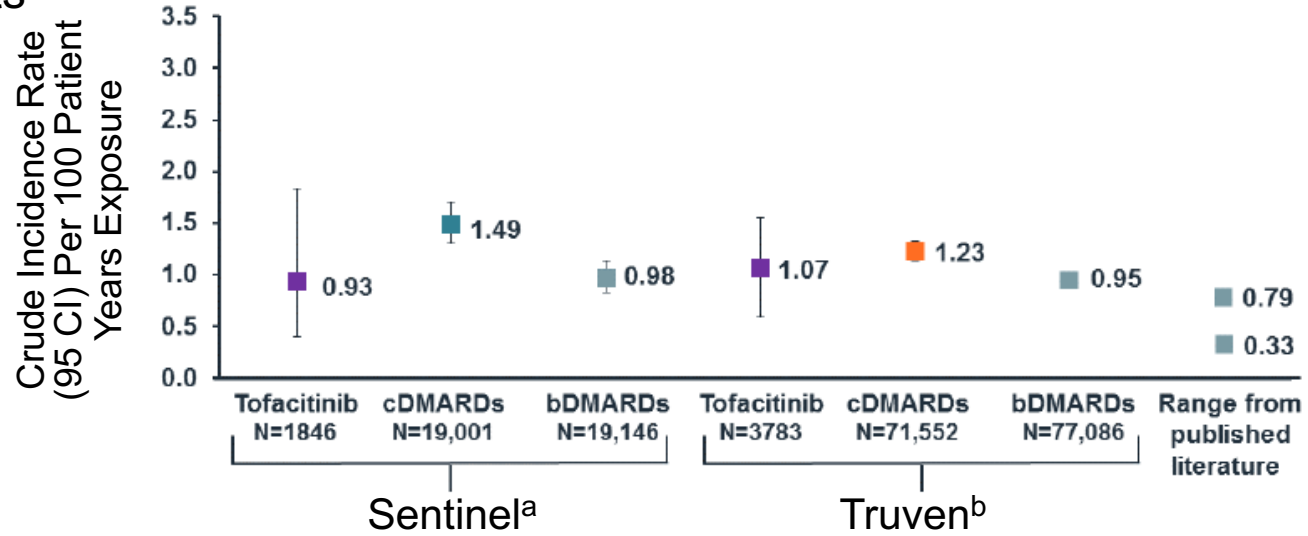
Treatment	PBO	Bari 4 mg[a]
Subset	4 mg PC Dataset	
All Patients	1070	997
With Events	0	6
Patient Years	406	418

[a]**FDA-approved dose is 2 mg QD.**

FDA Advisory Committee Meeting. April 23, 2018.
https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm605062.pdf.

VTE Rates in Observational Databases

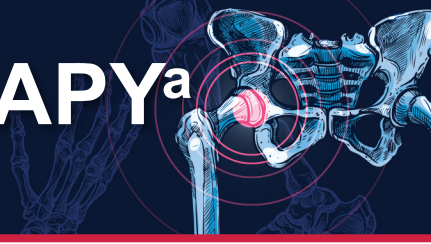
- External databases and literature demonstrate VTE incidence rate in RA patients



[a]Results from 5 Sentinel System data partners, offered through the Reagan-Udall Foundation's Innovation in Medical Evidence Development and Surveillance (IMEDS) program. [b]Results from Truven Marketscan database.
FDA Advisory Committee Meeting. April 23, 2018.
https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm605062.pdf.

Upadacitinib: SELECT-MONOTHERAPY[a]

AEs of Special Interest



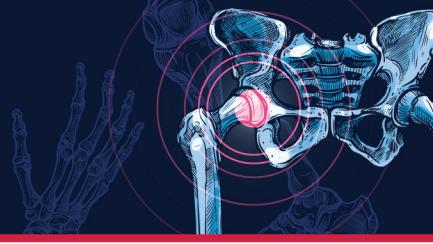
AE, n (%)	cMTX N = 216	UPA 15 mg Mono N = 217	UPA 30 mg Mono N = 215
Infection	57 (26.4)	42 (19.4)	54 (25.1)
-Serious Infection (SI)	1 (0.5)	1 (0.5)	0
-Opportunistic Infection (OI)[‡]	1 (0.5)	0	3 (1.4)
-Herpes Zoster	1 (0.5)	3 (1.4)	6 (2.8)
-Tuberculosis	0	0	0
Hepatic Disorder	4 (1.9)	4 (1.8)	5 (2.3)
Gastrointestinal Perforation	0	0	0
Any Malignancy (including NMSC)	1 (0.5)	2 (0.9)	0
-NMSC	1 (0.5)	0	0
MACE (adjudicated)[§]	0	1 (0.5)	2 (0.9)
Venous Thromboembolism (adjudicated)[δ]	0	1 (0.5)	0

[a]**Investigational agent.** [‡]OI: cMTX: Fungal esophagitis; UPA 30 mg: 2 oral candidiasis, 1 oropharyngeal candidiasis
[§]MACE: UPA 15 mg: 1 hemorrhagic stroke due to ruptured aneurysm (fatal); UPA 30 mg: 1 non-fatal MI, 1 non-fatal stroke
[δ]VTE: Pulmonary embolism in UPA 15 mg in pt with risk factors (BMI 36 kg/m^2, estrogen)

Smolen J, et al. Presented at: EULAR; 2018. Abstract No. OP0035.

Filgotinib: FINCH 2[a]

AEs of Interest

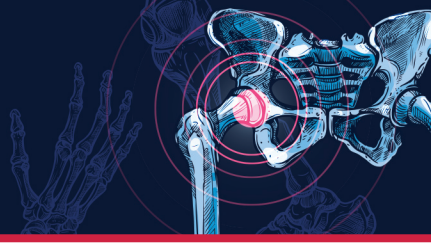


AE, n (%)	PBO n = 148	FIL 100 mg n = 153	FIL 200 mg N = 147
Infection	38 (25.7%)	52 (34%)	53 (36.1%)
-Serious Infection	2 (1.4%)	3 (2%)	1 (0.7%)
-Opportunistic Infection	0	0	0
-Herpes Zoster	0	2 (1.3%)	2 (1.4%)
-Active Tuberculosis	0	0	0
DVT/PE[b]	0	0	1 (0.7%)
MACE (adjudicated)	1 (0.7%)	1 (0.7%)	0
GI Perforation	0	0	0
Any Malignancy (excluding NMSC)	0	0	0
-NMSC	0	0	0

[a]**Investigational agent.** [b]Retinal vein occlusion.

Genovese M, et al. Presented at: ACR/ARHP; 2018. Abstract No. L06.

Jakinibs: Possible Laboratory Changes[1,2]



- LFT abnormalities: More prevalent with combination Rx
- Lipid: Increased HDL/LDL; ratio generally unchanged
- Hemoglobin: Reduced if JAK2 activity impacted; rarely clinically significant
- Neutrophils: Reduced; rarely <1000/mm^3; presumed part of MOA
- Lymphocytes: Reduced; rarely <500/mm^3; dose reduction or discontinuation indicated due to increased risk of SIEs
- Serum creatinine: Small nonsignificant elevations seen

LFT = liver function test; HDL/LDL = high-density lipoprotein/low-density lipoprotein.

1. Cohen S, et al. *Ann Rheum Dis*. 2017;76:1253-1262. 2. Genovese, et al. Presented at: ACR/ARHP; 2017. Abstract No. 511.

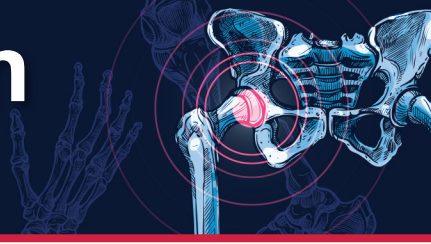
Jakinibs: Laboratory Findings

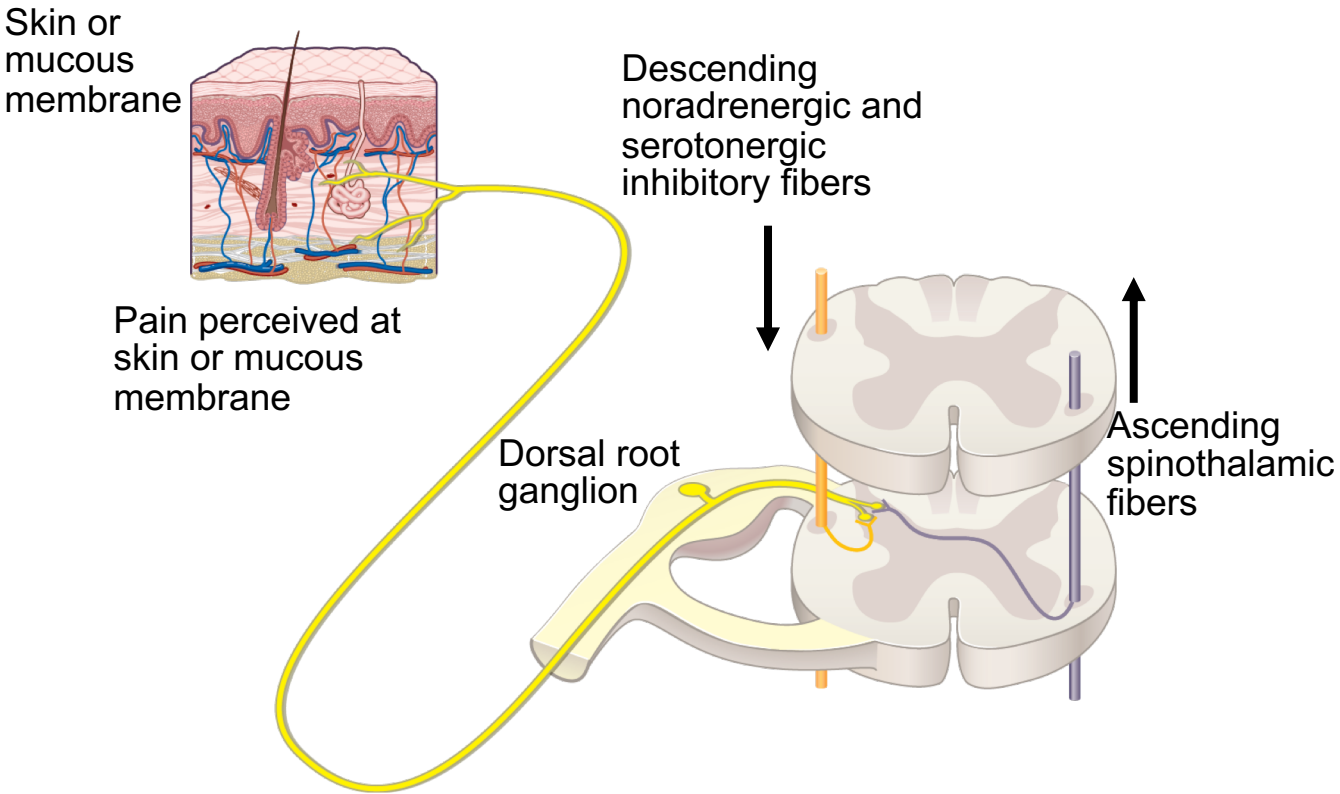
	Tofacitinib	Baricitinib	Filgotinib	Upadacitinib
Selectivity	JAK1, JAK3	JAK1, JAK2	JAK1	JAK1
Lymphocyte number	↓	No change	No change	↓
NK cell number	↓	↓*	No change	↓
Neutrophil number	↓	↓	↓	↓
Hemoglobin level	↑	↓	↑	↓
Platelet count	↓	No change	↓	N/A
Liver transaminase level	↑	↑	↑	↑
CPK level	↑	↑	N/A	↑
HDL level	↑	↑	↑	↑
LDL level	↑	↑	No change	↑
Creatinine level	↑	↑	↑	↑

*Initial rise followed by a decrease. CPK = creatine phosphokinase.

Winthrop K. *Nature Rev Rheum*. 2017.13:234-243.

Herpes Zoster: Viral Replication Results in Ganglionitis





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Herpes Zoster and the Risk of Stroke in Patients With Autoimmune Diseases

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[2] Departments of Epidemiology and School of Public Health and Division of Infectious Diseases (JWB) University of Alabama at Birmingham
[3] Division of Infectious Diseases Oregon Health and Science University

Varicella Vaccines

	Varicella Virus Vaccine[1]	Zoster Vaccine Live[2]	Herpes Zoster Subunit Vaccine[3]
CDC abbreviation	VAR	ZVL	RZV
Vaccine Type	Live	Live	Inactivated; Recombinant
Vaccine Components	1350 PFU VZV	19400 PFU VZV	VZV gE: 50 mcg MPL: 50 mcg QS-21: 50 mcg
Recommended Age	≥ 12 months	≥ 50 years	≥ 50 years
Number of Doses	2	1	2
Schedule	0, 1 month	1 dose	0, 2-6 months
Route	SubQ	SubQ	Intramuscular
Storage	Refrigerator	Freezer	Refrigerator
Diluent	Sterile Water	Sterile Water	AS01 adjuvant

gE = glycoprotein E; PFU = plaque-forming units; MPL = monophosphoryl lipid A;
QS-21 = saponin purified from plant extract *Quillaja saponaria* Molina

1. Varivax [package insert]. Merck: Whitehouse Station, NJ. 2017. 2. Zostavax [package insert]. Merck: Whitehouse Station, NJ. 2018.
3. Shingrix [package insert]. GSK: Research Triangle Park, NC. 2017.

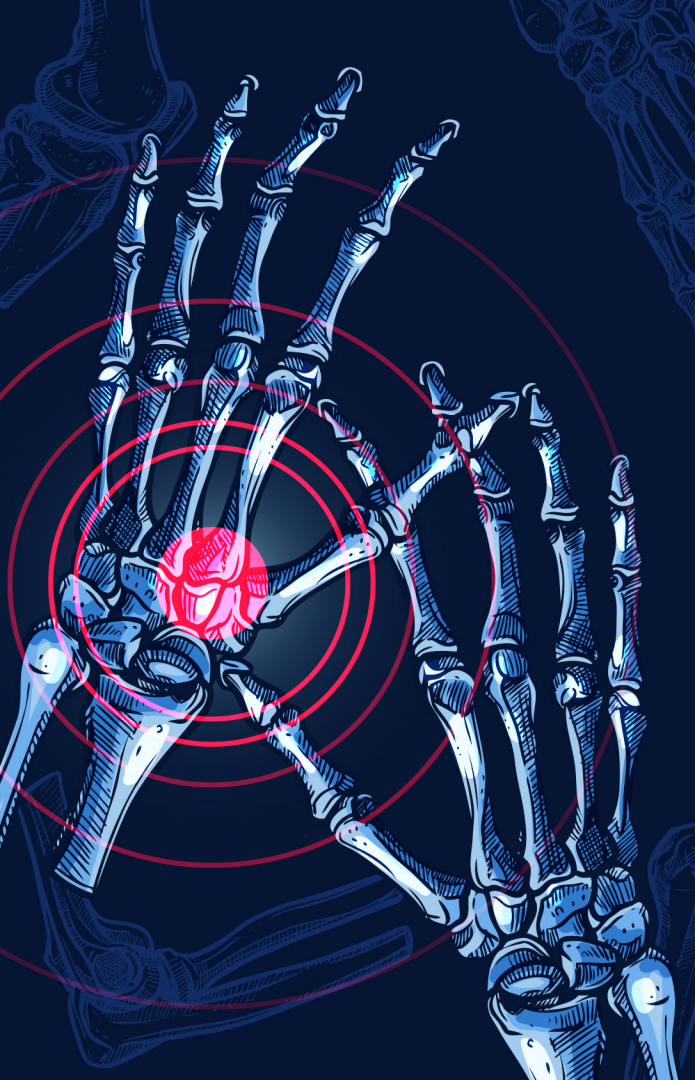
Updated ACIP Adult Vaccination Schedule

Prevention of HZ and Its Complications

- October 2017 recommendations for use of RZV:[1]
  - Immunocompetent adults aged ≥ 50 years to prevent HZ and related complications
  - Adults aged ≥ 50 years who previously received ZVL
  - Adults aged ≥ 60 years can receive ZVL or RZV, although **RZV is preferred**
- 2018 updates to immunization schedule:[2]
  - 2 doses of RZV, 2-6 months apart to adults aged ≥ 50 years, regardless of past episodes of HZ or receipt of ZVL
  - 2 doses of RZV 2-6 months apart to adults who received ZVL, at least 2 months afterward
    - No current recommendation on the use of RZV in pregnant women or adults with immunocompromising conditions
- No head-to-head studies of ZVL vs. RZV
- CDC still recommends VAR first

1. Dooling KL, et al. *MMWR Morb Mortal Wkly Rep.* 2018;67(3):103-108. 2. https://www.cdc.gov/vaccines/schedules/hcp/adult.html.

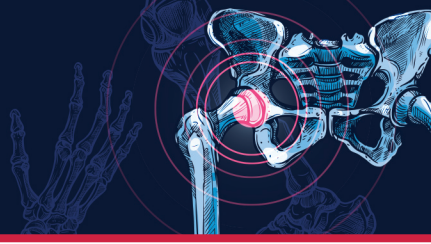
Is There a Role for Patient-Reported Outcomes (PROs) in Clinical Trials for New Agents?



Learning Objective 3

Assess the role of PROs as measures for the value of new therapeutics for RA in addition to safety and efficacy data

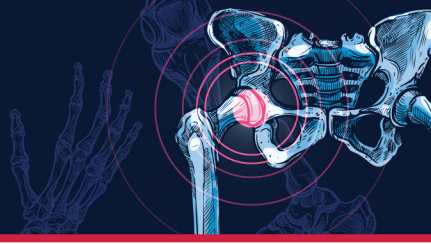
Audience Response



How often do you assess PROs in follow-up visits of patients with RA?

A. 0-10% of the time
B. 11-30% of the time
C. 31-60% of the time
D. 61-90% of the time

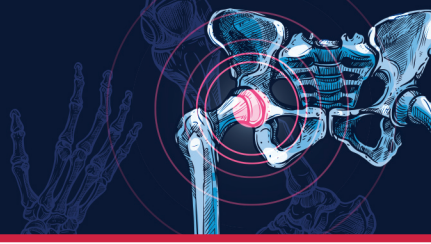
Audience Response



A 36-year-old female with RA has been receiving a TNF inhibitor plus methotrexate for 3 months. At her follow-up appointment, she has a a RAPID3 of 5.9 and complains of fatigue. Upon joint exam, she has 5 tender and 3 swollen joints. She also noted that she does not like receiving injections, and that they are inconvenient for her busy lifestyle. Which of the following would be a reasonable next step in managing her?

A. Continue the regimen for 1 more month and re-assess
B. Switch to another biologic with a different MOA
C. Switch from the TNF inhibitor to a JAK inhibitor
D. Switch the regimen to monotherapy with a JAK inhibitor

Definition of PRO

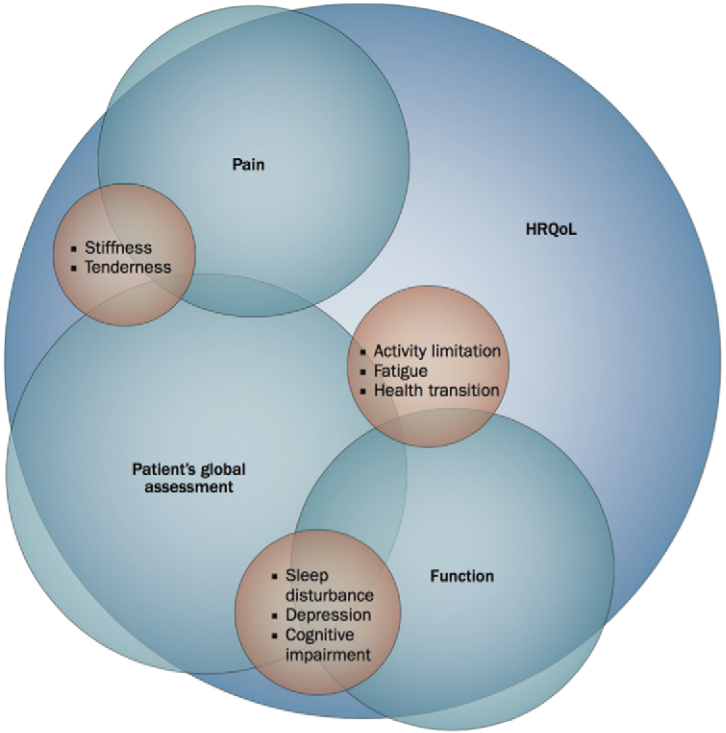


- **P**atient **R**eported **O**utcome measures are **reports of status of patient's health condition**
- PRO data collected directly from **questionnaires** completed by the patient themselves or via **interviews** by a clinician or anyone else

>> Outcome is measured in absolute terms

e.g., severity of a symptom, sign or state of disease, or as a change from a previous measure

Examples of PRO Measures (PROMs) in RA by Health Domain

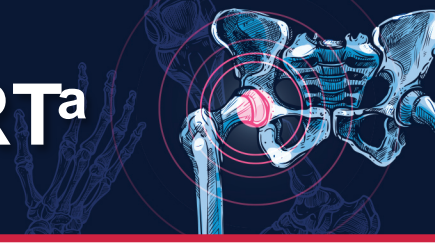


	Domain	PROMs
ACR Core measures	Physical function	HAQ, HAQ-II, MDHAQ, AIMS2, PROMIS PF-10, PF-20, AND PF-CAT
	Pain	VAS, NRS, RAPS, RPS, PROMIS pain intensity and pain interference
	Global assessment	VAS, NRS
Potential core measure candidates	Fatigue	VAS, NRS, MAF, SF-36 vitality, FACITFS, PMS, BRAF NRS
	Stiffness	Morning stiffness duration, severity
	Flares	Patent reported flare, worsening, and treatment change
Multi-dimensional RA activity measures		PAS, PAS-II, RAPID-3, RADAI, RAID
Others	Sleep	VAS, NRS, AIS, MOS Sleep Measure, Pittsburgh Sleep Diary, WHI Insomnia Rating Scale
	Depression	HADS, PHQ-8/9, BDI, MHI
	Work	WLQ, WALS, SPS-6, EWPS, RA WIS, disability/work status

AIS = Athens Insomnia Scale; BRAF = Bristol Rheumatoid Arthritis Fatigue; EWPS = Endicott Work Productivity Scale; FACITFS = Functional Assessment of Chronic Illness Therapy Fatigue Scale; MAF = Multidimensional Assessment of Fatigue scale; PMS = Profile of Mood States; SPS-6 = 6-item Stanford Presenteeism Scale; WALS = Workplace Activity Limitations Scale; WHI, Women's Health Initiative; WIS = Work Instability Scale; WLQ = Work Limitations Questionnaire.

Van Tuyl LH, et al. *Rheum Dis Clin North Am.* 2016;42:219-237.

Tofacitinib PROs From ORAL START[a]



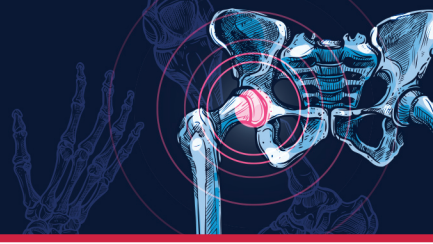
PROs at Baseline and LSM Changes From Baseline at 24 Months

Month 24 LSM Change From Baseline (SE)			
PRO	MTX N = 105	Tofacitinib 5 mg BID N = 261	Tofacitinib 10 mg BID N = 278
Patient Global Assessment	-28.95 (1.94)	-34.41 (1.29)*	-35.79 (1.24)*
Pain	-29.67 (1.94)	-34.79 (1.29)*	-37.62 (1.25)**
HAQ-DI[b]	-0.71 (0.05)	-0.91 (0.03)**	-1.02 (0.03)***
SF-36 PCS	7.72 (0.69)	11.14 (0.46)***	12.49 (0.45)***

[a]**FDA-approved dose is 5 mg BID or 11 mg XR QD.**
[b] A change of 0.22 – 0.25 in the HAQ-DI is currently accepted as the MCID in RCTs.
*$p < .05$, **$p < .001$, *** $p < .0001$ vs. MTX.

Strand V, et al. *RMD Open.* 2016;2(2):e000308.

Baricitinib PROs From RA-BEGIN



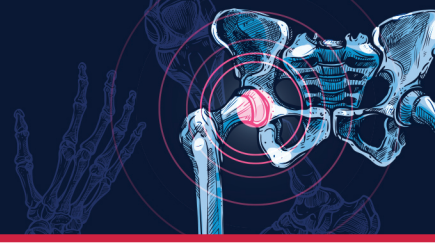
Change From Baseline at Week 52 for PROs

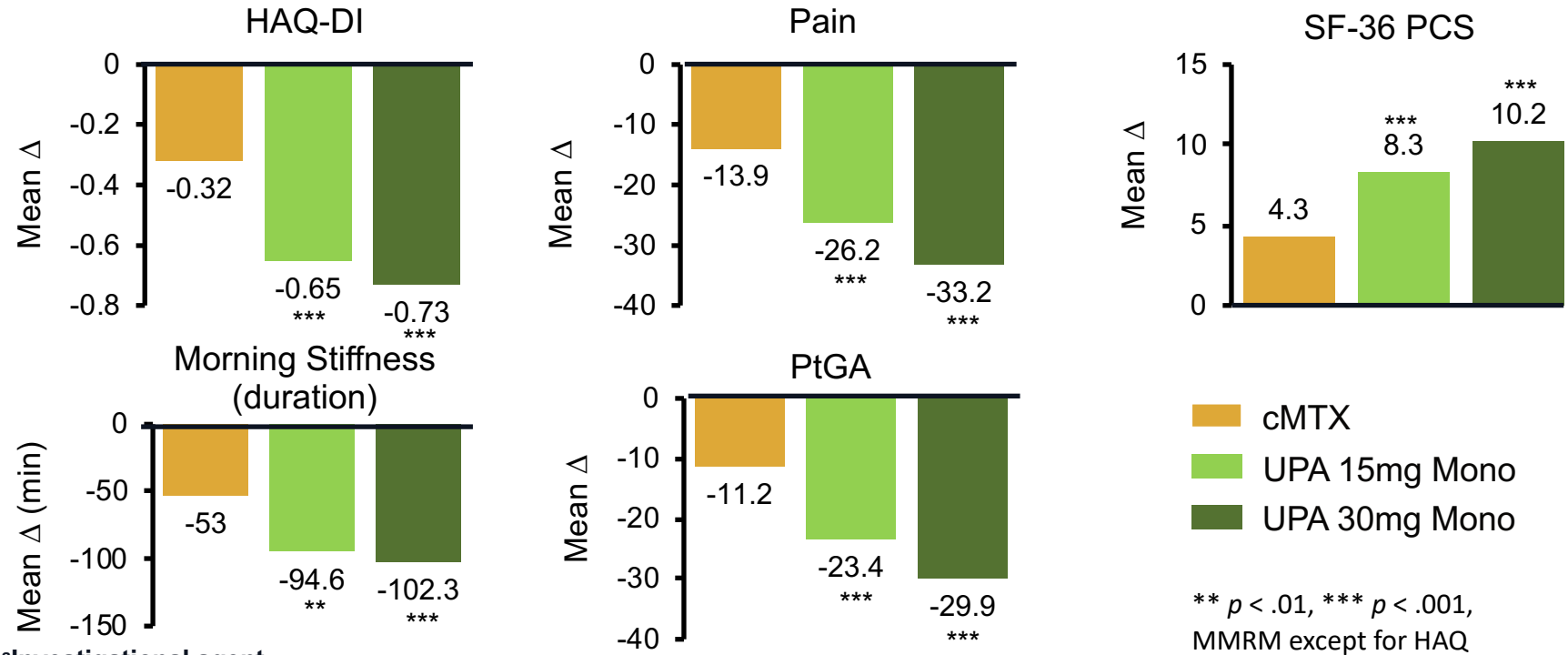
PRO Measure (95% CI)[a]	MTX (n = 210)	Baricitinib 4 mg (n = 159)[c]	Baricitinib 4 mg + MTX (n = 215)[c]
HAQ-DI[b]	-0.71 (-0.79, -0.62)	-0.99 (-1.08, -0.89)***	-1.06 (-1.14, -0.97)***
PtGA	-29 (-32, -26)	-40 (-44, -37)***	-43 (-46, -39)***
Patient's Assessment of Pain	-31 (-34, -27)	-40 (-44, -37)***	-43 (-47, -40)***
MJS Duration, Median Change From Baseline	-40 (-55, -30)	-55 (-60, -40)	-60 (-80, -50)**

[a]Data are presented as least-squares mean unless otherwise stated. [b]A change of 0.22 – 0.25 in the HAQ-DI is currently accepted as the MCID in RCTs. [c]**FDA-approved dose is 2 mg QD.** ** $p \leq .01$, *** $p \leq .001$ vs. MTX.

Schiff M, et al. *Arthritis Res Ther.* 2017;19:208.

Upadacitinib PROs From SELECT-MONOTHERAPY[a,b]





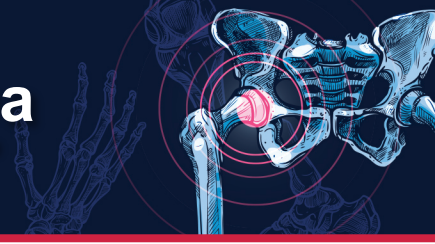
** $p < .01$, *** $p < .001$, MMRM except for HAQ (ANCOVA and MI)

[a]**Investigational agent.**

[b]A change of 0.22 – 0.25 in the HAQ-DI is currently accepted as the MCID in RCTs.

Smolen J, et al. Presented at: EULAR; 2018. Abstract No. OP0035.

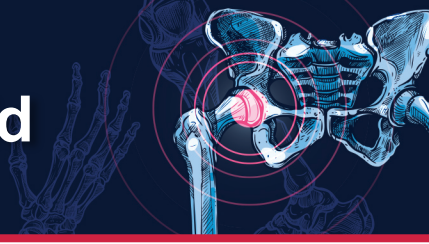
Filgotinib: PROs From FINCH 2[a]



PRO Measure	12 Weeks			24 Weeks		
	PBO n = 148	FIL 100 mg n = 153	FIL 200 mg n = 147	PBO n = 148	FIL 100 mg n = 153	FIL 200 mg N = 147
HAQ-DI, mean (SD)	1.40 (0.71)	1.15 (0.71)	1.15 (0.74)	1.22 (0.68)	1.04 (0.71)	0.95 (0.71)
HAQ-DI, mean CFB (SD)[b]	-0.23 (0.55)	-0.48 (0.60)***	-0.55 (0.59)***	-0.42 (0.60)	-0.60 (0.66)**	-0.75 (0.62)***
SF-36 PCS, mean CFB (SD)	3.6 (8.16)	6.8 (8.22)***	7.6 (7.68)***	6.6 (7.95)	9.0 (8.44)**	9.4 (8.23)***
FACIT-Fatigue, mean CFB (SD)	4.5 (10.37)	8.3 (10.80)**	9.6 (11.24)***	7.0 (10.23)	9.8 (10.39)	11.6 (11.67)***

[a]**Investigational agent.** [b]A change of 0.22 – 0.25 in the HAQ-DI is currently accepted as the MCID in RCTs. *$p < .05$, **$p < .01$, ***$p < .001$ vs. placebo. Genovese M, et al. Presented at: ACR/ARHP; 2018. Abstract No. L06.

Patient-Provider Discordance Between Global Assessments of Disease Activity in Rheumatoid Arthritis: A Comprehensive Clinical Evaluation



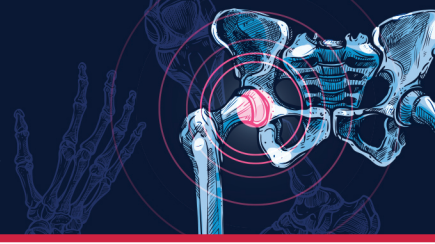
- Discordance correlated with
  - Seronegative status
  - Lack of erosions
  - + fibromyalgia or depression
  - Use of opioids, antidepressants, anxiolytics, or fibromyalgia medications
- Prospective analysis demonstrated
  - Widespread pain
  - Polysymptomatic distress
  - Neuropathic pain
  - Depression
  - No difference in MUS

MUS = musculoskeletal ultrasound.

Challa D, et al. *Arthritis Res Ther.* 2017;19:212.

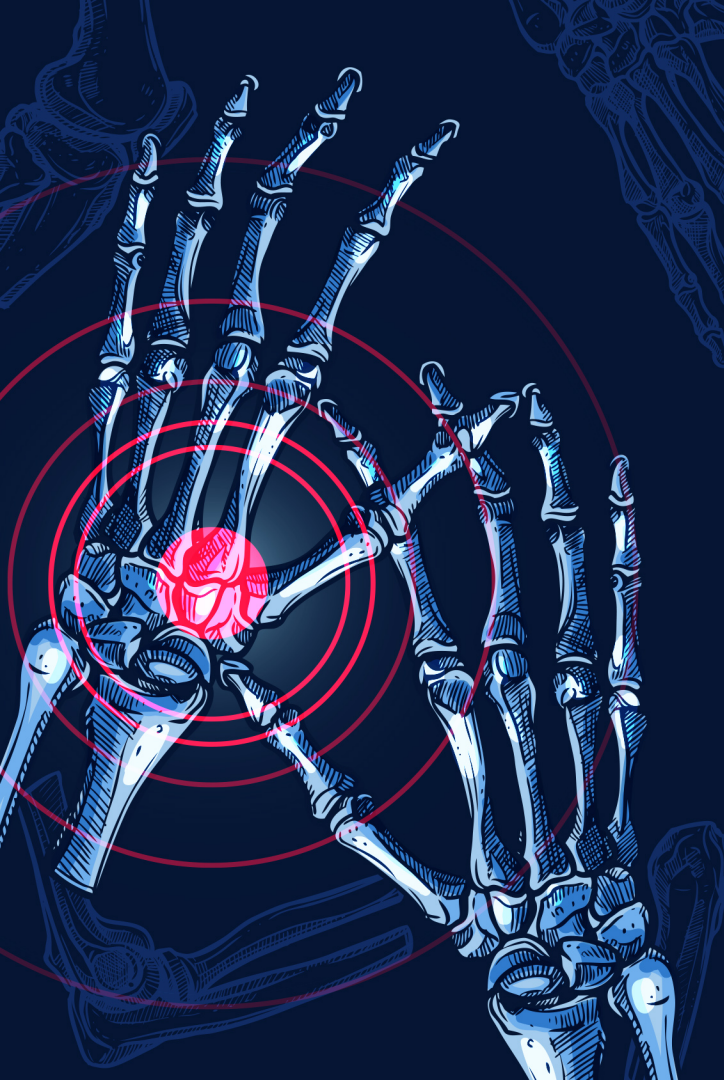
SMART Goals

Specific, Measurable, Attainable, Relevant, Timely



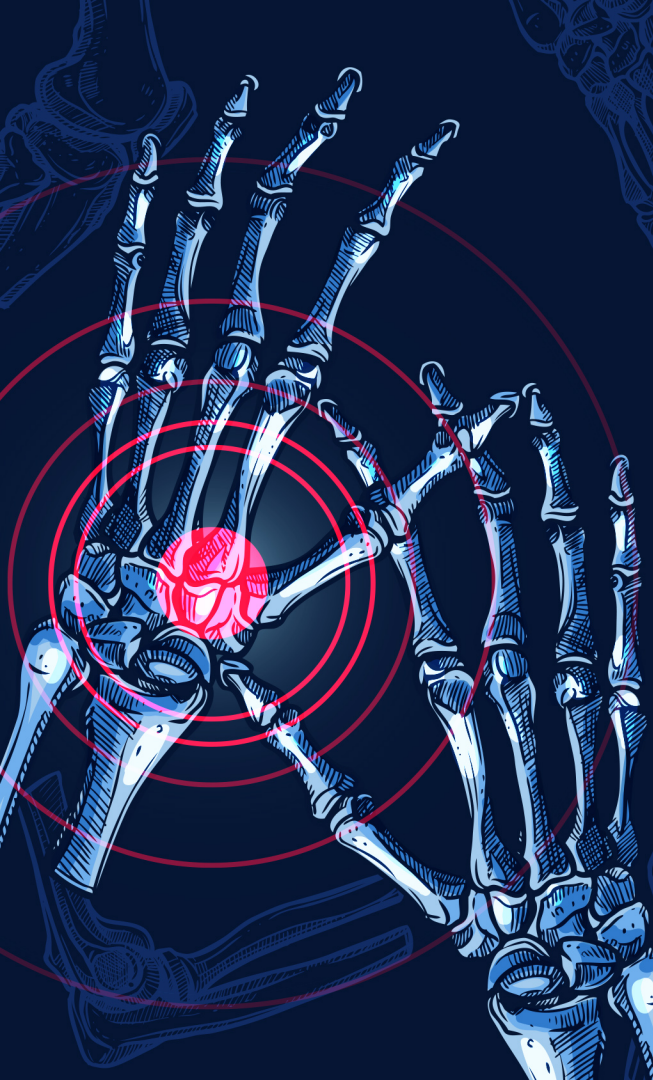
- Jakinibs have similar efficacy to biologic DMARDs and are appropriate treatment options for MTX-IR or biologic DMARD-IR patients with RA
- Data support use in DMARD-naïve patients with RA but present use limited due to insurers/governmental authorities
- Safety issues well delineated and similar to biologic DMARDS except for an increased risk for herpes zoster
- Differences in JAK specificity exist in preclinical evaluation but data to date suggest limited impact on clinical response to individual Jakinibs


Questions
& Answers



Get Your Credit

To receive credit, please **complete the demographics survey** upon login **and the evaluation** during Q&A on your mobile device. **You will receive an email with your certificate after the event.**



Downloadable Resources

Available for your convenience at **www.cmeoutfitters.com/RheumCMEresources**