



RhAPP

RHEUMATOLOGY ADVANCED
PRACTICE PROVIDERS

RHAPP NATIONAL CONFERENCE

SEPTEMBER 8-10, 2022

Year in Review:
Drugs



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Faculty Disclosures

- Jessica Farrell, PharmD:
 - Speaker: Abbvie, Pfizer
 - Consultant: Boehringer Ingelheim
- Danielle Gatti-Palumbo, PharmD
 - There are no relevant financial relationships to disclose.

Objectives

- Evaluate evidence to support new indications for medications used to treat rheumatic diseases
- Review updated guidelines for the use of vaccines in patients with rheumatic disease
- Discuss COVID-19 pre-exposure prophylaxis and treatment options for immunosuppressed patients

Secukinumab New FDA Indication Dec. 2021

Weight based dosing: 75 mg (≥ 15 kg and <50 kg) OR 150 mg (≥ 50 kg)

Weeks 0, 1, 2, 3, and 4, then every 4 weeks

Two subtypes of **Juvenile Idiopathic Arthritis (JIA)**

Active enthesitis-related arthritis (ERA) ≥ 4 years

- Pediatric correlate to axial spondyloarthritis
- Arthritis and enthesitis
- Axial involvement (spondylitis, sacroiliitis)
- HLA-B27
- Anterior uveitis
- Tarsitis

Active juvenile psoriatic arthritis (JPsA) ≥ 2 years

- Pediatric correlate to psoriatic arthritis
- Early stage, Arthritis
- Psoriasis
- Dactylitis
- Nail pitting or onycholysis
- Late onset, enthesitis, and axial disease
- Positive antinuclear antibody (ANA) titer

JUNIPERA

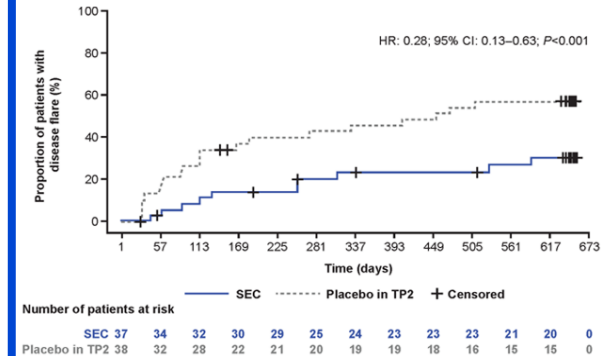
Phase III, 2 year, 3-part, double-blind, PBO-controlled, randomized-withdrawal

- **Treatment-period 1 (TP1) weeks 1,2,3,4,8, and 12**
 - Open label
 - 90.4% JIA achieved ACR 30 and 69.9% JIA achieved ACR 70
 - Responders in TP1 (JIA ACR 30 \geq at week 12) randomized to TP2
- **Treatment-period 2 (TP2) weeks 12 to week 104**
 - Double-blind, PBO controlled every 4 week until flare or week 104
 - 86 pts age 2-18 years with ERA or JPsA
- **Primary Endpoint: Time to flare**
 - ERA- 53% reduction in risk of flare
 - JPsA- 85% reduction in risk of flare ($p < 0.001$)
 - 21 flares in PBO vs 10 in Secukinumab
 - 72% risk of flare reduction in Secukinumab vs PBO
- **Secondary Endpoints:** JIA ACR 30/50/70/90/100, inactive disease, JADAS, enthesitis count, safety
- Safety similar to adult

Efficacy of secukinumab in Treatment Periods 1 and 2 (Key secondary endpoints)

Efficacy Outcomes, %	TP1	TP2 [‡]		P-value
	SEC (N=83) [^]	SEC (N=37)	PBO (N=37)	
JIA ACR 30	90.4	89.2	64.9	0.014
JIA ACR 50	86.7	78.4	62.2	0.152
JIA ACR 70	69.9	67.6	43.2	0.042
JIA ACR 90	39.8	51.4	40.5	0.431
JIA ACR 100	25.3	43.2	37.8	0.745
Inactive disease [#]	36.1	47.2	37.8	0.500
JADAS-27, mean (SD)	15.1 (7.2)	14.6 (8.1)	13.3 (5.8)	NA
Enthesitis count, mean change from BL (SD)	-1.8 (2.3)	-2.1 (2.0)	-1.9 (1.2)	NA

Time to flare in Treatment Period 2 (Primary Endpoint)



Baricitinib New Indication June 2022

• Alopecia Areata (AA)

– Autoimmune nonscarring hair loss

- Dose: 2-4mg daily
- Increase to 4 mg daily if inadequate response
- For patients with nearly complete or complete scalp hair loss, with or without substantial eyelash or eyebrow hair loss, consider treating with 4 mg once daily
- Reduce the dose to 2 mg once daily when an adequate response has been achieved



BRAVE-AA1 and BRAVE-AA2

Phase III, double-blind, parallel-group, randomized, PCB-controlled 36 week trials

- BRAVE-AA1 is an adaptive phase 2-3, phase 3 included here
- 1,200 pts severe AA ($\geq 50\%$ scalp hair loss, Severity of Alopecia Tool (SALT) score ≥ 50)
- Randomized (3:2:2): 4mg, 2mg, or PBO

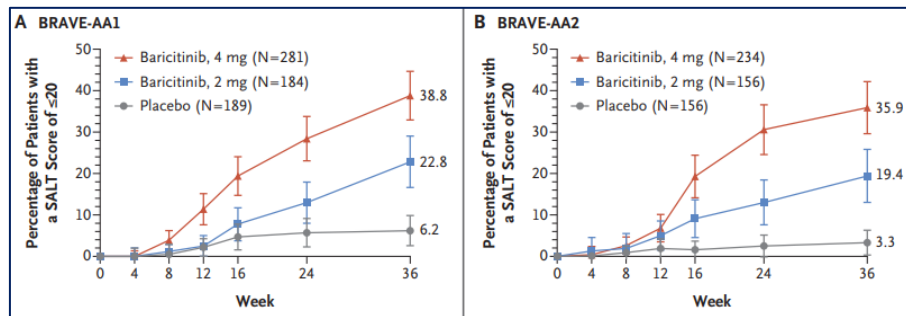
- **Primary Endpoint: SALT ≤ 20 at week 36**

- Achieved $\geq 80\%$ scalp hair coverage ($p \leq 0.001$ all vs. PBO)
 - 17-22% of 2-mg/day
 - 32-35% of 4-mg/day
 - 3-5% in PBO
- Achieved $\geq 90\%$ hair coverage
 - 11-13% of 2-mg/day ($p \leq 0.01$ vs. PBO BRAVE-AA1)
 - 24-26% of 4-mg/day ($p \leq 0.001$ vs. PBO BRAVE-AA1)
 - 1-4% in PBO

- **Secondary Endpoint: SALT ≤ 10 , ClinRO for Eyebrow, Eyelash Hair Loss with a ≥ 2 -point improvement from baseline**

- Improvements in eyebrow and eyelash coverage in 4-mg daily at 36 weeks, not significant for 2mg

- **BRAVE-AA2:** if achieved SALT ≤ 20 on 4mg at 52 weeks, entered randomized down-titration to 2 mg or continue 4mg. After 24 weeks (76 wks total), 75%(2mg) and 98%(4mg) maintained response



Apremilast Expanded Indication Dec 2021

- Treatment Of Adult Patients With Plaque Psoriasis Who Are Candidates For Phototherapy Or Systemic Therapy
- Regardless of severity level
- Based on findings from the Phase 3 **ADVANCE** trial

ADVANCE

Phase 3, multicenter, randomized, PBO-controlled, double-blind study

- Mild-Mod plaque psoriasis, BSA 2%-15%, PASI 2-15, static Physician's Global Assessment (sPGA) of 2 to 3 [(clear [0] or almost clear [1]), inadequately controlled ≥ 1 topical
- 595 pts randomized (1:1) apremilast 30 mg twice daily or PBO for 16 weeks, followed by open-label extension phase through week 32 (All received apremilast)
 - **Primary Endpoint at week 16:**
 - % with sPGA of 0 or 1 with ≥ 2 -point reduction from baseline: 21.6 % in apremilast vs 4.1% PBO ($p < .0001$)
 - **Secondary Endpoints:**

Secondary Endpoints at week 16	Apremilast	Placebo	P-value
% with $\geq 75\%$ improvement in BSA (BSA-75)	33%	7.4%	$p < .0001$
BSA $\leq 3\%$	61%	22.9%	
BSA $\leq 1\%$	31.7%	7.2%	
Δ baseline in BSA	-3.45%	-0.07%	
Δ baseline in PASI	-3.47	-0.54	
Whole Body Itch Numeric Rating Scale (NRS) response (≥ 4 -pt reduction from baseline, 0 [no itch], 10 [worst imaginable itch])	43.2%	18.6%	
Scalp Physician Global Assessment (ScPGA) of 0 -1 (clear [0] or almost clear [1]) with ≥ 2 -point reduction from baseline	44%	16.6%	
Δ baseline in Dermatology Life Quality Index (DLQI) total score	-5.2	-2.4	

Upadacitinib New FDA Indications

- **Psoriatic Arthritis Dec. 2021**
 - **15 mg once daily**
 - **SELECT-PsA 1 and SELECT-PsA 2**
- Atopic Dermatitis Jan. 2022
 - 15 mg once daily; may increase to 30 mg once daily
- Ulcerative Colitis Mar. 2022
 - 45 mg once daily for 8 weeks; maintenance: 15 mg once daily; may increase to 30 mg once daily
- **Ankylosing Spondylitis Apr. 2022**
 - **15 mg once daily**
 - **SELECT-AXIS 1, SELECT-AXIS 2 AS bDMARD-IR , SELECT-AXIS 2 nr-axSpA**

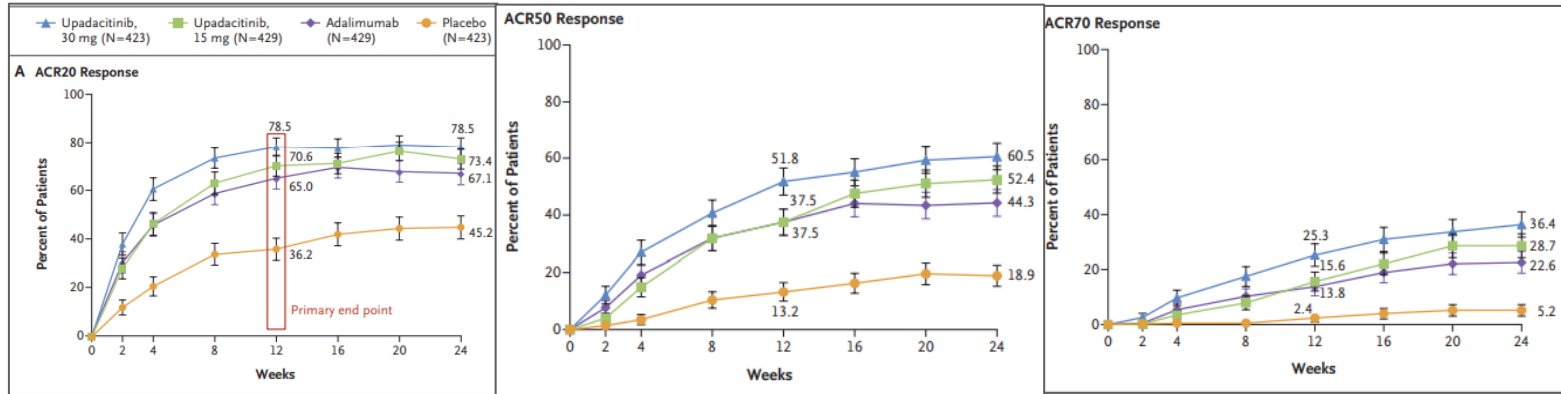
SELECT-PsA 1

Inadequate response to non-biologic DMARDs and Biologic naïve

- Double-blind, phase 3 trial comparing UPA with PBO and with adalimumab as an active comparator
- 1,704 pts randomized to 1/4 arms: UPA 15mg, UPA 30mg, PBO or adalimumab (40 mg every two weeks) for 24 weeks
- Followed by UPA 15 mg or UPA 30 mg at week 24 for 56-week extension

Primary Endpoint:

ACR20 at 12 weeks:
Both UPA doses achieved non-inferiority and only the 30 mg dose showed superiority



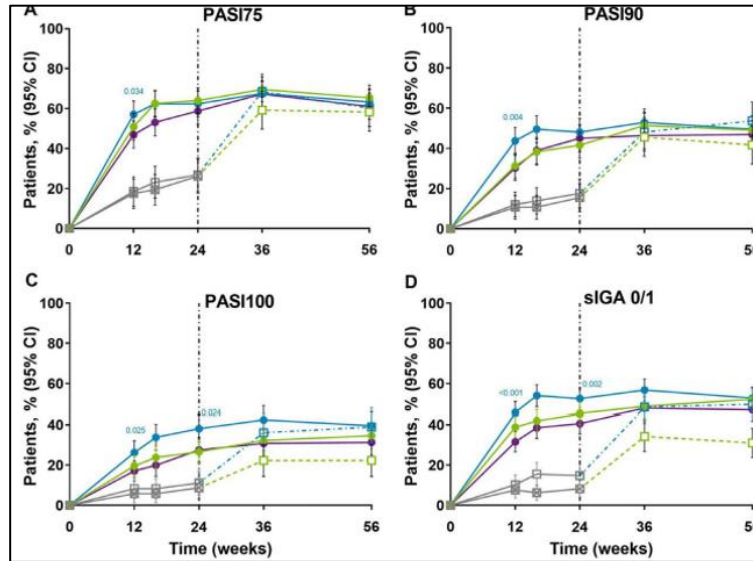
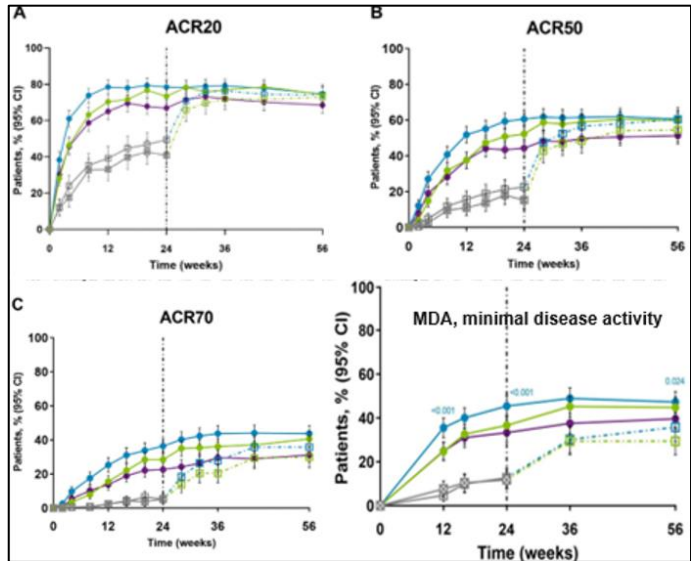
Secondary Endpoint:

Secondary Endpoints	15 mg	30mg	Placebo	Adalimumab
HAQ-DI at week 12	-0.42	-0.47	-0.14	-.034
PASI 75 at week 16	62.6%	62.4%	21.3%	53.1%
MDA at week 24	36.6%	45.4%	12.3%	33.3%
ACR50 at 12 weeks	37.5%	51.8%	13.2%	37.5%
ACR70 at 12 weeks	15.6%	25.3%	2.4%	13.8%

SELECT-PsA 1

56 Week Extension

- 83.2% completed 56 weeks
- ACR20/50/70, PASI75/90/100 and MDA responses were maintained with UPA through week 56
- Pts who switched from PBO → UPA exhibited comparable improvements at week 56 as pts originally randomized to UPA

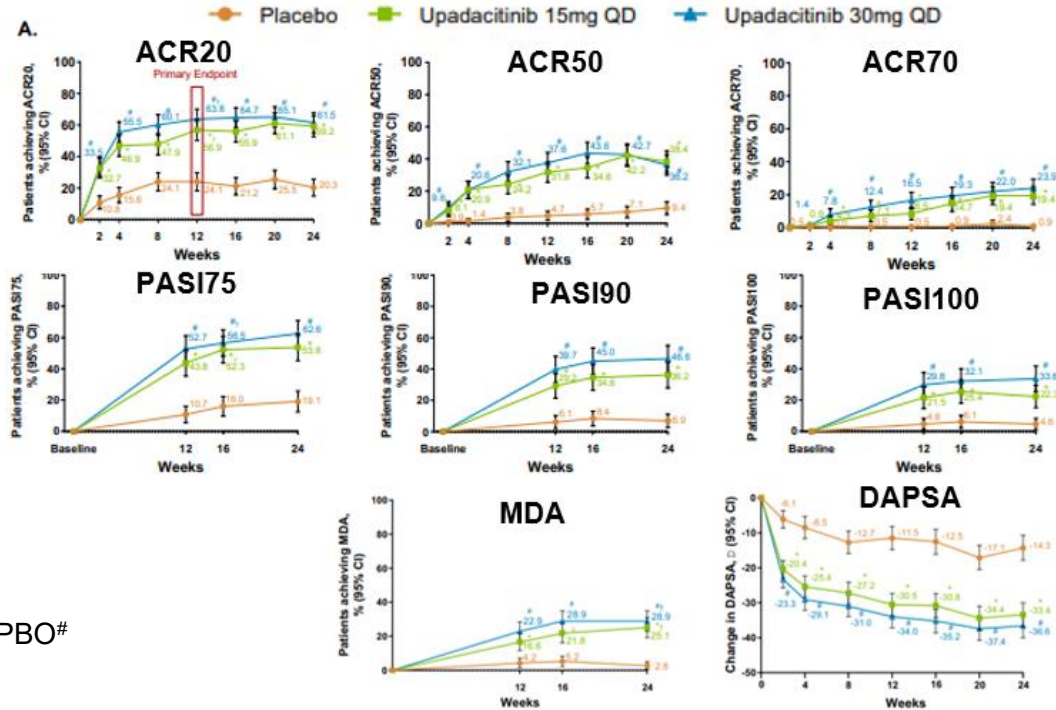


SELECT-PsA 2

Inadequate response ≥ 1 biologic DMARD

- 24-week randomized, PBO-controlled, double-blind, phase 3
- 642 pts randomized (2:2:1:1) to UPA 15 mg, UPA 30 mg, PBO \rightarrow UPA 15 mg or PBO \rightarrow UPA 30 mg at week 24

- **Primary Endpoint:** ACR20 at 12 weeks
 - ACR20/50/70: $p \leq 0.05$ UPA 15 mg vs PBO, and 30mg vs PBO
- **Secondary Endpoints:** MDA at week 24, HAQ-DI, FACIT-F, SF-36, PCS, sIGA, PASI75/90/100, BSA, MDA, Δ from baseline in Disease Activity in Psoriatic Arthritis (DAPSA)
 - $p \leq 0.05$ UPA 15 mg vs placebo*, and 30mg vs PBO#



- 56-week extension: Efficacy maintained over 56 weeks and pts who switched from PBO at week 24 were similar to pts originally on UPA

- All pts who completed week 56 were eligible to remain in extension period for up to 3 years

Upadacitinib for Axial Spondyloarthritis: SELECT-AXIS 1 in Active Ankylosing Spondylitis (AS)

- Phase 2/3, multicenter, randomized, double-blind, parallel-group, PBO-controlled
- Biologic naïve and with inadequate response to NSAIDs
- 187 pts randomized (1:1) UPA 15 mg or PBO for 14 weeks period 1
 - Period 2- open-label extension to 104 weeks for safety, tolerability, efficacy
- Primary Endpoint:** Assessment of SpondyloArthritis international Society 40 (ASAS40) response at week 14
 - Upadacitinib 52% vs PBO 26% (p=0.0003)
- Secondary Endpoint:**
 - ASDAS, BASDAI, SPARCC, BASDAI50, ASQoL, ASAS, MASES, WPAI improved with UPA vs PBO

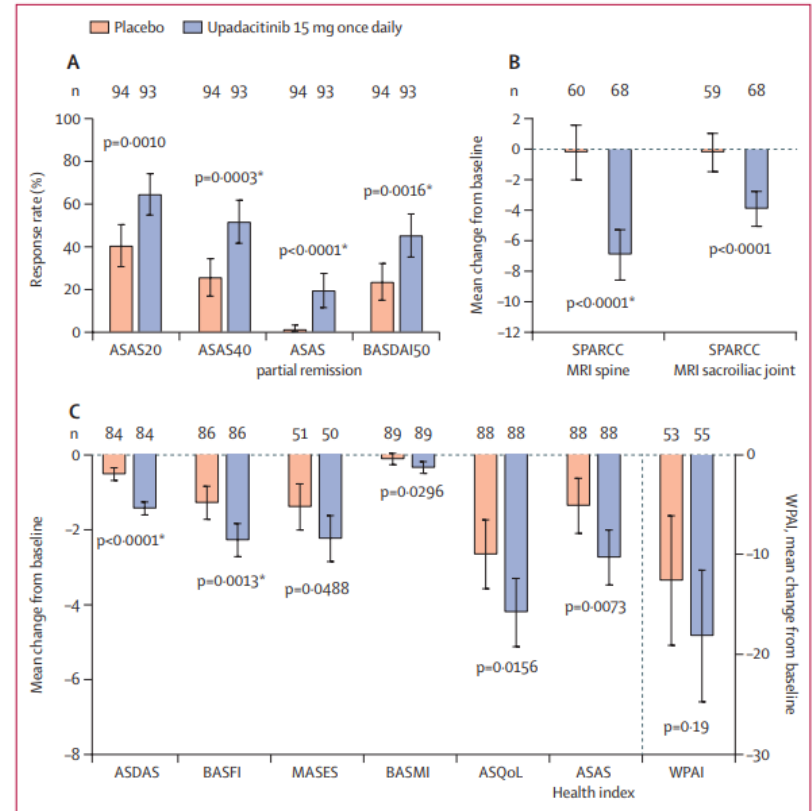


Figure 2: Multiplicity-controlled and key secondary endpoints at week 14

Study 1: SELECT-AXIS 2 AS bDMARD-IR

- Randomized, double-blind, PBO-controlled Phase 3, UPA vs PBO
- 420 AS pts who met modified New York criteria, had BASDAI score ≥ 4 and total back pain score ≥ 4 (scale of 0-10)
- Inadequate response (IR) to bDMARDs
- Randomized (1:1) to UPA 15mg or PBO during the 14-week double-blind treatment period
 - **Primary Endpoint:** Assessment of SpondyloArthritis international Society 40 (ASAS40) response at week 14
 - 45% UPA vs 18% PBO ($P < 0.0001$)
 - Onset of effect as early as week 4
 - **Secondary Endpoints:** ASDAS [CRP], ASDAS ID, ASDAS LD, BASDAI50, ASAS20, ASAS, etc.

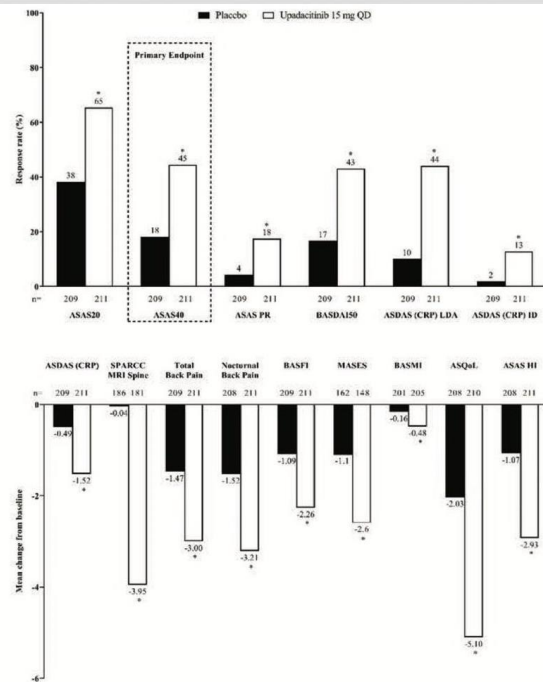
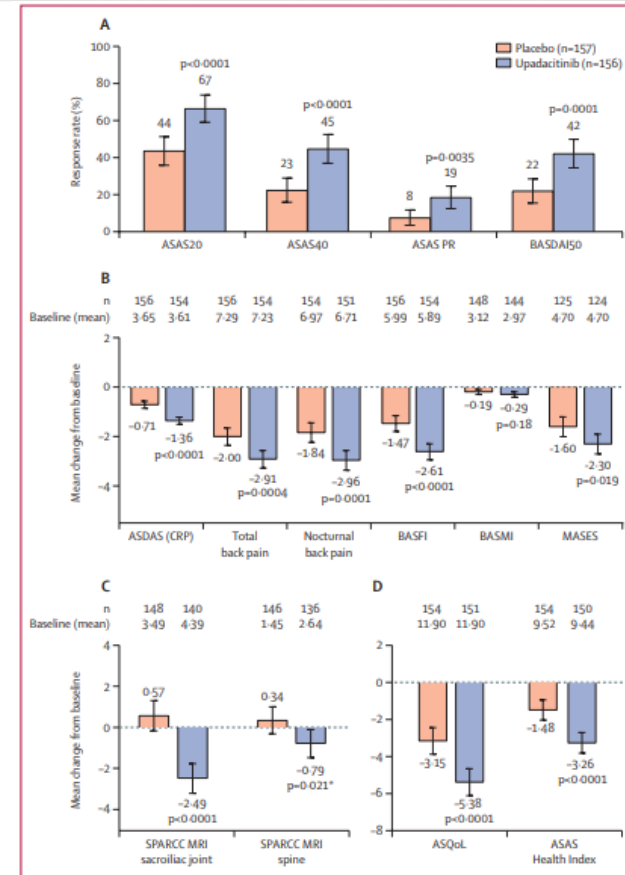


Figure. Analysis of Primary and Multiplicity-Controlled Secondary Endpoints at Wk 14

Study 2: SELECT-AXIS 2 nr-axSpA

Non-Radiographic Axial Spondyloarthritis

- Randomized, double-blind, PBO-controlled, Phase 3 trial UPA vs PBO, in 314 nr-axSpA pts
- 35 day screening period, 52 week double-blind, randomized, PBO-controlled, followed by 52 week open-label extension
- Active nr-axSpA with objective signs of inflammation based on MRI or elevated CRP and failed NSAIDs
- Randomized (1:1) to UPA 15 mg or PBO
 - **Primary Endpoint:** ASAS40 response at week 14
 - 45% UPA vs 23 % in PBO $p < 0.0001$
 - **Secondary Endpoints:** ASDAS, SPARCC MRI, BASDAI, etc.



Risankizumab New Indication

- **Adult Psoriatic Arthritis Jan. 2022**
 - 150 mg at weeks 0, 4, and then every 12 weeks thereafter
 - May be administered alone or in combination with csDMARD
 - **KEEPSAKE-1** and **KEEPSAKE-2**

- Adult moderate to severe Crohn's disease Jun. 2022

KEEPsAKE-1

- Screening period, 24-week randomized, double-blind, PBO-controlled, parallel-group period, followed by 204-week open label period
- 964 pts with PsA randomized (1:1) risankizumab or PBO
- 150mg at weeks 0, 4 and 16
- All pts failed ≥ 1 csDMARD, can continue on ≤ 2 csDMARD (similar use in both groups, MTX)
 - **Primary Endpoint:** ACR20 at week 24
 - 57.3% risankizumab vs 33.5% PBO ($p < 0.001$)
 - **Secondary Endpoints:**
 - Significant for first eight ranks including skin and nail psoriasis endpoints, MDA, and resolution of enthesitis and dactylitis ($p < 0.001$)

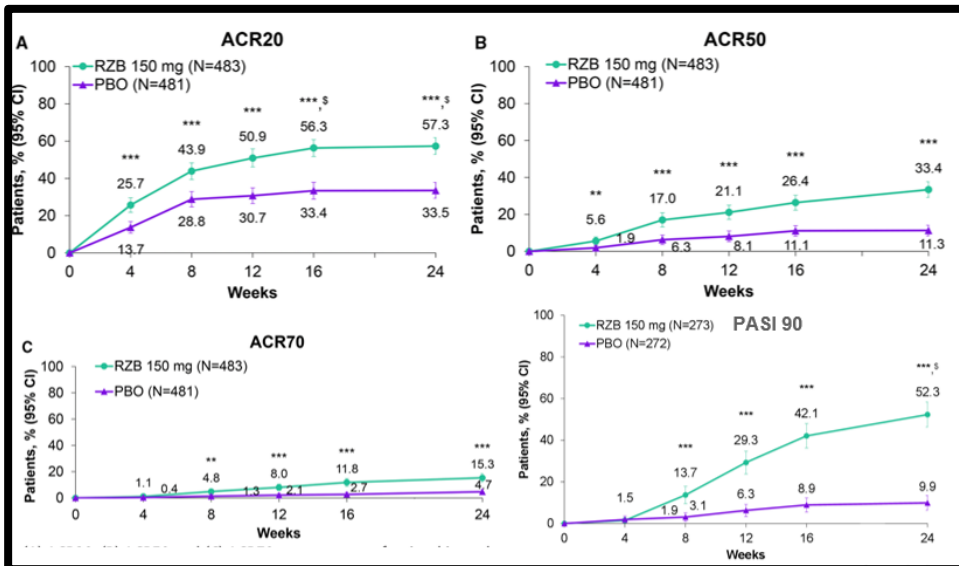
• Safety similar in both groups, nasopharyngitis, URI, increased AST/ALT, and HA

KEEP_sAKE-2

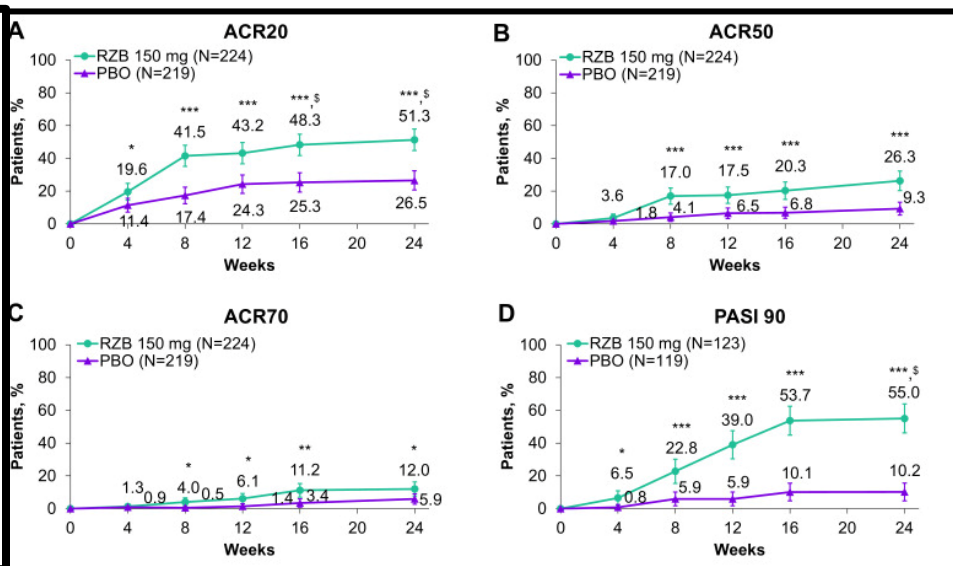
- Previous inadequate response or intolerance to ≤ 2 biologics (Bio-IR) and/or ≥ 1 csDMARD-IR
- Randomized (1:1) to double-blind risankizumab 150mg or PBO for 24 weeks at weeks 0, 4, and 16, followed by open-label risankizumab every 12 weeks through week 208
- 444 pts randomized, 46.5% Bio-IR
 - **Primary Endpoint:** ACR20 at week 24
 - 51.3% risankizumab vs 26.5% PBO ($p < 0.001$)
 - **Secondary Endpoints:** All key PSA domains ($p < 0.05$) vs with PBO

Primary Endpoint: ACR20 at week 24

KEEPSAKE 1



KEEPSAKE 2



Secondary Endpoints: All PSA Domains

KEEPSAKE 1

KEEPSAKE 2

Table 2 Primary and secondary efficacy endpoints								
Parameter	RZB 150 mg N=483	Placebo N=481	Difference (95% CI)	P value	RZB 150 mg N=224	PBO N=219	Difference (95% CI)	P value
Primary endpoint								
ACR20 at week 24, n (%)	277 (57.3)	161 (33.5)	24.0 (18.0 to 30.0)	<0.001*	115 (51.3)	58 (26.5)	24.5 (15.9, 33.0)	<0.001*
Ranked secondary endpoints								
Change in HAQ-DI at week 24, mean (95% CI)	-0.31 (-0.36, -0.27)	-0.11 (-0.16, -0.06)	-0.20 (-0.26 to 0.14)	<0.001*	-0.22 (-0.28 to -0.15)	-0.05 (-0.12 to 0.02)	-0.16 (-0.26 to 0.07)	<0.001*
PASI 90 at week 24, † n (%)	143 (52.3)	27 (9.9)	42.5 (35.6 to 49.3)	<0.001*	68 (55.0)	12 (10.2)	44.3 (33.9 to 54.6)	<0.001*
ACR20 at week 16, n (%)	272 (56.3)	161 (33.4)	23.1 (16.8 to 29.4)	<0.001*	108 (48.3)	55 (25.3)	22.6 (13.9 to 31.2)	<0.001*
MDA at week 24, n (%)	121 (25.0)	49 (10.2)	14.8 (10.2 to 19.4)	<0.001*	57 (25.6)	25 (11.4)	14.0 (7.0 to 21.0)	<0.001*
Change in mNAPSI at week 24, ‡ mean (95% CI)	-9.8 (-11.0, -8.6)	-5.6 (-6.7, -4.4)	-4.2 (-5.7 to -2.7)	<0.001*				
Change in PGA-F at week 24, ‡ mean (95% CI)	-0.8 (-1.0, -0.7)	-0.4 (-0.5, -0.3)	-0.4 (-0.6 to -0.3)	<0.001*				
Resolution of enthesitis at week 24, § n (%)	215 (48.4)	156 (34.8)	13.9 (7.6 to 20.2)	<0.001*				
Resolution of dactylitis at week 24, ¶ n (%)	128 (68.1)	104 (51.0)	16.9 (7.5 to 26.4)	<0.001*				
Change in PsA-mTSS at week 24, mean (95% CI)	0.23 (0.02, 0.44)	0.32 (0.11, 0.53)	-0.09 (-0.4 to 0.2)	0.50				
Change in SF-36 PCS at week 24, mean (95% CI)	6.5 (5.8, 7.2)	3.2 (2.5, 3.9)	3.3 (2.4 to 4.2)	<0.001	5.9 (4.9 to 6.9)	2.0 (0.9 to 3.1)	3.9 (2.4 to 5.3)	<0.001*
Change in FACIT-Fatigue, at week 24, mean (95% CI)	6.5 (5.6, 7.3)	3.9 (3.1, 4.7)	2.6 (1.5 to 3.7)	<0.001	4.9 (3.7 to 6.0)	2.6 (1.4 to 3.9)	2.2 (0.6 to 3.9)	<0.01*
Non-ranked secondary endpoints								
ACR50 at week 24, n (%)	162 (33.4)	54 (11.3)	22.2 (17.3 to 27.2)	<0.001	59 (26.3)	20 (9.3)	16.6 (9.7 to 23.6)	<0.001
ACR70 at week 24, n (%)	74 (15.3)	23 (4.7)	10.5 (6.9 to 14.2)	<0.001	27 (12.0)	13 (5.9)	6.0 (0.8 to 11.3)	<0.05
Resolution of enthesitis at week 24, ‡ n (%)					63 (42.9)	48 (30.4)	13.8 (3.5 to 24.2)	<0.01
Resolution of dactylitis at week 24, § n (%)					29 (72.5)	24 (42.1)	38.8 (22.9 to 54.8)	<0.001

Tofacitinib New Indication

- **Adult Ankylosing Spondylitis Dec. 2021**
 - IR: 5mg twice a day
 - XL: 11mg once daily

Tofacitinib for the treatment of ankylosing spondylitis a phase III, randomized, double-blind, PBO-controlled

- 16 weeks double-blind → 32-week open-label (week 48) → 28-day follow-up
- 269 pts randomized (1:1) tofacitinib 5mg twice daily or PBO who had failed ≥2 NSAIDs and/or anti-TNF

- Primary Endpoint:** ≥20% ASAS20 improvement at week 16

- Tofacitinib 56.4% vs 29.4% PBO ($p < 0.0001$)

- Secondary Endpoint:** ≥40% ASAS40 improvement at week 16

- ASAS40: tofacitinib 40.6% vs 12.5% PBO ($p < 0.0001$)

- Results similar when stratified by bDMARD, greater in bDMARD-naive

- ADEs: 54.9% tof vs 51.5% in PBO

- Hepatic, herpes zoster, infection.
- No deaths malignancies, major CV events, VTE or opportunistic infections

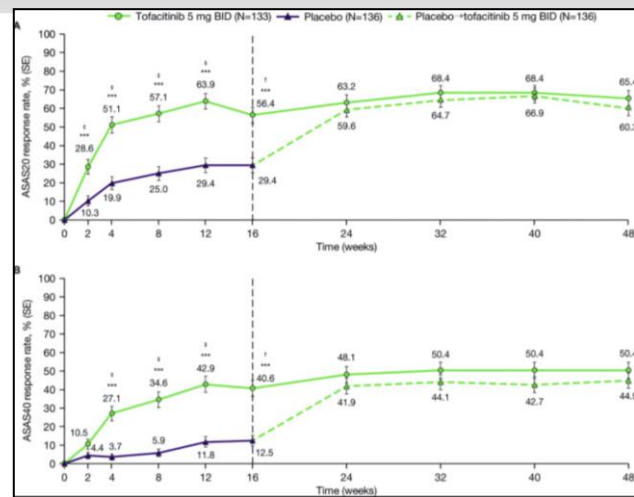


Table 2 Efficacy of tofacitinib 5 mg two times per day versus placebo at week 16: type I error-controlled primary and secondary endpoints†

	Tofacitinib 5 mg two times per day (N=133)	Placebo (N=136)	p value
Global type I error-controlled endpoints at week 16, tested in the sequence below			
ASAS20 response, † n (%)	75 (56.4)	40 (29.4)	<0.0001***§
ASAS40 response, † n (%)	54 (40.6)	17 (12.5)	<0.0001***§
ΔASAS, † LSM (SE) (N1)	-1.36 (0.07) (129)	-0.39 (0.07) (131)	<0.0001***§
ΔhsCRP (mg/dL), † LSM (SE) (N1)	-1.05 (0.10) (129)	-0.09 (0.10) (131)	<0.0001***§
ΔASQoL, ** LSM (SE) (N1)	-4.03 (0.40) (129)	-2.01 (0.41) (130)	0.0001***§
ΔSF-36v2 PCS score, ** LSM (SE) (N1)	6.69 (0.59) (129)	3.14 (0.59) (130)	<0.0001***§
ΔBASMI, † LSM (SE) (N1)	-0.63 (0.06) (129)	-0.11 (0.06) (131)	<0.0001***§
ΔFACIT-F total score, † LSM (SE) (N1)	6.54 (0.80) (129)	3.12 (0.79) (131)	0.0008***§
Type I error-controlled ΔASAS components at week 16†§§ tested in the sequence below			
ΔPtGA (NRS 0–10), LSM (SE) (N1)	-2.47 (0.20) (129)	-0.91 (0.20) (131)	<0.0001***††
ΔTotal back pain (NRS 0–10), LSM (SE) (N1)	-2.57 (0.19) (129)	-0.96 (0.19) (131)	<0.0001***††
ΔBASFI (NRS 0–10), LSM (SE) (N1)	-2.05 (0.17) (129)	-0.82 (0.17) (131)	<0.0001***††
ΔMorning stiffness (inflammation, NRS 0–10), ‡ LSM (SE) (N1)	-2.69 (0.19) (129)	-0.97 (0.19) (131)	<0.0001***††

Belimumab New Indication

- Pediatric Lupus Nephritis July 2022
 - 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter
- Based on extrapolated data of efficacy from IV study in adults with active lupus nephritis and supported by PK data from IV studies in adults with active LN and from pediatric patients with SLE

Pegloticase + MTX for Gout Jul. 2022

MIRROR

- 152 uncontrolled gout pts randomized (2:1) to 4 wk MTX/PBO run-in followed by bi-weekly pegloticase 8mg+MTX (oral 15mg/week) or pegloticase 8mg+PBO for 52 weeks
 - Uncontrolled (sUA \geq 7 mg/dL, ULT failure/intolerance, and \geq 1 of the following: \geq 1 tophus, \geq 2 flares in past yr, chronic gouty arthritis)
 - **Primary Endpoint: Treatment response at 6 months** (sUA $<$ 6mg/dL for \geq 80% of the time during Wks 20-24)
 - 71.0% Peg+MTX vs 38.5% Peg+PBO (p $<$ 0.0001)
 - Same seen in modified ITT [all pts receiving \geq 1 pegloticase dose]: 74.0% Peg+MTX vs 40.8% Peg+PBO (p $<$ 0.0001)
 - **Complete resolution of \geq 1 tophus improved by 20.8% (p=0.043):** 34.6% Peg+MTX vs. 13.8% Peg+PBO at Week 24
 - **Infusion reactions:** PBO (30.6%) > MTX (3.1% plus anaphylaxis in 1 MTX pt)
 - **Gout flare:** 66.7% Peg+MTX vs 69.4% Peg+PBO
 - Reduced the incidence of new anti-PEG antibody formation: 23.2% Peg+MTX vs 50.0% Peg+PBO
 - **ADE:** First 24 wks, 81.3% Peg+MTX vs 95.9% Peg+PBO experienced \geq 1 AE
 - A single CV event of MI in 1 MTX pt >2 wks after pegloticase infusion 3 (deemed unrelated)

Krill Oil in Osteoarthritis of the Knee

Double-blind, randomized, placebo-controlled multicenter trial

Patient Population

235 adults aged 40-65 with a BMI 18.5-35 kg/m², mild-moderate OA, <0.5 g/d LC ω-3 PUFAs, and knee pain

Treatment

4 capsules/day krill oil (0.88 g EPA + DHA [0.60 g EPA, 0.28 g DHA] and 0.45 g astaxanthin) or placebo

Anticoagulants, antiplatelets, high dose NSAIDs, IM or IA corticosteroids, oral corticosteroids, & opioids were not allowed

Primary Outcome

Knee pain

Secondary Outcomes

Knee stiffness and physical function

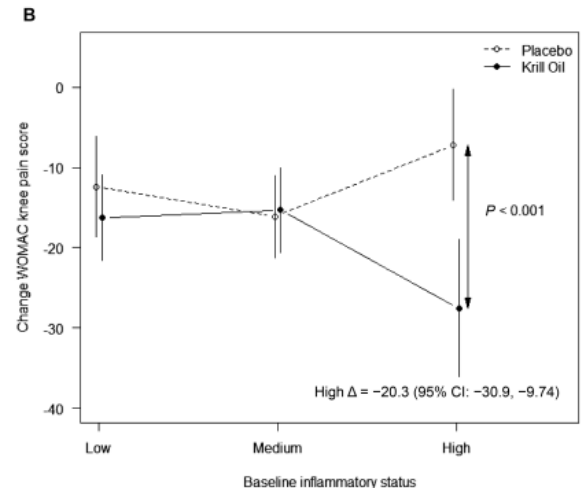
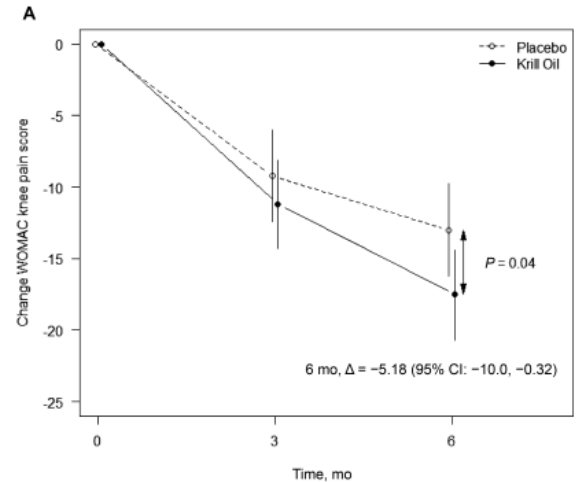
Monitoring

In clinic assessment at baseline, 3 months, and 6 months – *WOMAC Questionnaire, lipid levels, Omega-3 Index analysis, resting BP & HR, body temperature, physical exam, and blood hematology, biochemistry, and anticoagulation*

Online survey at 1, 2, 4, and 5 months – *treatment compliance, adverse events, use of other medications (including low dose NSAIDs)*

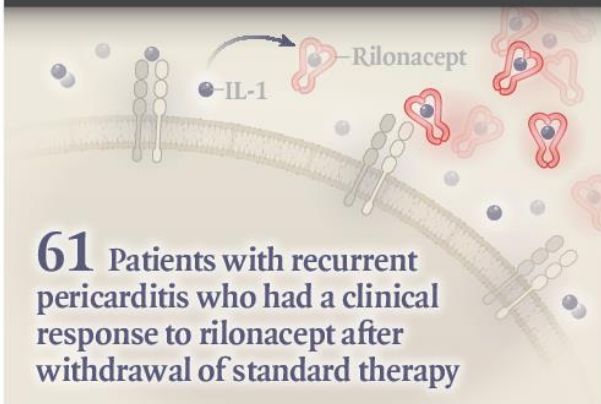
Results

Krill oil is safe to use and shows modest benefit in knee pain, stiffness, and physical function



Rilonacept in Recurrent Pericarditis


RHAPSODY: PHASE 3, MULTICENTER, DOUBLE-BLIND, RANDOMIZED-WITHDRAWAL TRIAL



61 Patients with recurrent pericarditis who had a clinical response to rilonacept after withdrawal of standard therapy

The diagram illustrates the mechanism of action of Rilonacept. It shows a cell membrane with IL-1 receptors. IL-1 molecules (represented as blue spheres) are shown binding to these receptors. Rilonacept molecules (represented as red, heart-shaped structures) are shown binding to the IL-1 receptors, preventing the IL-1 molecules from binding and thus inhibiting the inflammatory response.

Rilonacept




N=30

Subcutaneous injection once weekly

The image shows a white vial with a red cap and a syringe with a red plunger, representing the Rilonacept treatment group.

Placebo



N=31

Subcutaneous injection once weekly

The image shows a white vial with a blue cap and a syringe with a blue plunger, representing the placebo treatment group.

Median time to first pericarditis recurrence

Not reached
2 Patients (7%)

8.6 wk
23 Patients (74%)

Hazard ratio, 0.04; 95% CI, 0.01 to 0.18; P<0.001

Rilonacept resulted in rapid resolution of pericarditis and a lower risk of recurrence

Rilonacept in Recurrent Pericarditis

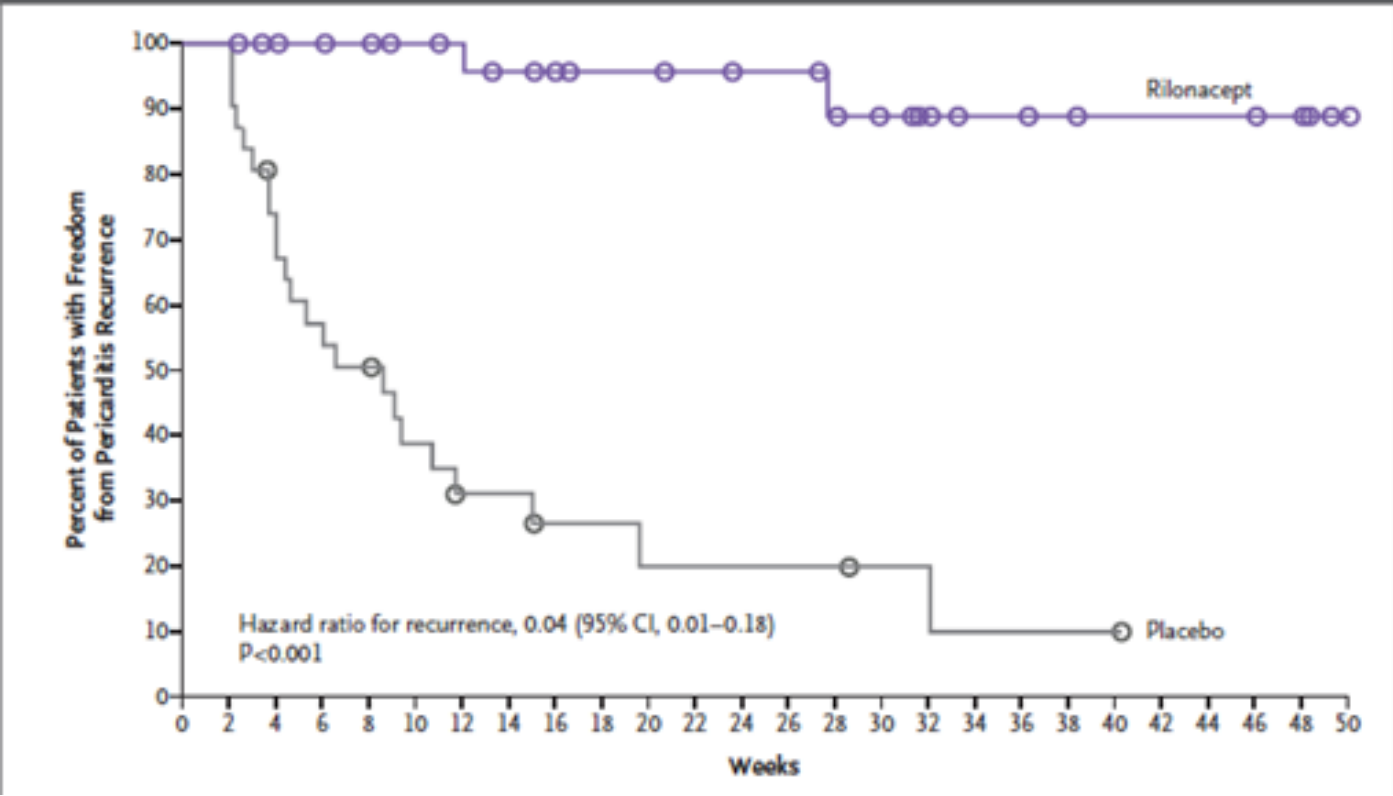


RHAPSODY

RILONACEPT INHIBITION OF IL-1 ALPHA AND BETA
FOR RECURRENT PERICARDITIS: A PIVOTAL
SYMPTOMATOLOGY AND OUTCOMES STUDY

- Phase 3, double-blind, placebo controlled, randomized withdrawal trial with an open-label extension
- Primary outcome measure was time to pericarditis recurrence in the randomized withdrawal period
- Secondary outcome measures were the proportion of patients maintaining clinical response and percentage of days with no or minimal pericarditis pain
- A total of 86 patients with symptomatic pericarditis recurrence were enrolled and received trial treatment for 16 weeks

Time to First Pericarditis Recurrence



Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases (RMD)

Expanded indications for specific vaccines in patients with RMDs on immunosuppression

- For RMD patients aged ≥ 65 years, and RMD patients aged >18 and <65 years who are on immunosuppressive medication, giving high-dose or adjuvanted influenza vaccination is conditionally recommended over giving regular-dose influenza vaccination.
- For patients with RMD aged <65 years who are on immunosuppressive medication, pneumococcal vaccination is strongly recommended.
- For patients with RMD aged >18 years who are on immunosuppressive medication, administering the recombinant zoster vaccine is strongly recommended.
- For patients with RMD aged >26 and <45 years who are on immunosuppressive medication and not previously vaccinated, vaccination against HPV is conditionally recommended.

Medication management at the time of non-live attenuated vaccine administration

	Influenza vaccination	Other non-live attenuated vaccinations
Methotrexate	Hold methotrexate for 2 weeks <i>after</i> vaccination*	Continue methotrexate
Rituximab	Continue rituximab**	Time vaccination for when the next rituximab dose is due, and then hold rituximab for at least 2 weeks after vaccination
Immunosuppressive medications other than methotrexate and rituximab	Continue immunosuppressive medication	Continue immunosuppressive medication

*Hold only if disease activity allows. Non-rheumatology providers, e.g., general pediatricians and internists, are encouraged to give the influenza vaccination and then consult with the patient's rheumatology provider about holding methotrexate to avoid a missed vaccination opportunity.

**Give influenza vaccination on schedule. Delay any subsequent rituximab dosing for at least 2 weeks after influenza vaccination if disease activity allows.


Whether to give or defer non-live attenuated vaccinations in patients taking glucocorticoids, regardless of disease activity

	Influenza vaccination	Other non-live attenuated vaccinations
Prednisone \leq 10 mg daily*	Give	Give
Prednisone $>$ 10 mg and $<$ 20 mg*	Give	Give
Prednisone \geq 20 mg daily*	Give	Defer**

*Or the equivalent dose of any other glucocorticoid formulation, or the equivalent pediatric dose

**Defer vaccination until glucocorticoids are tapered to the equivalent of prednisone $<$ 20 mg daily

 = Strong recommendation

 = Conditional recommendation

2022 American College of Rheumatology (ACR) Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases (RMD)

Immunosuppressive medication management at the time of live-attenuated virus vaccine administration

Immunosuppressive medication	Hold before live-attenuated virus vaccine administration	Hold after live-attenuated virus vaccine administration
Glucocorticoids ^a	4 weeks	4 weeks
Methotrexate, azathioprine ^b	4 weeks	4 weeks
Leflunomide, mycophenolate mofetil, calcineurin inhibitors, oral cyclophosphamide	4 weeks	4 weeks
JAK inhibitors	1 week	4 weeks
TNF, IL17, IL12/23, IL23, BAFF/BlyS inhibitors	1 dosing interval ^c	4 weeks
IL6 pathway inhibitors	1 dosing interval ^d	4 weeks

2022 American College of Rheumatology (ACR) Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases (RMD)

Immunosuppressive medication management at the time of live-attenuated virus vaccine administration

Immunosuppressive medication	Hold before live-attenuated virus vaccine administration	Hold after live-attenuated virus vaccine administration
IL1 inhibitors		
Anakinra	1 dosing interval ^d	4 weeks
Rilonacept	1 dosing interval ^d	4 weeks
Canakinumab	1 dosing interval ^d	4 weeks
Abatacept	1 dosing interval ^e	4 weeks
Anifrolumab	1 dosing interval ^e	4 weeks
Cyclophosphamide IV	1 dosing interval ^e	4 weeks
Rituximab	6 months	4 weeks
IVIg ^a		
300-400 mg/kg	8 months	4 weeks
1 gm/kg	10 months	4 weeks
2 gm/kg	11 months	4 weeks

2022 American College of Rheumatology (ACR) Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases (RMD)

Immunosuppressive medication management at the time of live-attenuated virus vaccine administration

a for patients taking the equivalent of prednisone < 20 mg/day or < 2 mg/kg/day for patients weighing < 10 kg, or alternate-day glucocorticoid therapy (i.e., “low level immunosuppression”), these low doses can be continued if vaccination is critical and the risk of a disease flare or adrenal insufficiency off glucocorticoids is high.

b for patients taking methotrexate ≤ 0.4 mg/kg/week or azathioprine ≤ 3 mg/kg/day (“low level” immunosuppression”) hold times can be shortened if vaccination is critical and the risk of a disease flare off immunosuppression is high.

c for medications with more than one FDA-approved dosing interval, the longest interval should be chosen (e.g., hold subcutaneous adalimumab for 2 weeks although it can be dosed every 1 or every 2 weeks).

d In children with autoinflammatory disorders or systemic juvenile idiopathic arthritis in whom the risk of disease flare if biologic DMARDs are held is very high, shorter hold times can be considered if live-attenuated vaccination is critical.

e the recommendation to hold IVIG prior to vaccination is designed to enhance vaccine efficacy, not safety. In some situations, such as during a measles outbreak, earlier vaccination would be preferred over delay.

ACR Guideline for Vaccinations in RMD 2022. Available at:

<https://www.rheumatology.org/Portals/0/Files/Vaccinations-Guidance-Summary.pdf>

COVID19: Pre-exposure prophylaxis in patients with rheumatic diseases

- Outcomes of SARS-CoV2 infection worst in patients with rheumatic diseases
- Individuals on mycophenolate, glucocorticoids and B-cell depleting therapy exhibited decreased antibody responses to the vaccine
 - Blood samples: chronic inflammatory disease vs. healthy control
 - Collected before 1st immunization and 1–2 weeks after their second
 - Analyzed magnitude and efficacy of humoral immune response after vaccination using serum anti-SARS-CoV-2 spike (anti-S) IgG binding and neutralizing antibody titers

	Chronic inflammatory disease independent of medication	Mycophenolate mofetil (CellCept)	Glucocorticoids (methylprednisolone, hydrocortisone etc.)	B-Cell Depleting Agents (rituximab, ocrelizumab)
Decrease in antibodies vs. control	3-fold	21-fold	9-fold	57-fold

Jena et al. *Autoimmun Rev.* 2022;21(1):102927.

Conway et al. *Arthritis Rheumatol.* 2022;74(5):766-775.

What is Evusheld?

- A combination of 2 different monoclonal antibodies:
 - Tixagevimab
 - Cilgavimab
- SARS-CoV-2 spike protein-directed attachment inhibitors.
- Recombinant human IgG1k antibodies with amino acid substitutions to extend the half-life, reduce antibody effector function, and decrease the risk of antibody-dependent enhancement of disease.
- Other antibodies have been used for treatment, but **Evusheld is the only one approved for pre-exposure prophylaxis and the only one with an affect against Omicron**

Indication

Moderate to severe immunocompromised individuals that can't receive the vaccine or may have an inadequate immune response to vaccination that:

1. Are not currently infected with COVID-19
2. Have not had a known recent exposure

Moderately/Severely Immunocompromising Conditions:

- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection
- Receipt of CAR T-cell therapy or hematopoietic cell transplant within previous 2 years
- Active treatment for a solid tumor or hematologic malignancy
- Use of immunosuppressive therapy after a solid organ transplant
- Active treatment with other immunosuppressive or immune-modulatory drugs

Dosage and Administration



- Two separate consecutive IM injections
- Come in cartons containing a vial of tixagevimab (150 mg/1.5 mL) and a vial of cilgavimab (150 mg/1.5 mL)

Storage: refrigerated and protected from light

- Preservative free and if immediate administration isn't possible syringes may be stored in the refrigerator or at room temperature for no longer than 4 hours from vial puncture

- **Administration:** gluteal muscle (one on each side consecutively)
- **Those that receive the vaccine:** Administered at least 2 weeks after the vaccine, but patients don't have to wait after administration of Evusheld to receive the vaccine

Dosage:

- Initially EVUSHELD dose was 150 mg of tixagevimab and 150 mg of cilgavimab, but because of reduced neutralization ability against the Omicron variant the dose was increased to 300 mg of tixagevimab and 300 mg of cilgavimab
- No recommendation for repeat dosing (has shown to last about 6 months but may vary depending on the variant)

Contraindications and Warnings

Contraindications: Severe hypersensitivity reactions to any component

-Clinically monitor individuals and observe for at least 1 h after administration

Warnings and Precautions:

- Thrombocytopenia or coagulation disorder (IM injection)
- Cardiovascular Events

Pre-Screening: cardiovascular risk factors and underlying cardiovascular disease

American College of Rheumatology Recommendations

1. All patients, especially immunocompromised patients, are encouraged to be vaccinated. As of right now vaccination remains the best defense against severe symptoms, hospitalization, and death.
2. Moderate to severe immunocompromised patients are eligible for Evusheld and should be actively considered for pre-exposure prophylaxis, however a guideline on appropriate use is still in development.
3. Allocation of resources may be needed and prioritization of the most severely immunocompromised individuals, like those on rituximab, mycophenolate, and high dose corticosteroids, should be considered first.

Nirmatrelvir/ritonavir (Paxlovid)**Molnupiravir (Lagevrio)****MOA**

Nirmatrelvir: SARS-CoV-2 main protease inhibitor
Inhibits mPRO, preventing viral replication

Ribonucleoside analogue. Viral lethal mutagenesis. Inhibits SARS-CoV-2 replication

Ritonavir: HIV-1 protease inhibitor & CYP3A inhibitor. Prolongs the half-life of nirmatrelvir

Indication

At risk patients with mild-moderate COVID-19 (outpatient)

At risk patients with mild-moderate COVID-19 (outpatient)

Age limit

Must be 12 years or older

Must be 18 years or older

Weight Limit

Must be 40 kg or more

None stated

Need Positive

Yes

Yes

Direct SARS-CoV-2 Test?**When to Start**

Within 5 days symptom onset

Within 5 days symptom onset

Dose

300 mg nirmatrelvir with 100 mg ritonavir (3 pills per dose) every 12 hours [eGFR \geq 60 mL/min]

800 mg (4 pills per dose) every 12 hours

Duration of Therapy

5 days

5 days

	Nirmatrelvir/ritonavir (Paxlovid)	Molnupiravir (Lagevrio)
Renal Dose Adjustment	For eGFR \geq 30 to < 60: 150 mg nirmatrelvir with 100 mg ritonavir (2 pills per dose) eGFR < 30 mL/min: avoid use	None
Hepatic Dose Adjustment	Avoid in severe hepatic impairment (Child-Pugh Class C)	None
Contraindications	Hypersensitivity to ingredients Use with certain drugs that have CYP3A4 interactions	None listed
Warnings	<ul style="list-style-type: none"> • Drug interactions (CYP3A4) • Hepatotoxicity • HIV-1 drug resistance in patients with HIV-1 infection 	<ul style="list-style-type: none"> • Embryo-fetal toxicity • Bone and cartilage toxicity (may affect bone and cartilage growth) • Hypersensitivity reactions
Common side effects	<ul style="list-style-type: none"> • Dysgeusia, diarrhea, hypertension, myalgia 	<ul style="list-style-type: none"> • Diarrhea, nausea, dizziness

Nirmatrelvir/ritonavir (Paxlovid)

Molnupiravir (Lagevrio)

Pregnancy/ breastfeeding

- No human data on use
- Risk in pregnancy may outweigh the potential risks
- Must use effective barrier contraception or abstain from sexual activity (hormonal contraceptive may have decreased efficacy while on Paxlovid)

- Not recommended in pregnancy or breastfeeding. Animal studies showed fetal harm. No studies in humans
- Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose
- Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose
- There is a surveillance program should molnupiravir be used in this population

Drug interactions

- Multiple identified due to ritonavir inhibition of CYP3A4
- <https://www.covid19-druginteractions.org/checker>
- <https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/>
- None identified

Treatment efficacy per clinical trials

- 88% reduction in hospitalizations/deaths (95% CI: 75%, 94%)
- <https://www.nejm.org/doi/full/10.1056/NEJMoa2118542>
- <https://www.fda.gov/media/155050/download>
- 30% reduction in hospitalizations/deaths (95% CI: 1%, 51%)
- <https://www.nejm.org/doi/full/10.1056/NEJMoa2116044>
- <https://www.fda.gov/media/155054/download>

Thank You