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Αθηνών

How to read and interpret clinical trials in systemic autoimmunity

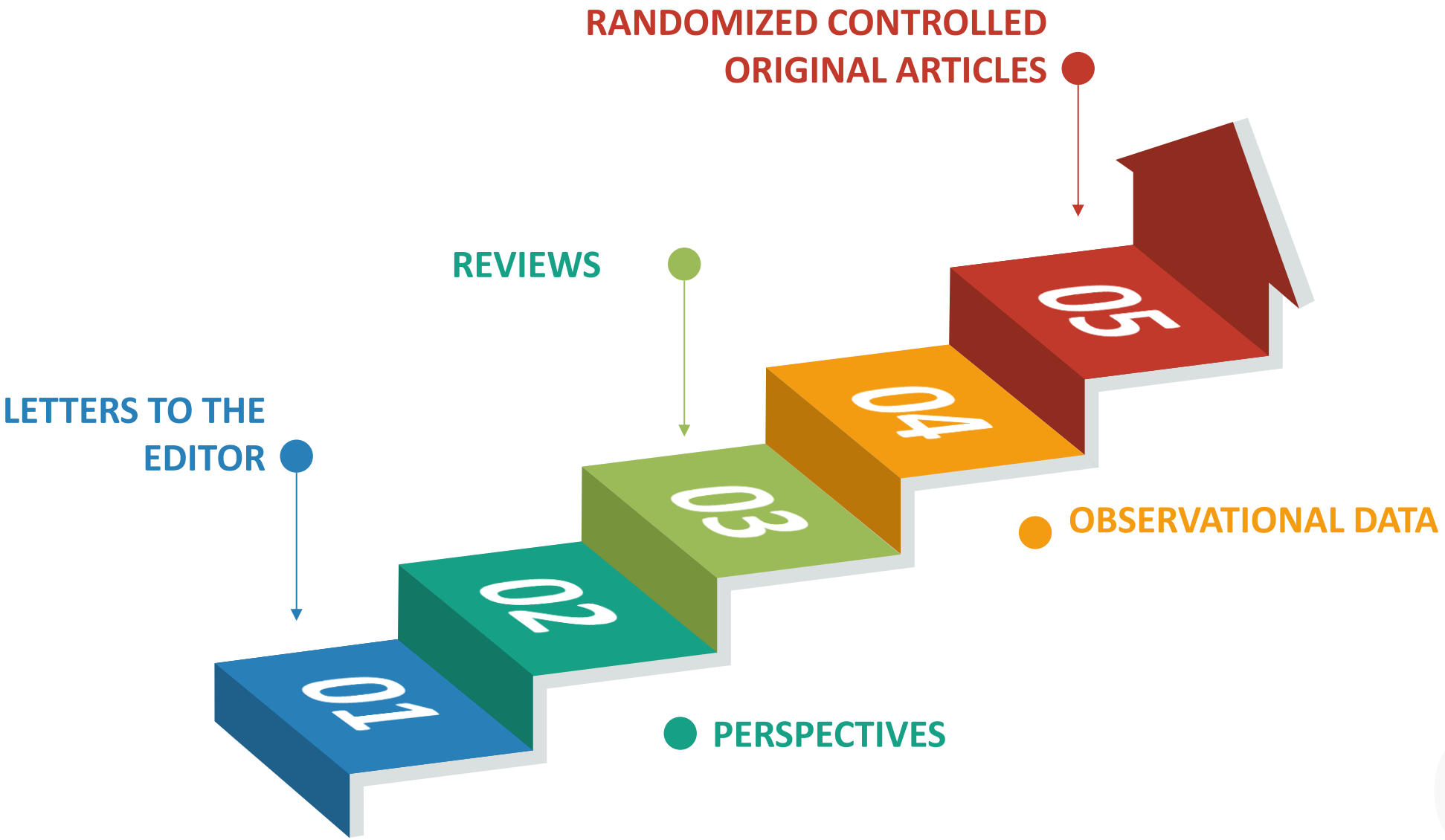
Loukas Chatzis

Academic fellow
Department of Pathophysiology
Laiko General Hospital

Disclosure

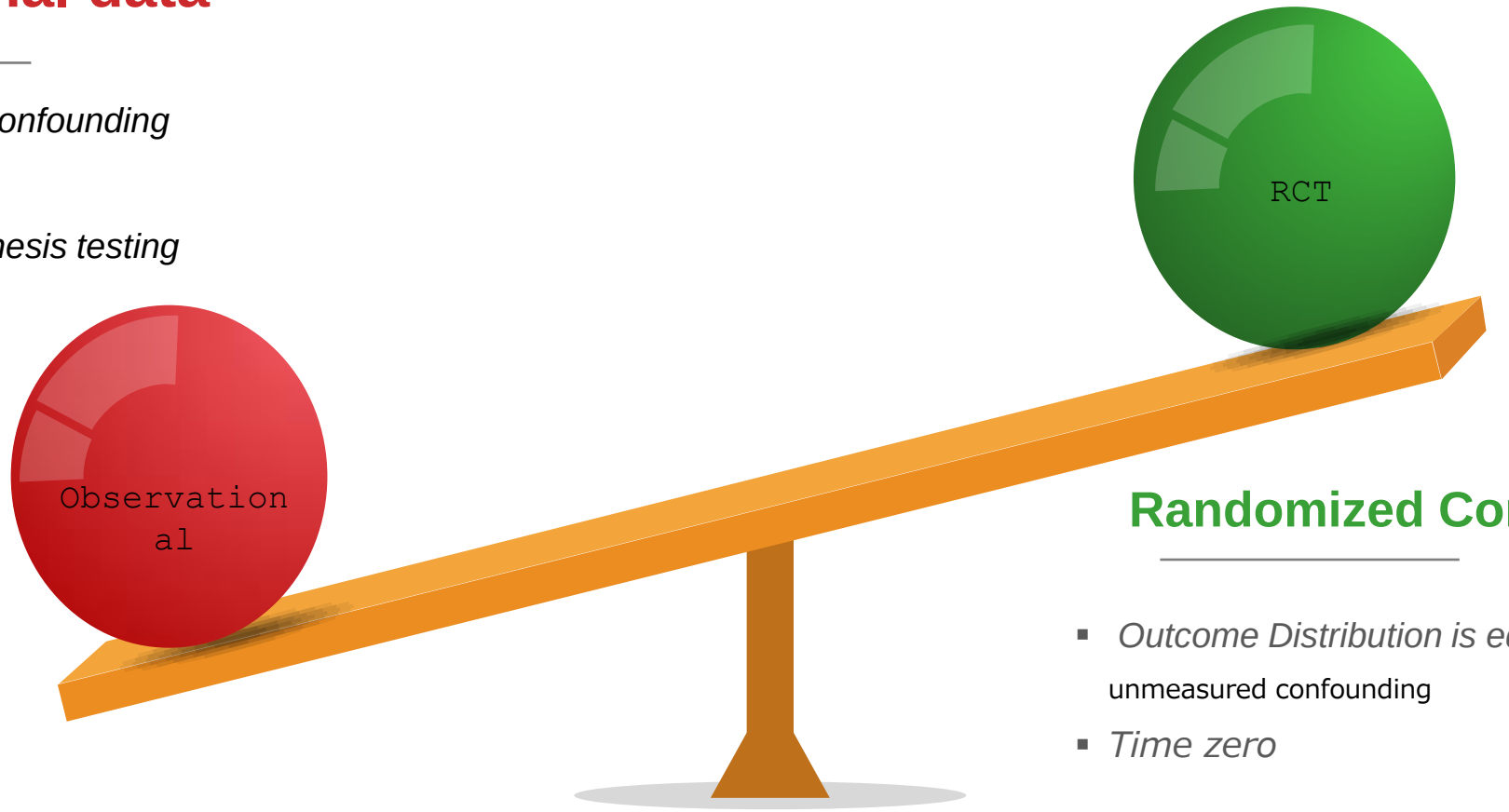
This is not evidence based

SKIM THROUGH THE LITERATURE



Observational data

- *Unmeasured confounding*
- *Immortal bias*
- *Multiple hypothesis testing*



Randomized Controlled trials

- *Outcome Distribution is equilibrated (*controls for unmeasured confounding
- *Time zero*

Whenever I read a trial

- Is it a phase II or a phase III clinical trial?

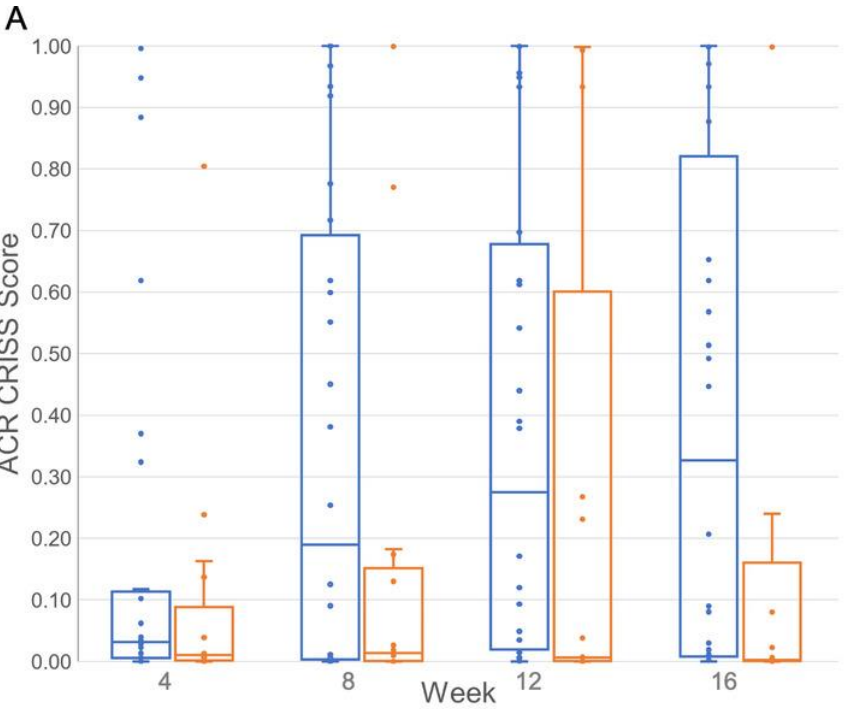
✓The lenabasum example

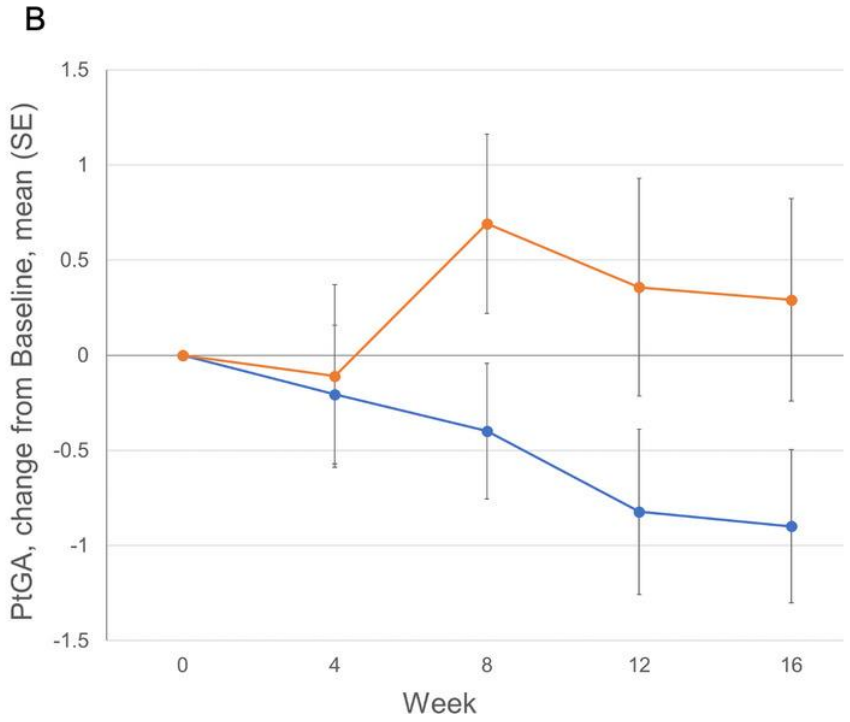
Arthritis&Rheumatology
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

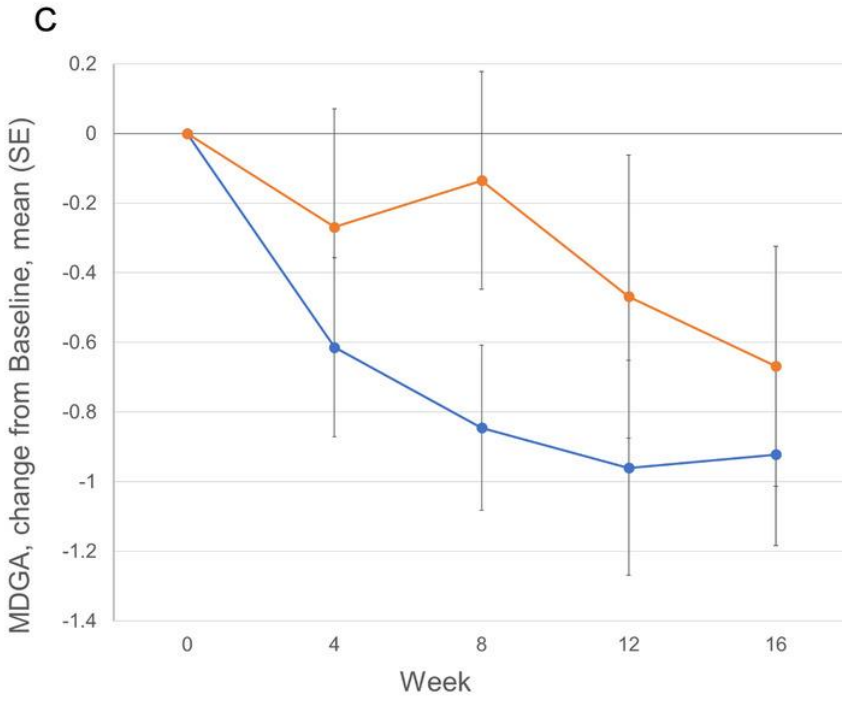
Original Article | Open Access

Safety and Efficacy of Lenabasum in a Phase II, Randomized, Placebo-Controlled Trial in Adults With Systemic Sclerosis

Robert Spiera, Laura Hummers, Lorinda Chung, Tracy M. Frech, Robyn Domsic, Vivien Hsu, Daniel E. Furst, Jessica Gordon, Maureen Mayes, Robert Simms, Robert Lafyatis ... See all authors







✓The lenabasum example

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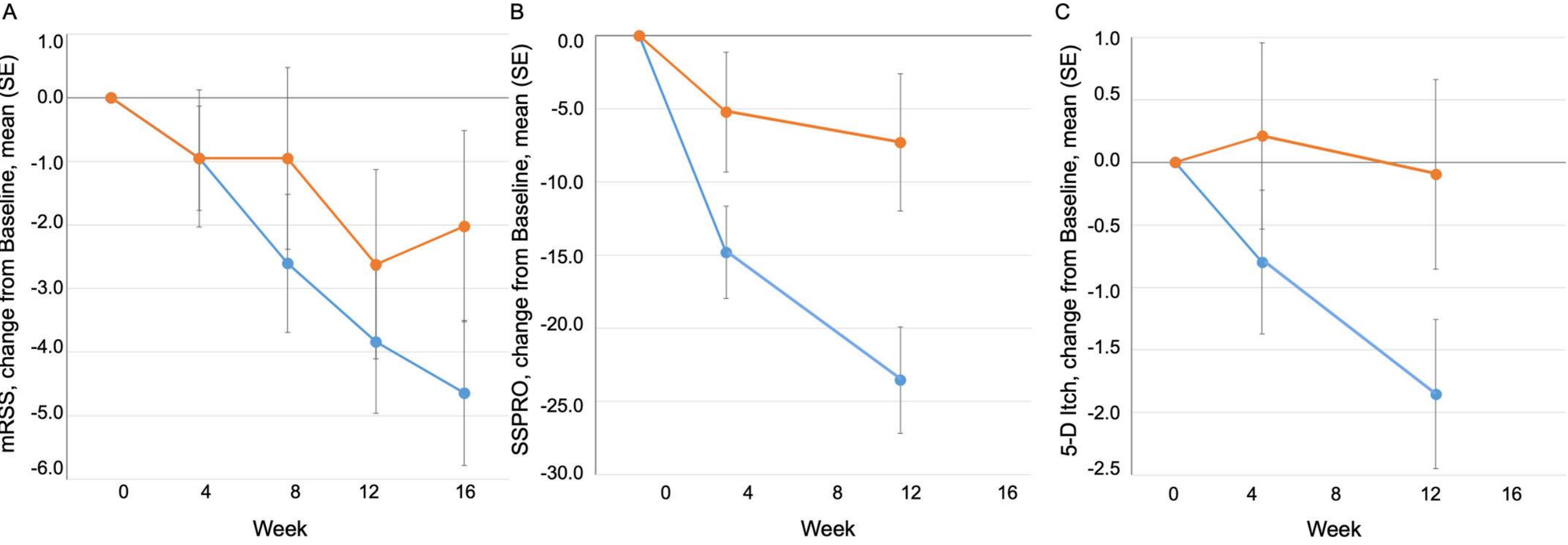

✓The lenabasum example

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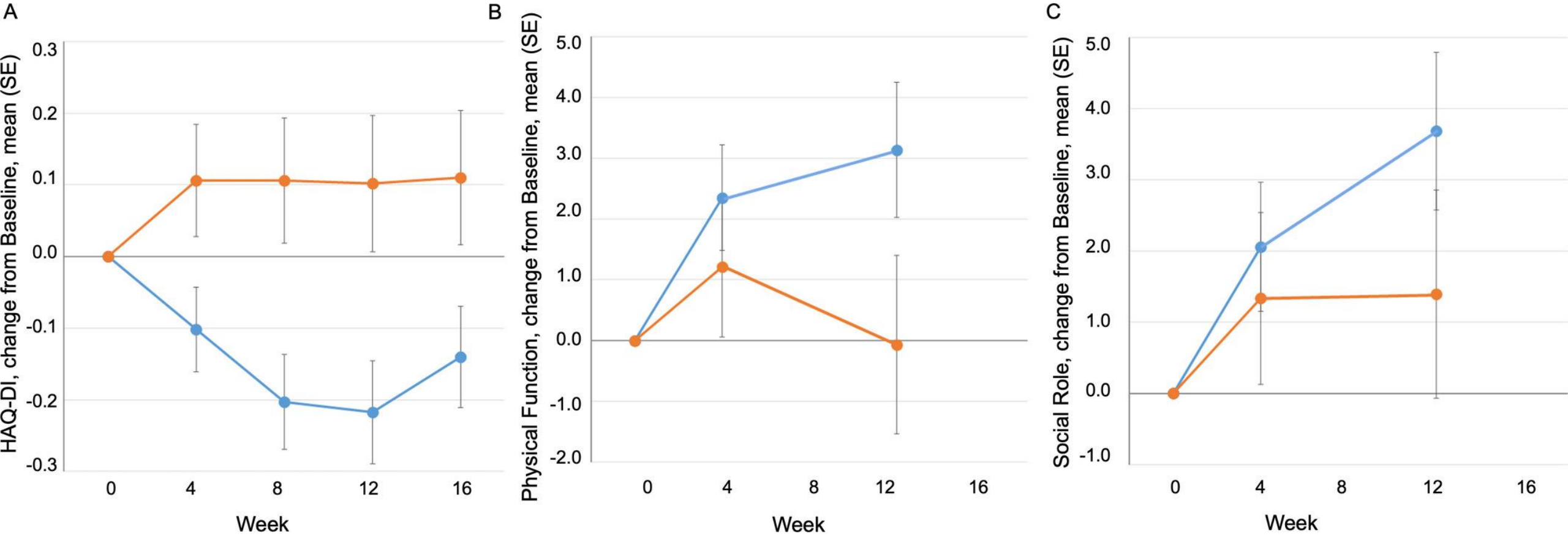


✓The lenabasum phase 3 study is completely negative

Arthritis&Rheumatology
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

Full Length | Open Access

Efficacy and Safety of Lenabasum, a Cannabinoid Type 2 Receptor Agonist, in a Phase 3 Randomized Trial in Diffuse Cutaneous Systemic Sclerosis

Robert Spiera, Masataka Kuwana, Dinesh Khanna, Laura Hummers, Tracy M. Frech, Wendy Stevens, Marco Matucci-Cerinic, Suzanne Kafaja, Oliver Distler, Jae-Bum Jun, Yair Levy ... See all authors

Table 2. ACR CRISS score and its core items at week 52 by cohort, mITT population, phase 3 RESOLVE-1 clinical trial*

Efficacy end point	Lenabasum 20 mg (n = 99–100)	Lenabasum 5 mg (n = 111–113)	Placebo (n = 112–115)
ACR CRISS score, median (IQR)	0.8880 (0.0610–0.9970)	0.8270 (0.0700–0.9880)	0.8870 (0.0710–0.990)
P versus placebo, ranked score, MMRM	0.4972	0.3486	
Change in MRSS, mean ± SD	−6.7 ± 6.59	−7.1 ± 6.24	−8.1 ± 7.72
P versus placebo, MMRM	0.1183	0.5036	–
Change in FVC%, mean ± SD	−1.6 ± 6.9	−2.2 ± 6.2	−1.0 ± 8.7
P versus placebo, MMRM	0.539	0.516	–
Change in HAQ DI, mean ± SD	−0.13 ± 0.44	−0.06 ± 0.39	−0.13 ± 0.47
P versus placebo, MMRM	0.745	0.322	–
Change in MDGA, mean ± SD	−1.7 ± 1.7	−1.9 ± 1.9	−1.8 ± 1.7
P versus placebo, MMRM	0.649	0.406	–
Change in PtGA, mean ± SD	−1.4 ± 2.7	−0.3 ± 2.4	−1.1 ± 2.2
P versus placebo, MMRM	0.598	0.015	–

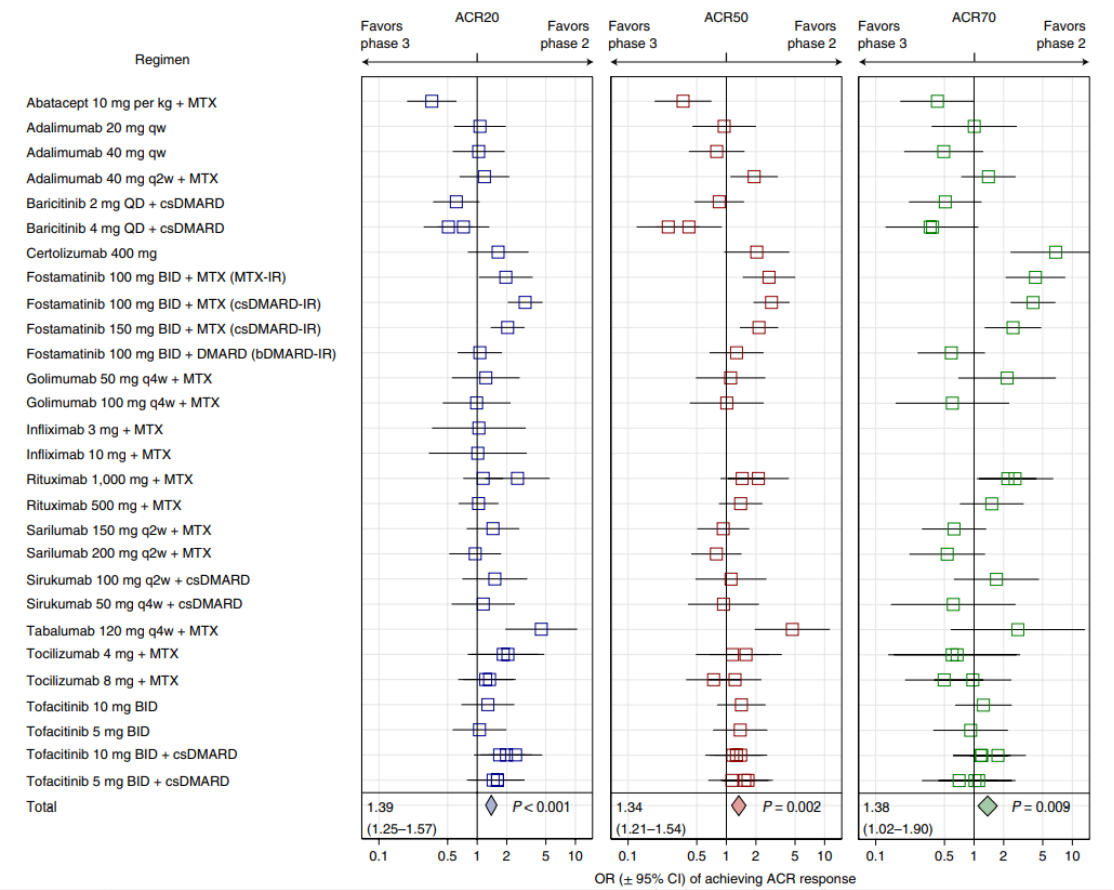
* ACR = American College of Rheumatology; CRISS = combined response index in diffuse cutaneous systemic sclerosis (dcSSc); IQR = interquartile range; MMRM = mixed models for repeated measures; MDGA = physician global assessment of health related to dcSSc; PtGA = patient global assessment of health related to dcSSc (see Table 1 for other definitions).

ANALYSIS
https://doi.org/10.1038/s41591-020-0833-4
nature medicine

Check for updates

Efficacy outcomes in phase 2 and phase 3 randomized controlled trials in rheumatology

Andreas Kerschbaumer[1], Josef S. Smolen[1], Harald Herkner[2], Tijen Stefanova[1], Eva Chwala[3] and Daniel Aletaha[1]✉

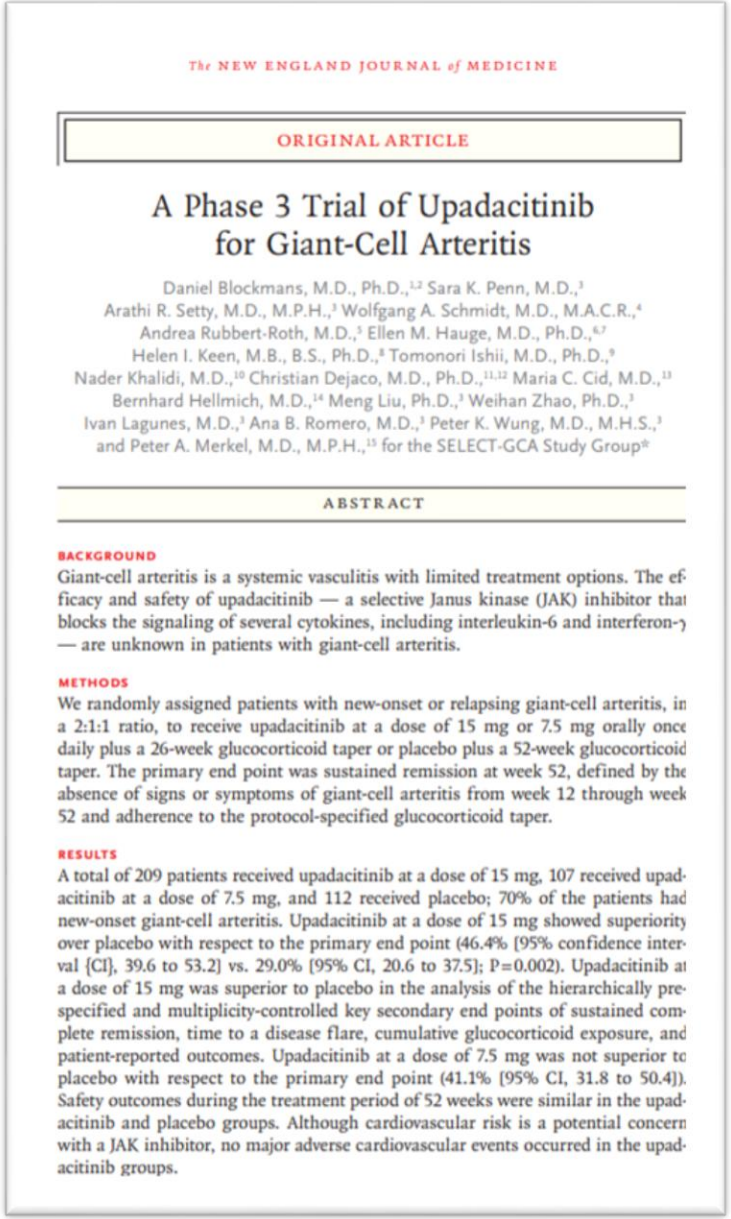


Select GCA paradigm

- No Phase 2 study.
- No observational data.
- No case reports!

April 08, 2025

AbbVie Announces European Commission Approval of RINVOQ® (upadacitinib) for the Treatment of Adults with Giant Cell Arteritis



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Upadacitinib for Giant-Cell Arteritis

Daniel Blockmans, M.D., Ph.D.,[1,2] Sara K. Penn, M.D.,[3] Arathi R. Setty, M.D., M.P.H.,[3] Wolfgang A. Schmidt, M.D., M.A.C.R.,[4] Andrea Rubbert-Roth, M.D.,[5] Ellen M. Hauge, M.D., Ph.D.,[6,7] Helen I. Keen, M.B., B.S., Ph.D.,[8] Tomonori Ishii, M.D., Ph.D.,[9] Nader Khalidi, M.D.,[10] Christian Dejaco, M.D., Ph.D.,[11,12] Maria C. Cid, M.D.,[13] Bernhard Hellmich, M.D.,[14] Meng Liu, Ph.D.,[3] Weihan Zhao, Ph.D.,[3] Ivan Lagunes, M.D.,[3] Ana B. Romero, M.D.,[3] Peter K. Wung, M.D., M.H.S.,[3] and Peter A. Merkel, M.D., M.P.H.,[15] for the SELECT-GCA Study Group*

ABSTRACT

BACKGROUND

Giant-cell arteritis is a systemic vasculitis with limited treatment options. The efficacy and safety of upadacitinib — a selective Janus kinase (JAK) inhibitor that blocks the signaling of several cytokines, including interleukin-6 and interferon-γ — are unknown in patients with giant-cell arteritis.

METHODS

We randomly assigned patients with new-onset or relapsing giant-cell arteritis, in a 2:1:1 ratio, to receive upadacitinib at a dose of 15 mg or 7.5 mg orally once daily plus a 26-week glucocorticoid taper or placebo plus a 52-week glucocorticoid taper. The primary end point was sustained remission at week 52, defined by the absence of signs or symptoms of giant-cell arteritis from week 12 through week 52 and adherence to the protocol-specified glucocorticoid taper.

RESULTS

A total of 209 patients received upadacitinib at a dose of 15 mg, 107 received upadacitinib at a dose of 7.5 mg, and 112 received placebo; 70% of the patients had new-onset giant-cell arteritis. Upadacitinib at a dose of 15 mg showed superiority over placebo with respect to the primary end point (46.4% [95% confidence interval {CI}, 39.6 to 53.2] vs. 29.0% [95% CI, 20.6 to 37.5]; P=0.002). Upadacitinib at a dose of 15 mg was superior to placebo in the analysis of the hierarchically prespecified and multiplicity-controlled key secondary end points of sustained complete remission, time to a disease flare, cumulative glucocorticoid exposure, and patient-reported outcomes. Upadacitinib at a dose of 7.5 mg was not superior to placebo with respect to the primary end point (41.1% [95% CI, 31.8 to 50.4]). Safety outcomes during the treatment period of 52 weeks were similar in the upadacitinib and placebo groups. Although cardiovascular risk is a potential concern with a JAK inhibitor, no major adverse cardiovascular events occurred in the upadacitinib groups.

Whenever I read a trial

- Is it a phase II or a phase III clinical trial?
- What did they do?

✓Why? Goals/ Hypothesis

No disease modifying treatment for SjD

1. Efficacy
2. Safety

OPEN ACCESS

CLINICAL SCIENCE

Efficacy and safety of abatacept in active primary Sjögren's syndrome: results of a phase III, randomised, placebo-controlled trial

Alan N Baer [1], Jacques-Eric Gottenberg [2], E William St Clair [3], Takayuki Sumida [4], Tsutomu Takeuchi [5], Raphaèle Seror [6], Gary Foulks [7], Marleen Nys [8], Sumanta Mukherjee, Robert Wong [10], Neelanjana Ray [11], Hendrika Bootsma [12]

ABSTRACT

Objectives To evaluate efficacy and safety of abatacept in adults with active primary Sjögren's syndrome (pSS) in a phase III, randomised, double-blind, placebo-controlled trial.

Methods Eligible patients (moderate-to-severe pSS [2016 ACR/European League Against Rheumatism (EULAR) criteria], EULAR Sjögren's Syndrome Disease Activity Index [ESSDAI] ≥5, anti-SS-related antigen A/anti-Ro antibody positive) received weekly subcutaneous abatacept 125 mg or placebo for 169 days followed by an open-label extension to day 365. Primary endpoint was mean change from baseline in ESSDAI at day 169. Key secondary endpoints were mean change from baseline in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and stimulated whole salivary flow (SWSF at day 169. Other secondary clinical endpoints included glandular functions and patient-reported outcomes. Selected biomarkers and immune cell phenotypes were examined. Safety was monitored.

✓Why? Goals/ Hypothesis

1. No disease modifying treatment for Osteoarthritis
2. No reason to think that the pleiotropic effects of metformin would affect cartilage
3. Tiny trial
4. Completely subjective endpoint measured in a soft way
5. No control for weight loss
6. Approach with a Bayesian perspective

Preliminary Communication

Metformin for Knee Osteoarthritis in Patients With Overweight or Obesity

A Randomized Clinical Trial

Feng Pan, PhD[1,2]; Yuanyuan Wang, PhD[1]; Yuan Z. Lim, PhD[1,3] ; et al

» Author Affiliations | Article Information

RELATED ARTICLES

OBJECTIVE To evaluate the effects of metformin on knee pain at 6 months in participants with symptomatic knee osteoarthritis and overweight or obesity.

DESIGN, SETTING, AND PARTICIPANTS Community-based randomized, parallel-group, double-blind, placebo-controlled clinical trial that used telemedicine to recruit and follow up participants remotely. Individuals with knee pain for 6 months or longer, a pain score greater than 40 mm on a 100-mm visual analog scale (VAS), and body mass index of 25 or higher were recruited from the community through local and social media advertisements in Victoria, Australia, between June 16, 2021, and August 1, 2023. Final follow-up occurred on February 8, 2024.

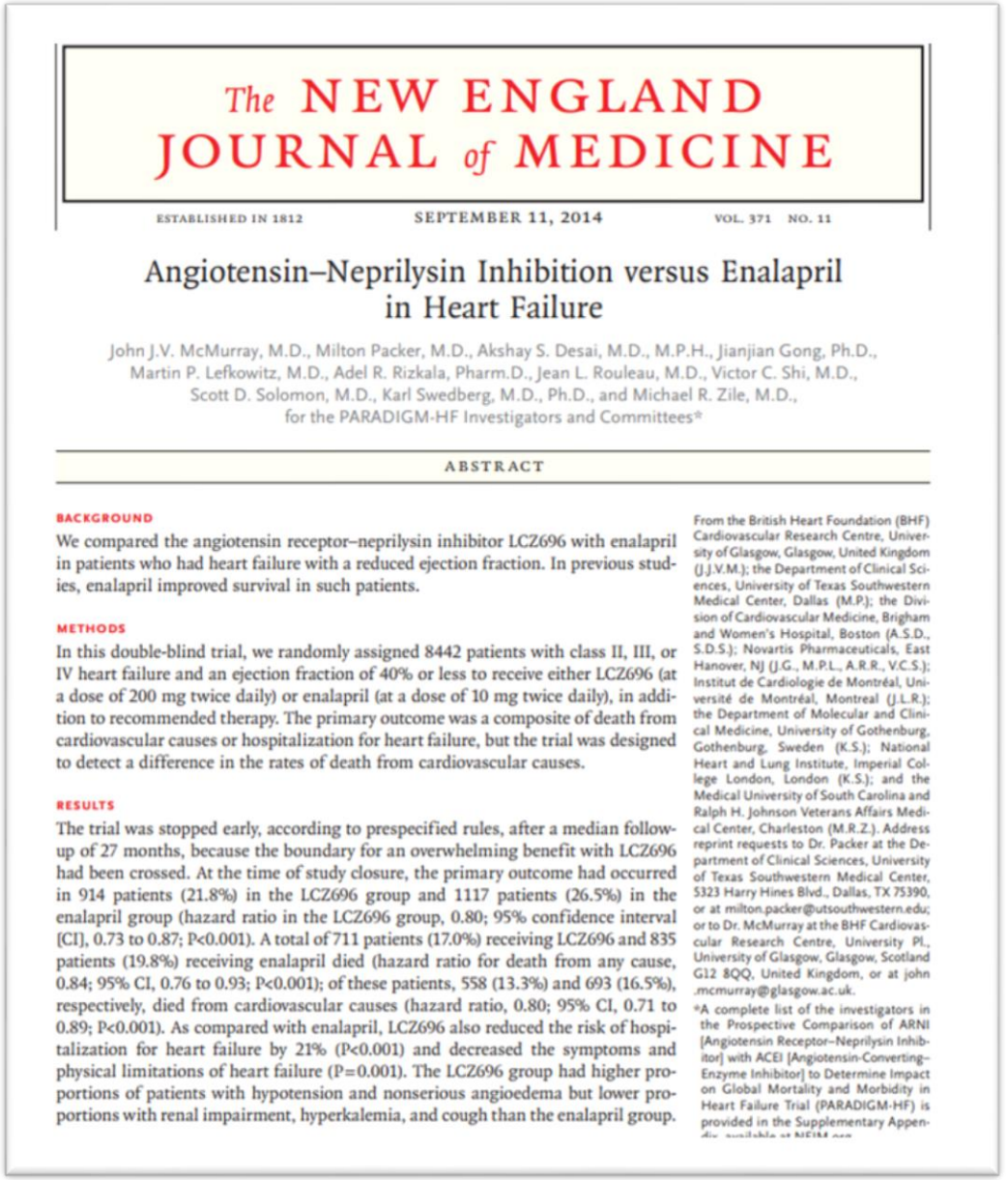
INTERVENTIONS Participants were randomly assigned to receive either oral metformin, 2000 mg/d (n = 54), or identical placebo (n = 53) for 6 months.

MAIN OUTCOMES AND MEASURES The primary outcome was change in knee pain, measured using a 100-mm VAS (score range, 0-100; 100 = worst; minimum clinically important difference = 15) at 6 months.

Whenever I read a trial

- Is it a phase II or a phase III clinical trial?
- What did they do?
- So its randomized, what is the control like?

So its randomized, what is the control like?



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

ABSTRACT

BACKGROUND

We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS

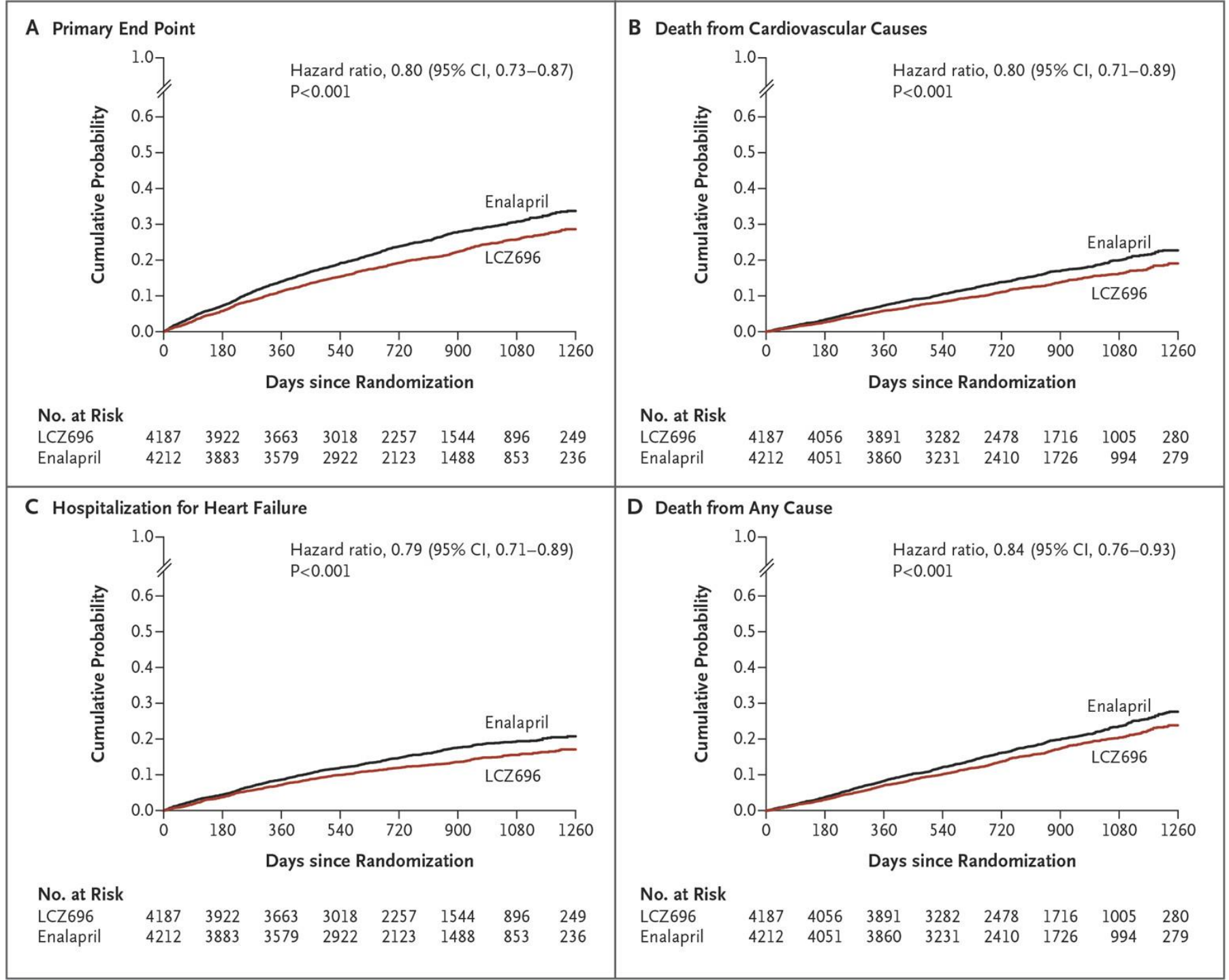
In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

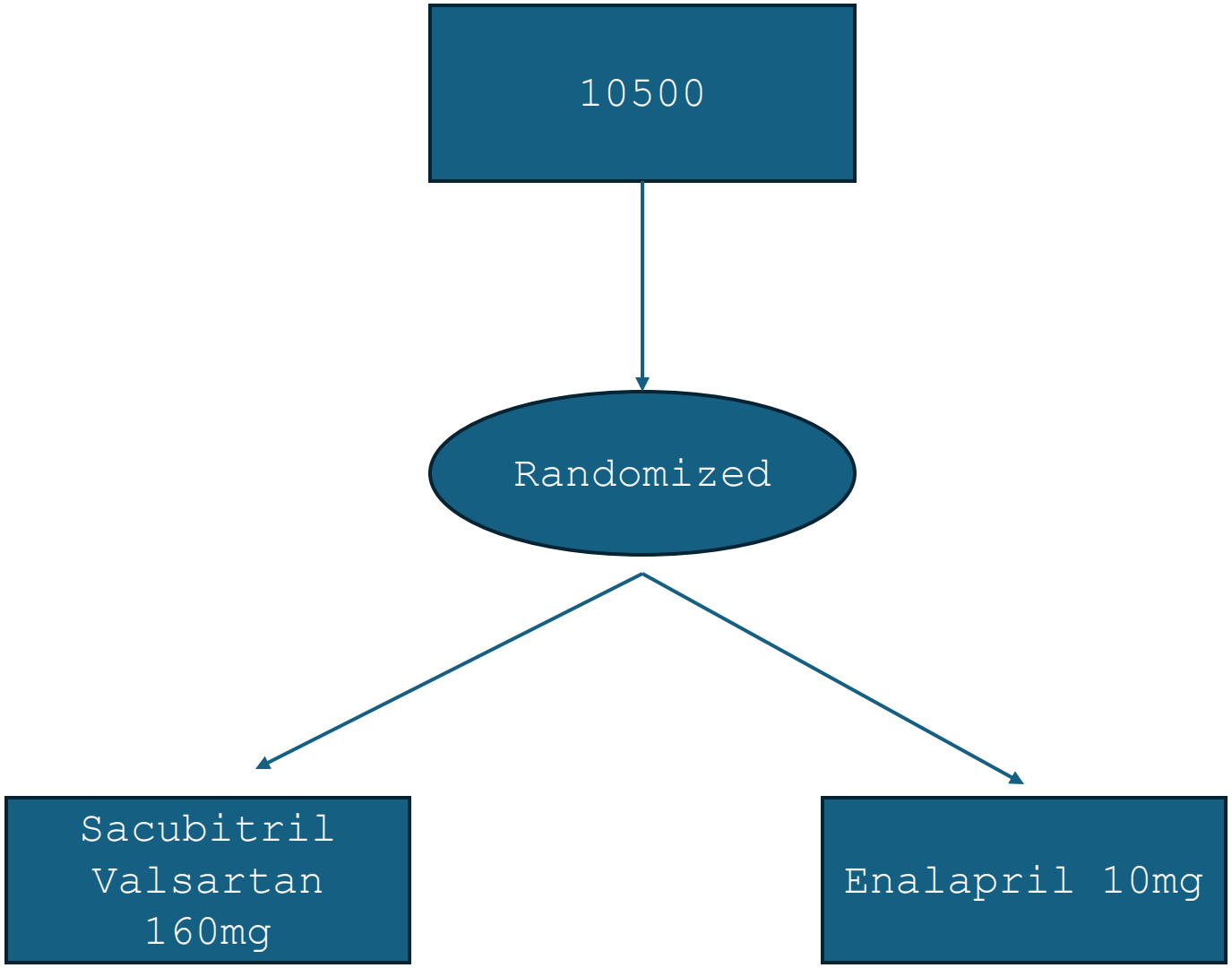
RESULTS

The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston (A.S.D., S.D.S.); Novartis Pharmaceuticals, East Hanover, NJ (J.G., M.P.L., A.R.R., V.C.S.); Institut de Cardiologie de Montréal, Université de Montréal, Montreal (J.L.R.); the Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden (K.S.); National Heart and Lung Institute, Imperial College London, London (K.S.); and the Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston (M.R.Z.). Address reprint requests to Dr. Packer at the Department of Clinical Sciences, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, or at milton.packer@utsouthwestern.edu; or to Dr. McMurray at the BHF Cardiovascular Research Centre, University Pl., University of Glasgow, Glasgow, Scotland G12 8QQ, United Kingdom, or at john.mcmurray@glasgow.ac.uk.

*A complete list of the investigators in the Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) is provided in the Supplementary Appendix, available at NEJM.org


A Primary End Point
Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001
Cumulative Probability
1.0
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Enalapril
LCZ696
0
180
360
540
720
900
1080
1260
Days since Randomization
No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236
B Death from Cardiovascular Causes
Hazard ratio, 0.80 (95% CI, 0.71–0.89)
P<0.001
Cumulative Probability
Enalapril
LCZ696
Days since Randomization
No. at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279
C Hospitalization for Heart Failure
Hazard ratio, 0.79 (95% CI, 0.71–0.89)
P<0.001
Cumulative Probability
Enalapril
LCZ696
Days since Randomization
No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236
D Death from Any Cause
Hazard ratio, 0.84 (95% CI, 0.76–0.93)
P<0.001
Cumulative Probability
Enalapril
LCZ696
Days since Randomization
No. at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279


10500
Randomized
Sacubitril Valsartan 160mg
Enalapril 10mg
Maximum FDA approved dose
Half the maximum FDA approved dose

Clinical Trial > Arthritis Res Ther. 2019 Aug 20;21(1):190. doi: 10.1186/s13075-019-1968-x.

Efficacy and safety of intravenous golimumab plus methotrexate in patients with rheumatoid arthritis aged < 65 years and those ≥ 65 years of age

John Tesser [1], Shelly Kafka [2], Raphael J DeHoratius [2 3], Stephen Xu [4], Elizabeth C Hsia [4 5], Anthony Turkiewicz [6]

Affiliations + expand

PMID: 31429794 PMCID: PMC6701065 DOI: 10.1186/s13075-019-1968-x

Trial Population: Adults with active RA despite MTX (stable regimen of 15–25 mg/week for ≥4 weeks) for 3 months

Trial Period: September, 2009 to March, 2011

Type of Control: placebo

For patients who had inadquate response to prior MTX and have high disease activity, the use of anti-TNF agents was recommended by 2008 ACR guidelines.

Clinical Trial > Lancet. 2020 Jan 4;395(10217):53-64. doi: 10.1016/S0140-6736(19)32971-X. Epub 2019 Dec 5.

Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial

Atul Deodhar [1], Désirée van der Heijde [2], Lianne S Gensler [3], Tae-Hwan Kim [4], Walter P Maksymowych [5], Mikkel Østergaard [6], Denis Poddubnyy [7], Helena Marzo-Ortega [8], Louis Bessette [9], Tetsuya Tomita [10], Ann Leung [11], Maja Hojnik [12], Gaia Gallo [12], Xiaoqi Li [12], David Adams [12], Hilde Carlier [12], Joachim Sieper [7]; COAST-X Study Group

Collaborators, Affiliations + expand

Trial Population: Active nr-axSpA patients aged ≥18 years, with an inadequate response to two or more NSAIDs or a history of intolerance of NSAIDs

Trial Period: August, 2016 to March, 2019

Type of Control: dose-response and placebo

In adults with active AS despite treatment with the first TNFi used, a different TNFi was recommended. ACR/SAA recommendation for the treatment of AS and nr-axSpA, 2015.

Clinical Trial > Ann Rheum Dis. 2022 Mar;81(3):351-358. doi: 10.1136/annrheumdis-2021-221048.
Epub 2021 Nov 23.

Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial

Andrew Östör [1], Filip Van den Bosch [2], Kim Papp [3], Cecilia Asnal [4], Ricardo Blanco [5], Jacob Aelion [6], Gabriela Alperovich [7], Wenjing Lu [7], Zailong Wang [7], Ahmed M Soliman [7], Ann Eldred [7], Lisa Barcomb [7], Alan Kivitz [8 9]

Affiliations + expand

PMID: 34815219 PMCID: PMC8862056 DOI: 10.1136/annrheumdis-2021-221048

Trial Population: Adults with active PsA, with inadequate response or intolerance to biological agents and/or inadequate response or intolerance to csDMARDs

Trial Period: March, 2019 to June, 2020

Type of Control: placebo

TNFi was recommended for the treatment of PsA patients with inadquate response to csDMARDs. In adult patients with active PsA despite treatment with a TNFi biologic monotherapy, switch to a different TNFi is

Clinical Trial > N Engl J Med. 2012 Dec 20;367(25):2396-406. doi: 10.1056/NEJMoa1205099.

Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis

Nicolino Ruperto [1], Hermine I Brunner, Pierre Quartier, Tamás Constantin, Nico Wulffraat, Gerd Horneff, Riva Brik, Liza McCann, Ozgur Kasapcopur, Lidia Rutkowska-Sak, Rayfel Schneider, Yackov Berkun, Inmaculada Calvo, Muferet Erguven, Laurence Goffin, Michael Hofer, Tilmann Kallinich, Sheila K Oliveira, Yosef Uziel, Stefania Viola, Kiran Nistala, Carine Wouters, Rolando Cimaz, Manuel A Ferrandiz, Berit Flato, Maria Luz Gamir, Isabelle Kone-Paut, Alexei Grom, Bo Magnusson, Seza Ozen, Flavio Sztajnbok, Karine Lheritier, Ken Abrams, Dennis Kim, Alberto Martini, Daniel J Lovell; PRINTO; PRCSG

Collaborators, Affiliations + expand

PMID: 23252526 DOI: 10.1056/NEJMoa1205099

Trial Population: Systemic JIA patients aged 2-19 years, with active systemic features and arthritis under the background therapy of a prednisone equivalent of up to 1.0 mg per kilogram per day and stable doses of NSAIDs and MTX.
Trial Period: July, 2009 to November, 2010

Type of Control: placebo

No validated guidelines offer recommendations for the treatment of JIA till 2011. Based on previous experience and limited evidence, glucocorticoids and csDMARDs, were always the first choice in treating SJIA. In cases of persisting disease activity beside combined therapy with glucocorticoids and csDMARDs, TNF

ARTICLES · Volume 7, Issue 9, E629-E641, September 2025 Download Full Issue

Dual JAK and ROCK inhibition with CPL'116 in patients with rheumatoid arthritis with inadequate response to methotrexate: a randomised, double-blind, placebo-controlled, phase 2 trial

Maciej Wieczorek, PhD [a] · Bartłomiej Kisiel, PhD, MD [b] · Dorota Włodarczyk, PhD [a] · Prof Piotr Leszczyński, MD [c] · Iryna V Kurylchyk, MD [d] · Ivan Vyshnyvetskyy, PhD, MD [e,f] · et al. Show more

Affiliations & Notes Article Info Linked Articles (1)

Trial Population: Moderate-to-severe rheumatoid arthritis for at least 6 months before screening, and inadequate response to current methotrexate treatment (oral or injected 15–25 mg once weekly, or ≥10 mg once weekly if reduced due to side-effects or intolerance)

Trial Period: May 2022, and Feb 2024

Type of Control: placebo

According to the EULAR Recommendations add a bDMARDS or JAKi or if poor prognostic factors are absent add a second convectional DMARD

From: **Control Groups in RCTs Supporting Approval of Drugs for Systemic Rheumatic Diseases, 2012-2022**

JAMA Netw Open. 2023;6(11):e2344767. doi:10.1001/jamanetworkopen.2023.44767

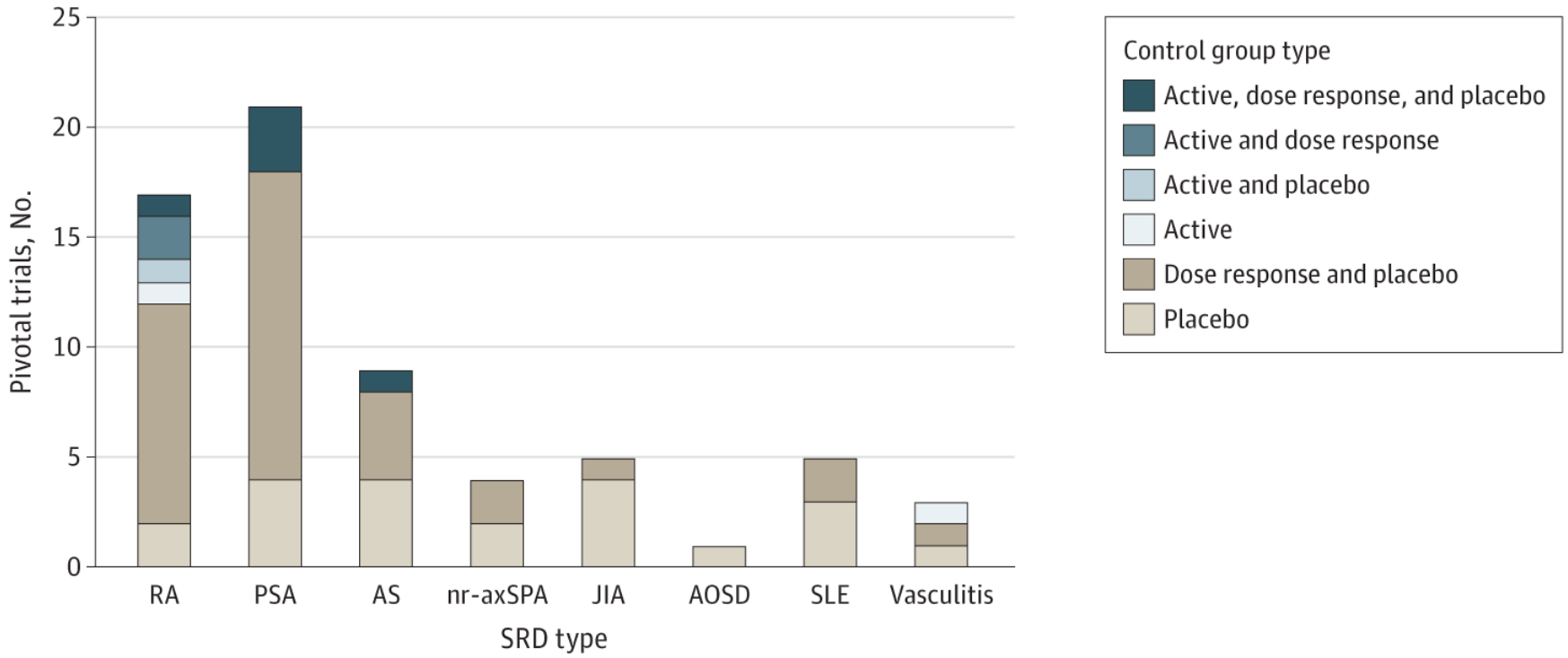


Figure Legend:

Pivotal Trials by Type of Control GroupAOSD indicates adult-onset Still disease; AS, ankylosing spondylitis; JIA, juvenile idiopathic arthritis; nr-axSPA, nonradiographic axial spondyloarthritis; PSA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SRD, systemic rheumatic disease.

Whenever I read a trial

- Is it a phase II or a phase III clinical trial?
- What did they do?
- So its randomized, what is the control like?
- Is the trial adequately powered?

Is the trial adequately powered

- Stick to the primary endpoint when you discuss a paper – take secondary endpoints with a grain of salt

1. Increased Risk of False Negatives (Type II Errors)
•An underpowered study may fail to detect a real effect because the sample size is too small to achieve statistical significance.
•This can result in misleading conclusions that no effect exists when one actually does.
2. Increased Risk of False Positives (Type I Errors)
•While underpowered studies primarily suffer from Type II errors, they can paradoxically also increase the likelihood of false positives.
•With small sample sizes, random variability may create spurious findings that appear significant but are not true associations.

Articles

Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial

Dr William D Tap MD [a b], Robin L Jones MD [c d], Brian A Van Tine MD [e], Bartosz Chmielowski MD [f], Prof Anthony D Elias MD [g], Prof Douglas Adkins MD [e], Mark Agulnik MD [h], Matthew M Cooney MD [i], Michael B Livingston MD [j], Gregory Pennock MD [k], Meera R Hameed MD [a], Gaurav D Shah MD [l], Amy Qin PhD [m], Ashwin Shahir MD [n], Damien M Cronier PhD [n], Robert Ilaria Jr MD [o], Ilaria Conti MD [o], Jan Cosaert MD [m], Prof Gary K Schwartz MD [p]

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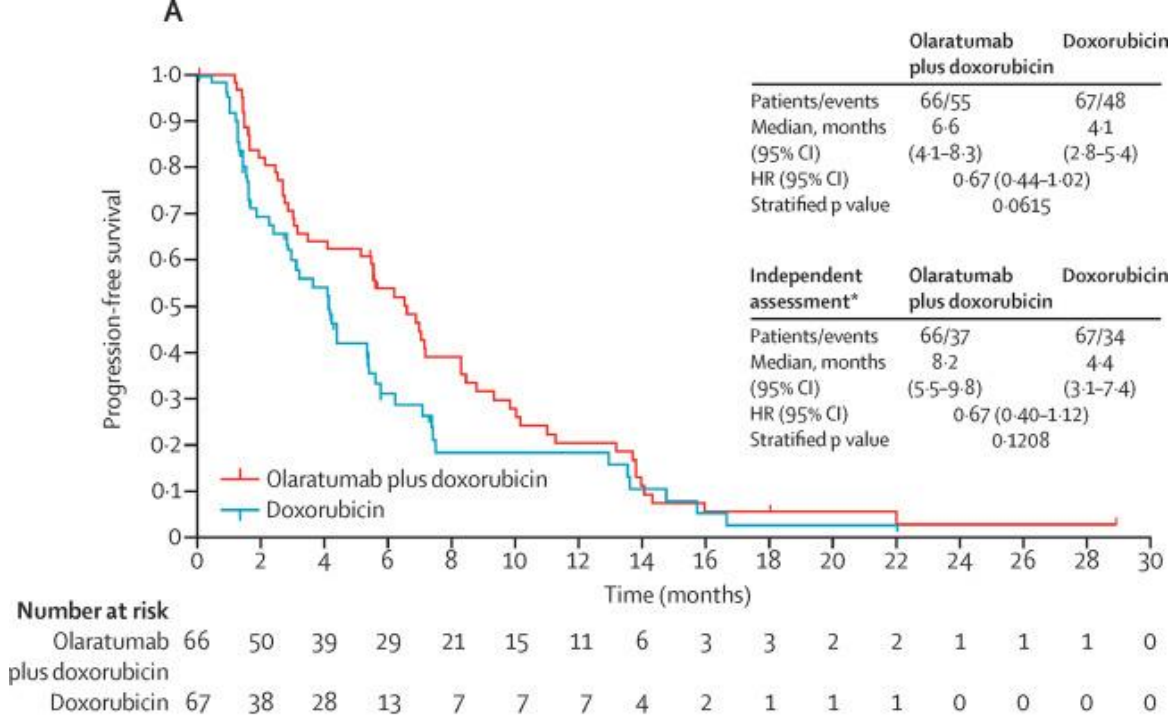
https://doi.org/10.1016/S0140-6736(16)30587-6

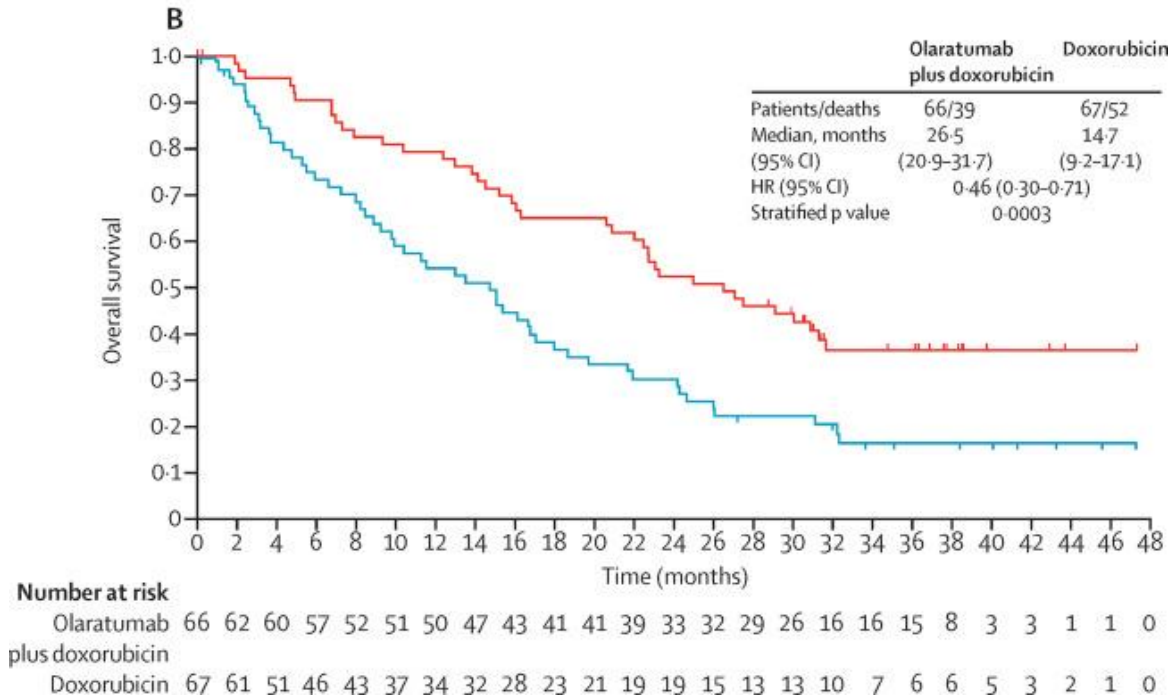
Olaratumab (LARTRUVO)

On October 19, 2016, the U.S. Food and Drug Administration granted accelerated approval to olaratumab (LARTRUVO, Eli Lilly and Company) for the treatment of patients with soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which an anthracycline-containing regimen is appropriate.

Approval was based on data from a randomized, active-controlled, clinical trial involving 133 patients with metastatic STS. Patients were required to have STS not amenable to curative treatment with surgery or radiotherapy, and a histologic type of sarcoma for which an anthracycline-containing regimen was appropriate, but had not been administered.

Patients were randomized (1:1) to receive the combination of olaratumab plus doxorubicin or doxorubicin as a single agent. Olaratumab was administered at 15 mg/kg as an intravenous (IV) infusion on days 1 and 8 of each 21-day cycle. All patients received doxorubicin 75 mg/m2 as an IV infusion on day 1 of each 21-day cycle for maximum of eight cycles and were permitted to receive dexrazoxane on cycles 5 to 8. Single-agent olaratumab was offered to patients in the doxorubicin alone arm at the time of disease progression. Sixty-six patients were randomized to the combination treatment and 67 to doxorubicin alone. Sixty-five percent of patients had no prior chemotherapy (excluding adjuvant and neoadjuvant therapy), 38% had leiomyosarcoma, 1.5% had synovial sarcoma, and 61% had other histologies (over 25 different STS histologies). All patients had metastatic disease and were enrolled in the United States.





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QUESTION In patients with advanced soft tissue sarcoma (STS), does the addition of olaratumab to doxorubicin improve overall survival?

CONCLUSION This randomized clinical trial found there was no significant difference in overall survival with the addition of olaratumab to doxorubicin in patients with advanced STS.

POPULATION

296 Women
213 Men

Anthracycline-naive adults with unresectable locally advanced or metastatic STS

Mean age: **56.9** years

LOCATIONS

110
Sites
in 25 countries

INTERVENTION

509 Patients randomized

258
Doxorubicin + olaratumab
- Doxorubicin, 75 mg/m^2 (day 1)
- Olaratumab, 20 mg/kg in cycle 1 and 15 mg/kg in subsequent cycles (days 1 and 8)

251
Doxorubicin + placebo
- Doxorubicin, 75 mg/m^2 (day 1)
- Placebo in all cycles (days 1 and 8)

PRIMARY OUTCOME

Overall survival with doxorubicin + olaratumab vs doxorubicin + placebo in total STS and leiomyosarcoma (LMS) populations

FINDINGS

Median overall survival (months)

Total STS population

Doxorubicin + olaratumab	Doxorubicin + placebo
20.4	19.7

LMS population

Doxorubicin + olaratumab	Doxorubicin + placebo
21.6	21.9

Hazard ratio:

Total STS population: **1.05** (95% CI, 0.84 to 1.30)

LMS population: **0.95** (95% CI, 0.69 to 1.31)

Tap WD, Wagner AJ, Schöffski P, et al; ANNOUNCE Investigators. Effect of doxorubicin plus olaratumab vs doxorubicin plus placebo on survival in patients with advanced soft tissue sarcomas: the ANNOUNCE randomized clinical trial. Published April 7, 2020. *JAMA*. doi:10.1001/jama.2020.1707

FOR FURTHER INFORMATION CONTACT:

Kimberly Lehrfeld, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6226, Silver Spring, MD 20993-0002, 301-796-3137.

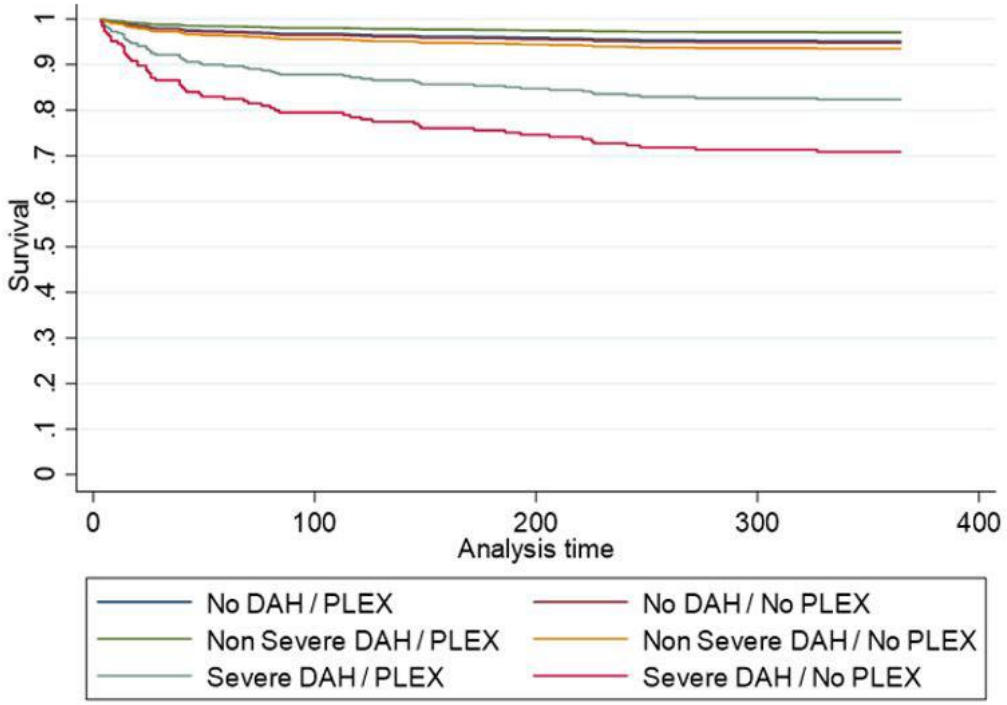
SUPPLEMENTARY INFORMATION:

On October 19, 2016, FDA approved the BLA for LARTRUVO (olaratumab) injection held by Eli Lilly and Co. (Eli Lilly), Lilly Corporate Center, Indianapolis, IN 46285, indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery, under the Agency's accelerated approval regulations at 21 CFR part 601, subpart E. On January 18, 2019, Eli Lilly reported in a press release that the confirmatory study required as a condition of LARTRUO's accelerated approval, entitled "Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin Plus Olaratumab Versus Doxorubicin Plus Placebo in Patients With Advanced or Metastatic Soft Tissue Sarcoma" (ANNOUNCE trial), "did not meet the primary endpoints of overall survival in the full study population or in the leiomyosarcoma subpopulation." On September 27, 2019, Eli Lilly requested withdrawal (revocation), in writing, of the BLA for LARTRUVO (olaratumab) injection (BLA 761038) under § 601.5(a) (21 CFR 601.5(a)) because the ANNOUNCE trial failed to demonstrate improvement in overall survival for olaratumab in combination with doxorubicin compared to doxorubicin alone. In that letter, Eli Lilly waived its opportunity for a hearing. On February 25, 2020, the Agency issued a letter to Eli Lilly revoking the approval to manufacture and market LARTRUVO (olaratumab) injection (BLA 761038).

Therefore, under § 601.5(a), the Agency revoked the BLA for LARTRUVO (olaratumab) injection (BLA 761038), applicable as of February 25, 2020.

Check for updates

Figure 1: One year survival in PEXIVAS by plasma exchange (PLEX) and severity of diffuse alveolar hemorrhage (DAH), adjusted for age, sex, ANCA type, kidney function, and initial treatments



Group	Died 3 months		Died 1 year		Effect of PLEX	
	PLEX	No PLEX	PLEX	No PLEX	HR (95% CI)	Interaction p value
Overall	18 (5.1)	21 (6.0)	25 (7.1)	32 (9.1)	0.74 (0.44 to 1.26)	
No DAH	12 (4.7)	9 (3.5)	17 (6.6)	17 (6.6)	0.86 (0.43 to 1.71)	
Any DAH	6 (6.3)	12 (12.5)	8 (8.4)	15 (15.6)	0.52 (0.21 to 1.24)	0.37
Non-severe DAH	1 (1.6)	3 (4.6)	2 (3.1)	5 (7.6)	0.43 (0.08 to 2.31)	0.42
Severe DAH	5 (16.1)	9 (30.0)	6 (19.4)	10 (33.3)	0.45 (0.14 to 1.40)	0.44

dard-dose group (incidence rate ratio, 0.69; 95% CI, 0.52 to 0.93), but other secondary outcomes were similar in the two groups.

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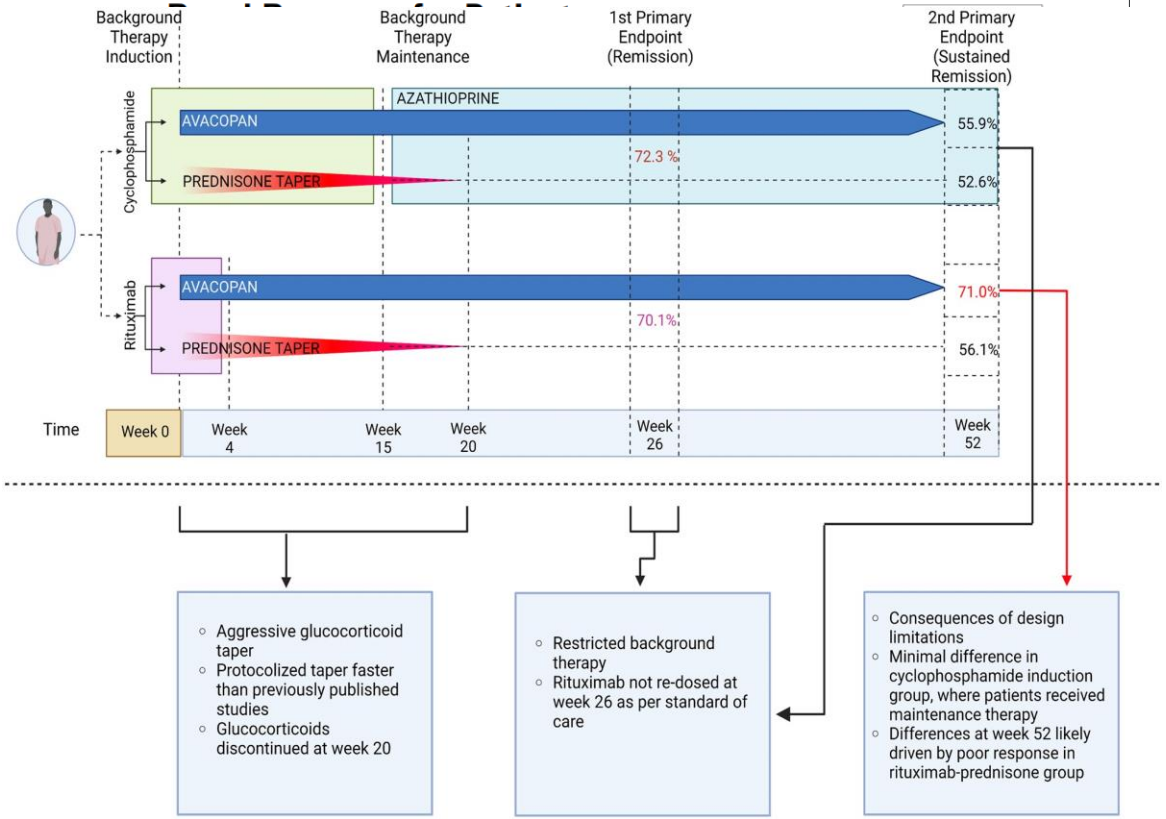

Figure 2. Change in kidney function among patients in the ADVOCATE trial with baseline eGFR ≤20 ml/min per 1.73 m². Least squares mean (± SEM) change from baseline in eGFR by treatment group over the 52-week treatment period. *$P < 0.05$, **$P < 0.01$ for comparison of the avacopan group to prednisone group by mixed effects model for repeated measures analysis with treatment group, study visit, and treatment-by-visit interaction as factors, and baseline as covariate. eGFR, estimated glomerular filtration rate.

of the patients receiving avacopan and in 39.0% of those receiving prednisone.

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- Is it a phase II or a phase III clinical trial?
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- Is the trial adequately powered?

Change our practice

Original Investigation FREE

Effects of Hydroxychloroquine on Symptomatic Improvement in Primary Sjögren Syndrome

The JOQUER Randomized Clinical Trial

Jacques-Eric Gottenberg, MD, PhD[1]; Philippe Ravaud, MD, PhD[2]; Xavier Puéchal, MD, PhD[3]; et al

Author Affiliations | Article Information

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Treatment of Primary Sjögren Syndrome With Rituximab

A Randomized Trial

Valérie Devauchelle-Pensec, MD, PhD; Xavier Mariette, MD, PhD; Sandrine Jousse-Joulin, MD; Jean-Marie Berthelot, MD; Aleth Perdriger, MD, PhD; Xavier Puéchal, MD, PhD; Véronique Le Guern, MD, PhD; Jean Sibilia, MD, PhD; Jacques-Eric Gottenberg, MD, PhD; Laurent Chiche, MD, PhD; Eric Hachulla, MD, PhD; Pierre Yves Hatron, MD; Vincent Goeb, MD, PhD; Gilles Hayem, MD; Jacques Morel, MD, PhD; Charles Zarnitsky, MD; Jean Jacques Dubost, MD; Jacques Olivier Pers, MD, PhD; Emmanuel Nowak, PhD; and Alain Saraux, MD, PhD

STUDY PROTOCOL Open Access

The TRACTISS Protocol: a randomised double blind placebo controlled clinical TRial of Anti-B-Cell Therapy In patients with primary Sjögren's Syndrome

Sarah Brown[1*†], Nuria Navarro Coy[2,6†], Costantino Pitzalis[3], Paul Emery[2,6], Sue Pavitt[8], Janine Gray[1], Claire Hulme[7], Frances Hall[4], Robert Busch[4,17], Pete Smith[5], Luke Dawson[5], Michele Bombardieri[3], Ng Wan-fai[9], Colin Pease[10], Elizabeth Price[11], Nurhan Sutcliffe[12], Clodagh Woods[13], Sharon Ruddock[1], Colin Everett[1], Catherine Reynolds[1], Emma Skinner[18], Ana Poveda-Gallego[14], John Rout[14], Iain Macleod[15], Saaeha Rauz[16], Simon Bowman[19] and TRACTISS trial team

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JOURNAL ARTICLE

A randomized placebo-controlled trial of methotrexate in psoriatic arthritis

Gabrielle H. Kingsley, Anna Kowalczyk, Helen Taylor, Fowzia Ibrahim, Jonathan C. Packham, Neil J. McHugh, Diarmuid M. Mulherin, George D. Kitas, Kuntal Chakravarty, Brian D. M. Tom, Aidan G. O'Keeffe, Peter J. Maddison, David L. Scott

Rheumatology, Volume 51, Issue 8, August 2012, Pages 1368–1377,
https://doi.org/10.1093/rheumatology/kes001
Published: 17 February 2012 **Article history**

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Arthritis & Rheumatology

Volume 62, Issue 1
January 2010
Pages 222-233

Systemic Lupus Erythematosus | Full Access

Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: The randomized, double-blind, phase ii/iii systemic lupus erythematosus evaluation of rituximab trial†

Joan T. Merrill, C. Michael Neuwelt, Daniel J. Wallace, Joseph C. Shanahan, Kevin M. Latinis, James C. Oates, Tammy O. Utset, Caroline Gordon, David A. Isenberg, Hsin-Ju Hsieh ... See all authors

First published: 28 December 2009 | https://doi.org/10.1002/art.27233 | Citations: 1,141

† ClinicalTrials.gov identifier: NCT00137969.

Arthritis & Rheumatology

Volume 64, Issue 4
April 2012
Pages 1215-1226

Systemic Lupus Erythematosus | Full Access

Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The lupus nephritis assessment with rituximab study†

Brad H. Rovin, Richard Furie, Kevin Latinis, R. John Looney, Fernando C. Fervenza, Jorge Sanchez-Guerrero, Romeo Maciuca, David Zhang, Jay P. Garg, Paul Brunetta, Gerald Appel, LUNAR Investigator Group

First published: 09 January 2012 | https://doi.org/10.1002/art.34359 | Citations: 1,196

† ClinicalTrials.gov identifier: NCT00282347.

From clinical research to basic/translational research

Clinical trials
Adaptive trials
Pilot studies
Feasibility studies
Pivotal studies

Reproducibility project

CENTER FOR OPEN SCIENCE

The reproducibility in preclinical research

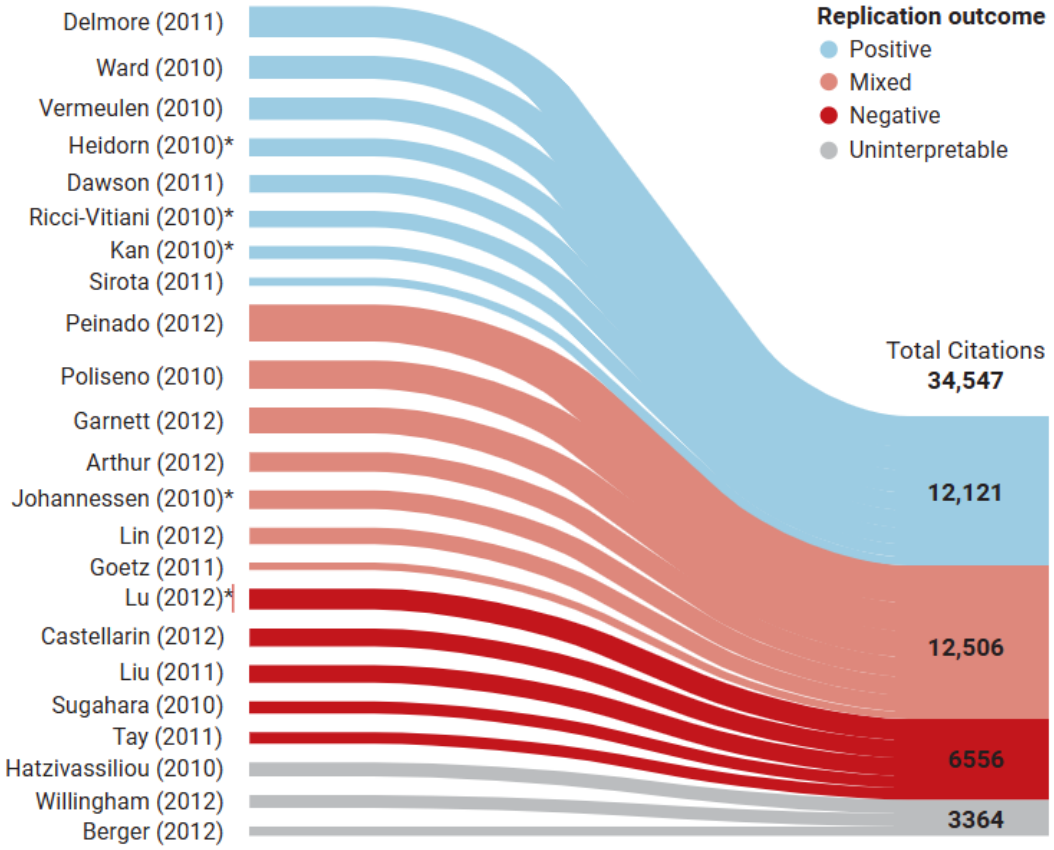
They selected 193 experiments from 53 high-impact papers published in 2010–2012.

Planned to repeat all 193 experiments, with peer-reviewed protocols (Registered Reports), pre-specified analysis plans, and attempts to use original materials / get clarifications from original authors.

They ended up completing replication on 50 experiments from 23 papers—so only about 26% of what was planned.

The reproducibility in preclinical research

- **Effect sizes were much smaller** in the replications. For positive effects, replication median effect size was ~85% smaller than in the original studies.
- **Statistical significance**: Many replications failed to reach statistical significance, even when direction matched. For example, only ~40% of positive effects were "successful" by a criterion of matching direction *and* statistical significance.
- When combining positive and null effects, the overall replication success rate was



MUCH MORE TO TALK ABOUT

Thank you

Contact info:

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Alveolar Hemorrhage in Antineutrophil Cytoplasmic Antibody–Associated Vas
Results of an International R

Lynn A. Fussner[1], Luis Felipe Flores-Suár
David R. W. Jayne[9], Peter A. Merkel[10,11],

[1]Division of Pulmonary, Critical Care, and Sleep M
[2]La Clínica de Vasculitis Sistémicas Primarias, Ins
[3]Division of Pulmonary Medicine, Department of Ir
Care Medicine, Department of Internal Medicine, I
Nephrology, Department of Medicine, [7]Departm
Research Institute, Hamilton Health Sciences, Mc
Cambridge, Cambridge, United Kingdom; [10]Divis
Department of Biostatistics, Epidemiology, and Ir

ORCID IDs: 0000-0003-0944-0216 (L.A.F.); 0000-0002-
0000-0002-3104-8600 (P.G.C.); 0000-0002-1712-0637

	PLEX
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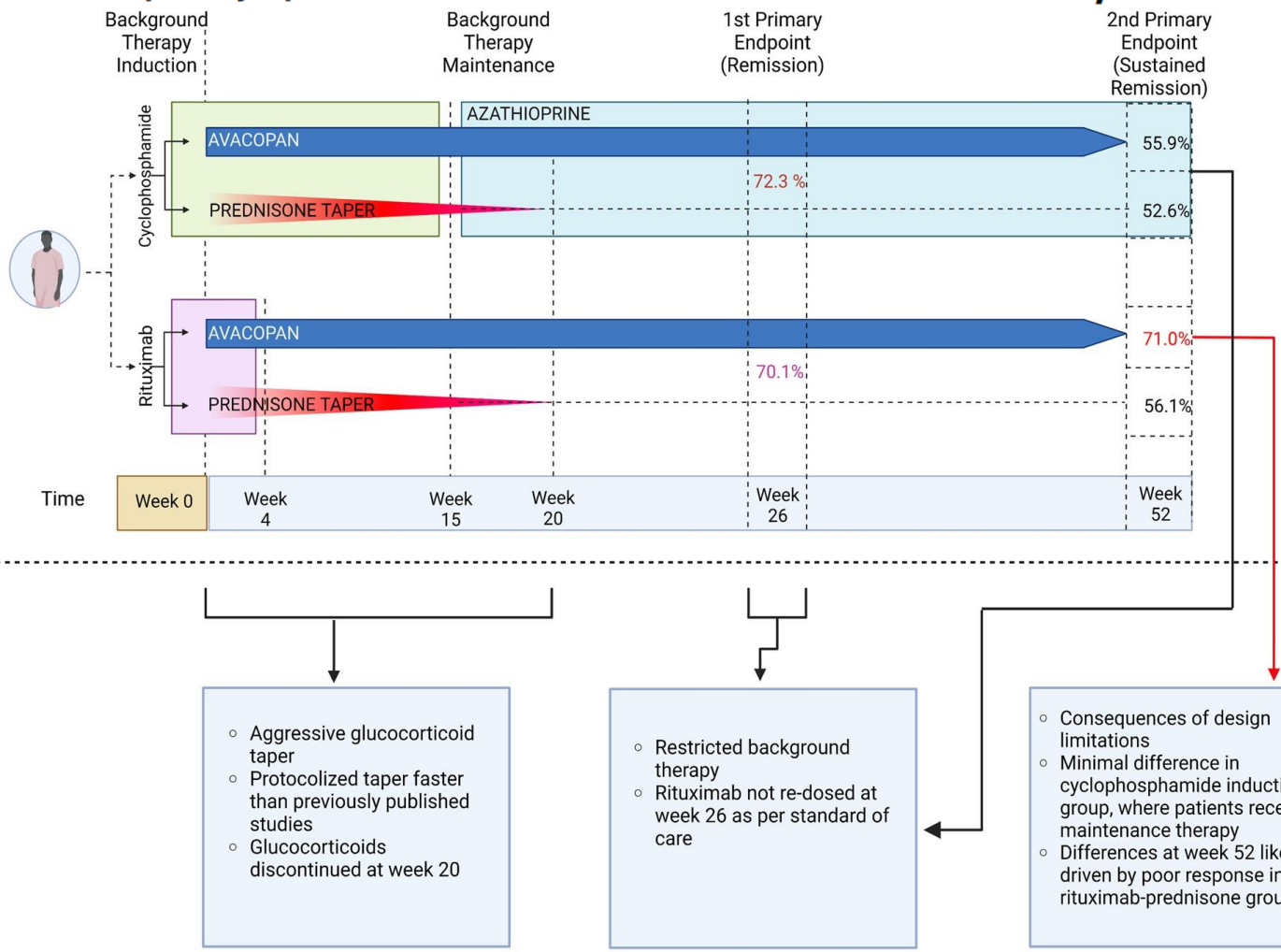
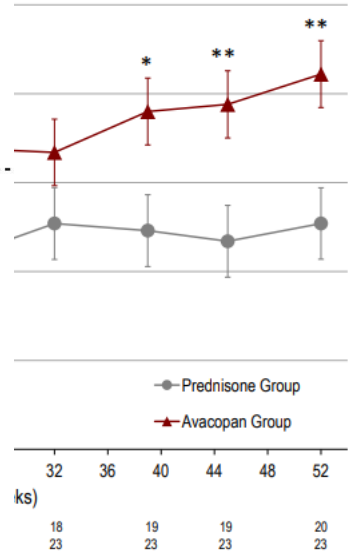
Renal Recovery for Patients



tis and Low
f Avacopan

, Peter A. Merkel[4], Annette Bruchfeld[5,6],
behalf of the ADVOCATE Study Group[7]

Hospital-Albany, Albany, New York, USA; [2]Nephrology
A; [3]Department of Medicine, University of Cambridge,
Division of Epidemiology, Department of Biostatistics,
a, Pennsylvania, USA; [5]Department of Renal Medicine,
len, and Department of Health, Medicine and Caring
/x, Inc., San Carlos, California, USA



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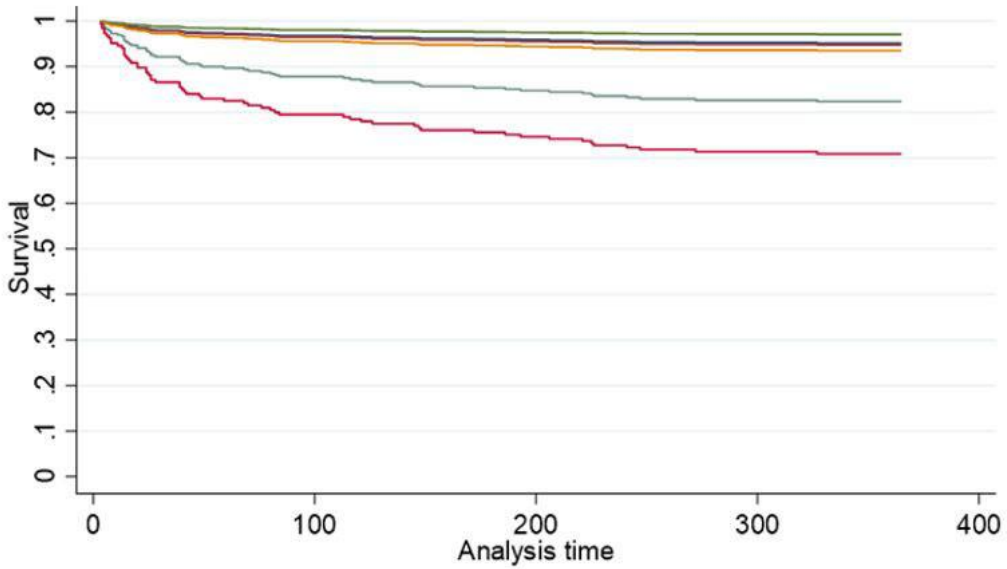

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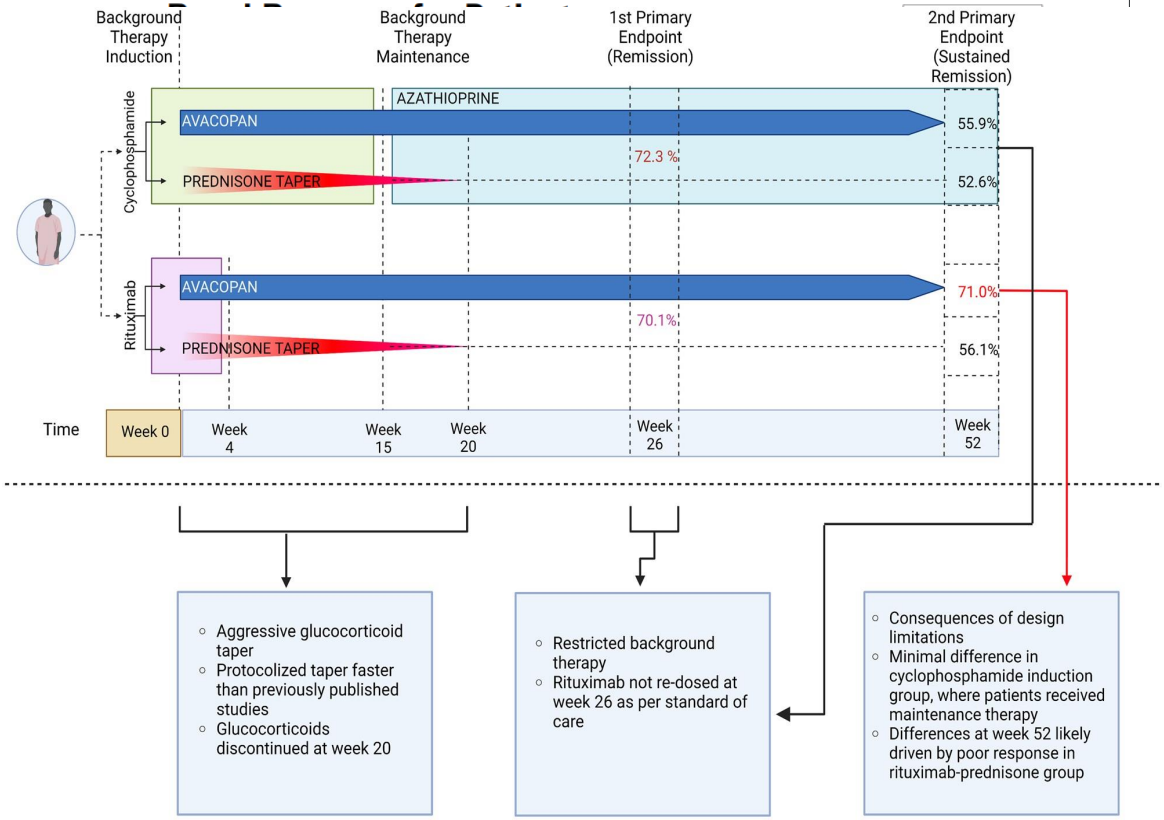

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