Update on Long COVID trials

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University of Toronto | University Health Network
December 12, 2025

Disclosures

Industry

- MediciNova provided drugs for RECLAIM trial

Non-industry

- NPI for Long COVID Web
- NPI for RECLAIM
- NPI for CANCOV
- Served as an advisor for CIHR, Chief Science Advisor's office, CADTH, CITF

Where are we?

Impact in Canada

- 400 million people affected worldwide
- Loss of 1% GDP

Al-Aly Z et al.
Nat Med 2024

- 3.5 million with LC (2023 Stats Can)
- 100,000 Canadians have been unable to return to work or school (CCAHS-FQ 2023, Stats Can)
- Census 40.5 m (2023) –> 41.7 m (2025)

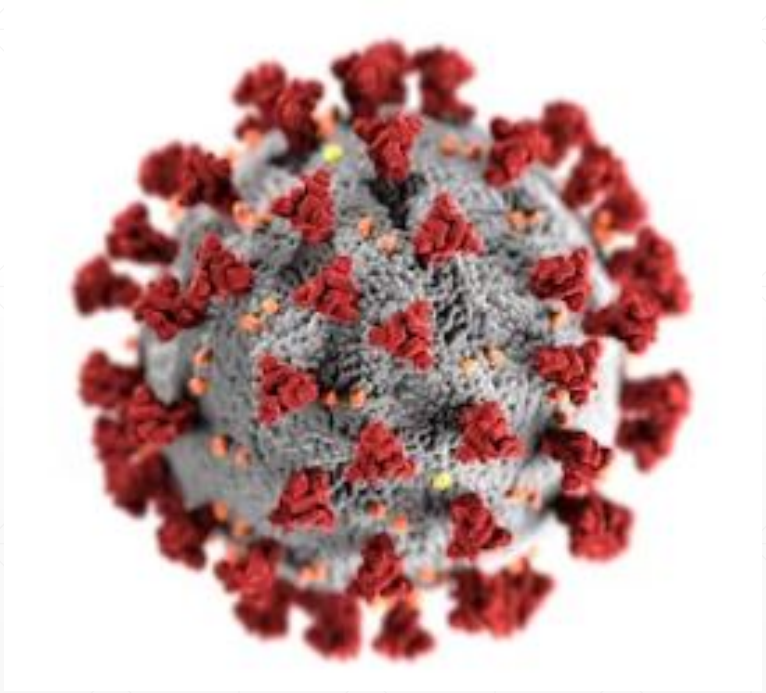
Current Understanding

- Multisystem disease

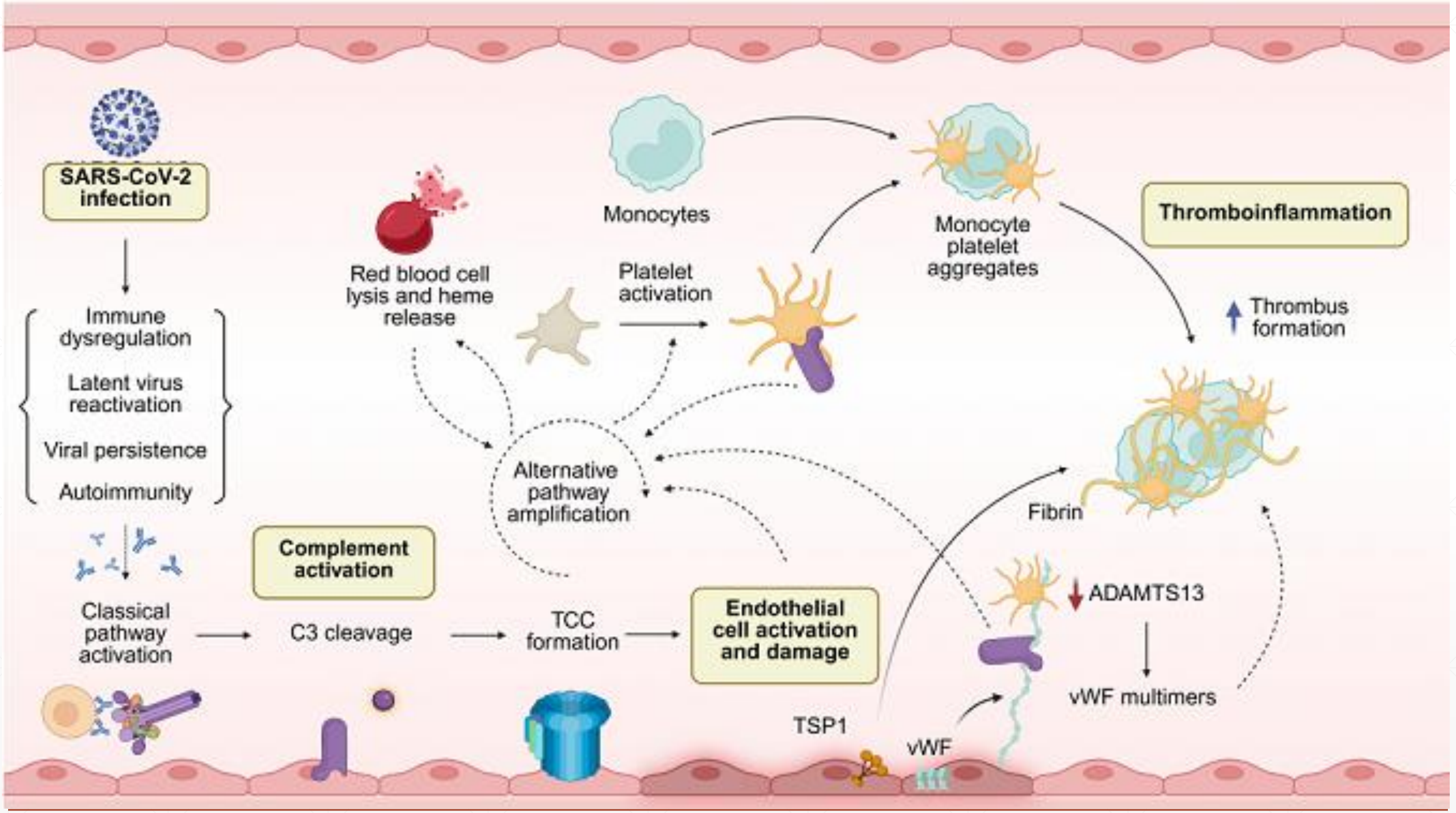
- Affects physical, cognitive, and emotional health, as well as social well-being
- Decreases quality of life, increases morbidity and mortality
- Affects the individual, family, social circle

Pathogenic Mechanisms

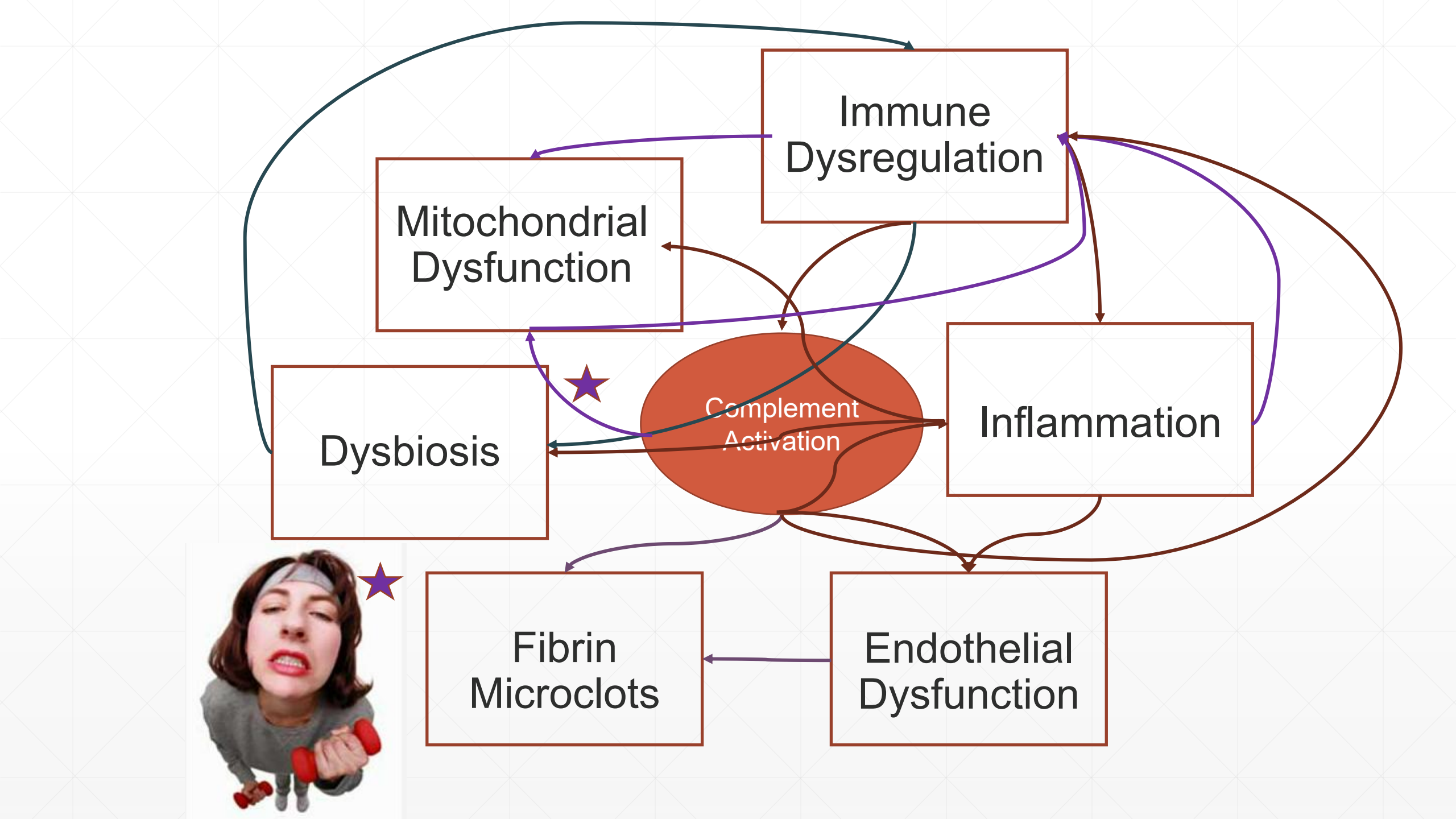
- Immune dysregulation
- Inflammation
- Endothelial dysfunction
- Viral or viral particle persistence
- Thrombotic microclots
- Mitochondrial dysfunction
- Perturbations to microbiome



*WHO Report: Expanding our understanding of Post COVID-19 condition. 2021. ISBN 978-92-4-002503-5



Bayarri-Olmos R et al. *JCI Insight* 2025;10(16):e194314.
https://doi.org/10.1172/jci.insight.194314.


Immune Dysregulation
Mitochondrial Dysfunction
Dysbiosis
Complement Activation
Inflammation
Fibrin Microclots
Endothelial Dysfunction

SARS-CoV-2 mRNA
Spike protein

Viral / Viral particle persistence

EBV
CMV
Herpes
Chlamydia
Syphyllis
Lymes etc

Reactivation of latent viruses

Complement, chemokine, cytokine, TLR signaling

Genetic susceptibility/ autoimmunity

Immune Dysregulation

Viral / Viral Particle Persistence

JAMA Internal Medicine

Published Online: June 7, 2024
2024;184;(9):1024-1034.
doi:10.1001/jamainternmed.2024.2007

Original Investigation

Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection

The STOP-PASC Randomized Clinical Trial

Linda N. Geng, MD, PhD[1]; Hector Bonilla, MD[1]; Haley Hedlin, PhD[1] ; et al

» Author Affiliations | Article Information

RELATED ARTICLES FIGURES SUPPLEMENTAL CONTENT

- 102 nirmatrelvir-ritonavir vs 53 placebo-ritonavir (2:1 randomization)
- 15-day intervention, 15-week follow-up
- Primary outcome – core symptom severity on Likert scale (no difference)

THE LANCET
Infectious Diseases

ARTICLES · Volume 25, Issue 8, P936-946, August 2025 Download Full Issue

Nirmatrelvir–ritonavir versus placebo–ritonavir in individuals with long COVID in the USA (PAX LC): a double-blind, randomised, placebo-controlled, phase 2, decentralised trial

Mitsuaki Sawano, MD [a,b,*] · Bornali Bhattacharjee, PhD [d,e,*] · César Caraballo, MD [g] · Rohan Khera, MD [a,b,h] · Shu-Xia Li, PhD [b] · Jeph Herrin, PhD [a] · et al. Show more

Affiliations & Notes Article Info Linked Articles (1)

- 49 nirmatrelvir-ritonavir vs 51 placebo-ritonavir (1:1 randomization)
- 15-day intervention, 6-week follow-up
- Primary outcome – PROMIS-29 PHSS (no difference)

Clinical Infectious Diseases

MAJOR ARTICLE

Assessment of the Impact of RNase in Patients With Severe Fatigue Related to Post-Acute Sequelae of SARS-CoV-2 Infection: A Randomized Phase 2 Trial of RSLV-132

James S. Andrews,[1] Jim B. Boonyaratanakornkit,[2,3] Eva Krusinska,[4] Suzanne Allen,[4] and James A. Posada[4]

[1]Department of Rheumatology, University of Alabama, Birmingham, Alabama, USA; [2]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, Washington, USA; [3]Department of Infectious Disease, University of Washington, Seattle, Washington, USA; and [4]Resolve Therapeutics, LLC, Miami, Florida, USA

- N = 68 vs 37 (2:1 randomization)
- 6 doses, F/U to day 71
- Primary Outcome: PROMIS Fatigue (no difference)

outsmart-LC: mAbs for Long COVID

Presented summary of unpublished data

Presented by Ameila Deitchman PharmD, PhD
3rd International Long COVID Conference | November 2025

outsmart-LC: Top line results

Presented summary of unpublished data

Presented by Ameila Deitchman PharmD, PhD
3rd International Long COVID Conference | November 2025

Autoimmunity

Completed

To Investigate Efficacy, Pharmacodynamics, and Safety of BC 007 in Participants With Long COVID (BLOC)

ClinicalTrials.gov ID NCT05911009

Sponsor Berlin Cures GmbH

Information provided by Berlin Cures GmbH (Responsible Party)

Last Update Posted 2024-11-18

- N=119 (1:1 randomization rovunaptabin vs placebo)
- 2 infusions 2-week apart, 90-day follow-up
- Primary outcome – FACIT Fatigue Scale (no difference)

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Study Details | Researcher View | No Results Posted | Record History

On this page

Study Overview

Brief Summary

This study is an interventional, randomized, multinational, multicenter, double-blind, phase 2 study with a follow-up period of 90 days.

The intension of this clinical trial is to investigate the long-term sequelae (named Long COVID syndrome; post COVID or PASC) of an infection with Corona Virus Type 2 that has resulted in a condition known as Severe Acute Respiratory Syndrome Corona Virus Type 2 (SARS-CoV-2).

The purpose of this study is to evaluate the efficacy and safety of BC 007 as a treatment for long-lasting COVID-symptoms in patients who were neither intubated nor supported with extracorporeal blood oxygenation (ECMO) during their acute COVID-19 infection.

The study drug acts by neutralizing functional autoantibodies directed against G-protein coupled receptors (GPCRs).

Study Start (Actual)
2023-06-16

Primary Completion (Actual)
2024-06-26

Study Completion (Actual)
2024-09-04

Enrollment (Actual)
119

Study Type

eClinicalMedicine
Part of THE LANCET Discovery Science

ARTICLES · Volume 86, 103358, August 2025 · *Open Access* Download Full Issue

Safety, tolerability and clinical effects of rovunaptabin, also known as BC007 on fatigue and quality of life in patients with Post-COVID syndrome (reCOVer): a prospective, exploratory, placebo-controlled, double-blind, randomised phase IIa clinical trial (RCT)

Bettina Hohberger [a,b,j] · Marion Ganslmayer [c,j] · Thomas Harrer [b,d,e] · Friedrich Kruse [a] · Stefanie Maas [f] · Tobias Borst [g] · et al.
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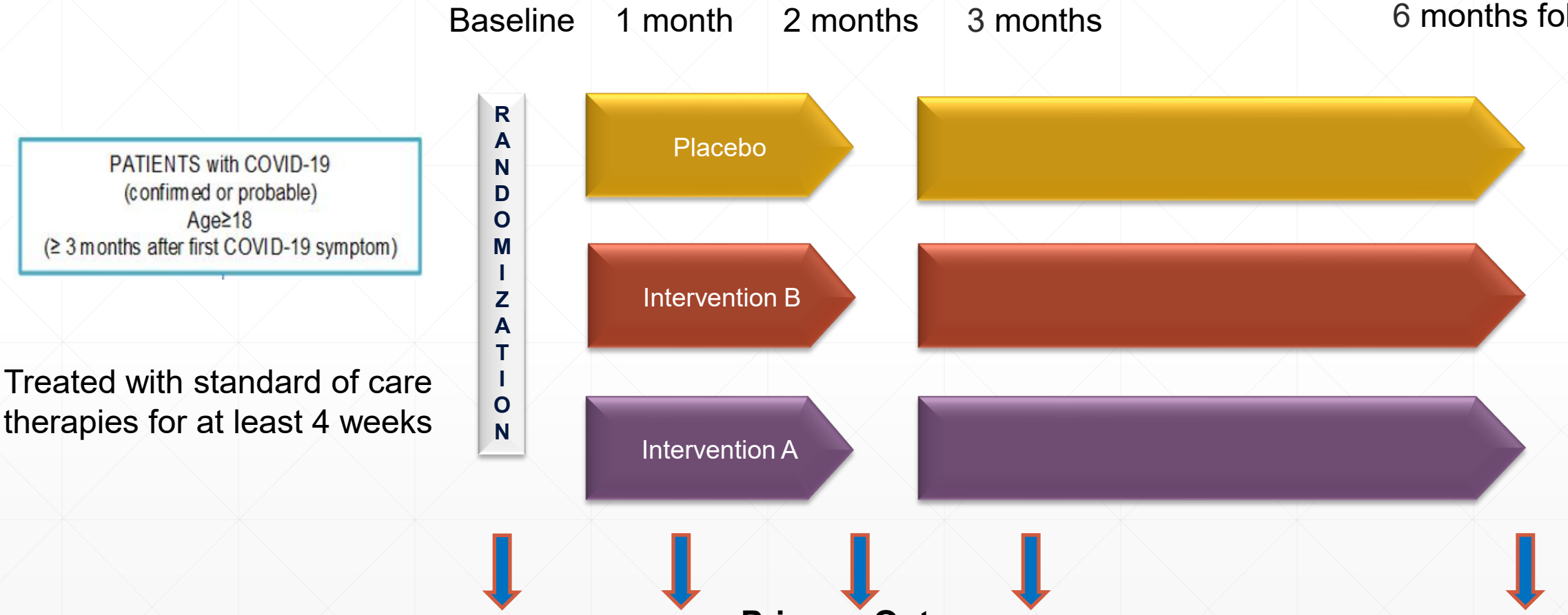
Affiliations & Notes Article Info

- 16 rovunaptabin vs 14 placebo (1:1 randomization)
- Day 0 and Day 48 intervention, 28-day follow-up
- Primary outcome – TEAEs [9 vs 5, ns]
- Secondary outcomes – Fatigue (FACIT, Bell score, Fatigue Severity Scale), QOL

Immune dysfunction

Structure of RECLAIM



Ibudilast (MN-166)

Small Molecule / Oral meds

Same Active ingredient approved in 1989 in Japan with lower dose

- Asthma (20mg/day) Post-stroke symptoms (30mg/day)

Mechanism of action

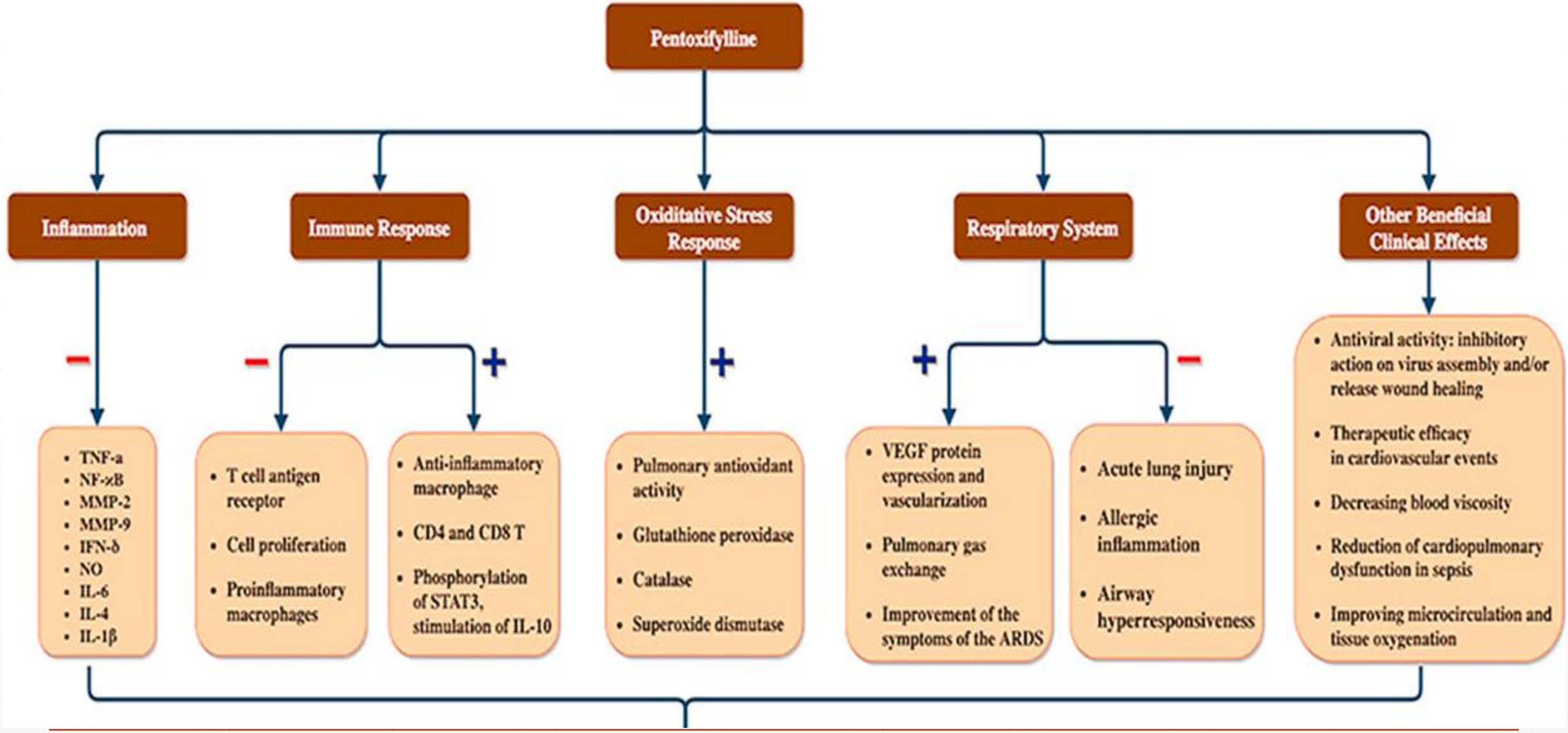
- PDE 3,4,10,11 inhibition
- MIF inhibition (Macrophage migration inhibitory factor)
- TLR4 inhibition

Expected Clinical Effects in Neurological Indication

- Anti-platelet aggregation / Vasodilation=> **increase cerebral blood flow**
- **Anti-inflammation**
- Glia attenuation
- **Neuroprotective** cytokine /chemokine

Pentoxifylline

- Xanthine derivative (1H-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-xanthine)
- Oral medication taken 3 times a day
- Used for occlusive vascular disease / intermittent claudication for decades in North America
- First approved in Europe in 1972


Pentoxifylline
Inflammation
Immune Response
Oxiditative Stress Response
Respiratory System
Other Beneficial Clinical Effects
−
−
+
+
+
−
• TNF-a
• NF-κB
• MMP-2
• MMP-9
• IFN-δ
• NO
• IL-6
• IL-4
• IL-1β
• T cell antigen receptor
• Cell proliferation
• Proinflammatory macrophages
• Anti-inflammatory macrophage
• CD4 and CD8 T
• Phosphorylation of STAT3, stimulation of IL-10
• Pulmonary antioxidant activity
• Glutathione peroxidase
• Catalase
• Superoxide dismutase
• VEGF protein expression and vascularization
• Pulmonary gas exchange
• Improvement of the symptoms of the ARDS
• Acute lung injury
• Allergic inflammation
• Airway hyperresponsiveness
• Antiviral activity: inhibitory action on virus assembly and/or release wound healing
• Therapeutic efficacy in cardiovascular events
• Decreasing blood viscosity
• Reduction of cardiopulmonary dysfunction in sepsis
• Improving microcirculation and tissue oxygenation

Characteristics of Participants

- Presented unpublished data

*First patient entered on May 31, 2023 and last patient entered on Dec 20, 2024. N=460

Characteristics of Participants

- Presented unpublished data

*First patient entered on May 31, 2023 and last patient entered on Dec 20, 2024.

Primary Outcome – SF-36 PCS

Trajectories of mean PCS over 6 months

- Presented unpublished data

Secondary Outcomes

- SF-36 MCS
- Neurocognitive testing using Test My Brain (6 different tests)
- 6-minute walk test
- Borg Dyspnea Scale
- Fatigue
- PEM
- Symptoms

Subgroup and Sensitivity Analyses

- Age
- Sex
- No. of COVID infections
- Certainty of COVID infection
- Wave of COVID infection/variant
- Duration of Long COVID

Limitations

- Duration of intervention
- Dose of intervention
- Primary outcome-SF-36 PCS
- Heterogeneity of phenotype
- Heterogeneity of endotype

Conclusions

Presented unpublished data

AIM ImmunoTech Announces Publication of Final Clinical Study Results for AMP-518 Clinical Trial on Ampligen as a Therapeutic for Post-COVID Conditions

January 23, 2025 08:50 ET | Source: AIM ImmunoTech Inc. Follow

OCALA, Fla., Jan. 23, 2025 (GLOBE NEWSWIRE) -- **AIM ImmunoTech Inc. (NYSE American: AIM)** ("AIM" or the "Company") today announced that the final Clinical Study Results for the "Study to Evaluate the Efficacy and Safety of Ampligen in Patients With Post-COVID Conditions" ("AMP-518") was posted yesterday to ClinicalTrials.gov (See: NCT05592418).

CEO Thomas K. Equels stated: "The results of AMP-518 support AIM's belief in Ampligen as a potential therapeutic for people with the moderate-to-severe Post-COVID condition of fatigue. Our analysis of the final Clinical Study Results has helped us to identify a likely subject population that would experience the greatest benefit from Ampligen in AIM's planned follow-up clinical trial. The AMP-518 data also comes on the heels of a new analysis of data that was generated through the National Institutes of Health RECOVER initiative, demonstrating a clear link between Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. The report found that the

Rintatolimod (dsRNA)

- 40 rintatolimod vs 40 placebo (1:1)
- 36 vs 30 completed
- Twice weekly for 12 weeks
- F/U to week 13
- Primary Outcome: PROMIS Fatigue Score at week 13 (no difference)

Other trials

eClinicalMedicine
Part of THE LANCET Discovery Science

ARTICLES · Volume 89, 103633, November 2025 · *Open Access* Download Full Issue

Effects of nicotinamide riboside on NAD+ levels, cognition, and symptom recovery in long-COVID: a randomized controlled trial

Chao-Yi Wu [a] · William Cody Reynolds [a] · Isabel Abril [a] · Alison J. McManus [a] · Charles Brenner [b] · Gabriel González-Irizarry [a] · et al.
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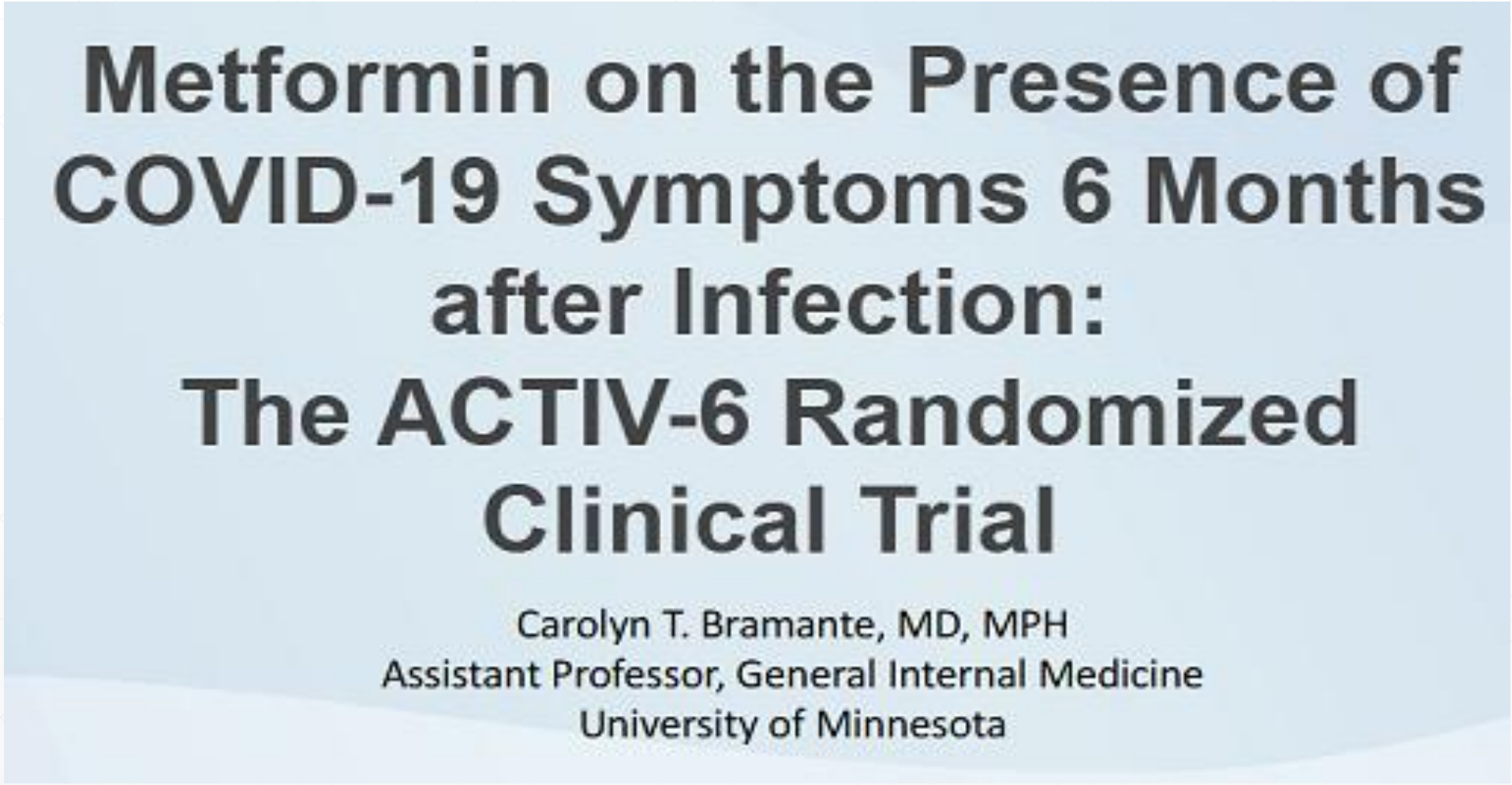
- 24-week RCT, single center in Boston
- N = 37 vs 21, high drop out rate
- Increased NAD+ levels, but did not improve cognition or symptom recovery

Honorable Mention

Prevention of Long COVID



Presented by Carolyn T. Bramante MD, MPH
3rd International Long COVID Conference | November 2025

medRxiv [Preprint]. 2025 Aug 12:2025.08.08.25333305. doi: 10.1101/2025.08.08.25333305.

Metformin on the Presence of COVID-19 Symptoms Over 6 Months: The ACTIV-6 Randomized Clinical Trial

Carolyn T Bramante, Thomas G Stewart, David R Boulware, Matthew W McCarthy, Yue Gao, Russell L Rothman, Ahmad Mourad, Florence Thicklin, Jonathan B Cohen, Idania T Garcia Del Sol, Nirav S Shah, Manisha Mehta, Orlando Quintero Cardona, Jake Scott, Adit A Ginde, Mario Castro, Dushyantha Jayaweera, Mark Sulkowski, Nina Gentile, Kathleen McTigue, G Michael Felker, Sean Collins, Sarah E Dunsmore, Stacey J Adam, Christopher J Lindsell, Adrian F Hernandez, Susanna Naggie;
Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group and Investigators

PMID: 40832427 PMCID: PMC12363699 DOI: 10.1101/2025.08.08.25333305

Background: The effect of metformin on preventing long-term COVID-19 symptoms among low-risk adults has not been studied. The objective of this study was to Assess metformin compared with placebo during acute SARS-CoV-2 infection on the presence of COVID-19 symptoms 180 days later.

Methods: The ACTIV-6 platform evaluated repurposed medications for mild to moderate COVID-19. Between September 19, 2023 and May 1, 2024, 2983 outpatient adults ≥30 years with confirmed SARS-CoV-2 infection and ≥2 COVID-19 symptoms for ≤7 days were included from 90 sites. Participants were randomized to metformin (titrated to 1500 mg daily) or placebo for 14 days. Post-acute sequelae of SARS-CoV-2 or death (PASCD) was ascertained by asking whether participants had symptoms they attributed to COVID-19 on day 180. Secondary outcomes included clinician diagnosis of long COVID. For the primary outcome, the single-sided threshold for efficacy was 0.975.

Results: Among 2983 participants, the median age was 47 years (interquartile range [IQR] 38-57); 63% were female; 47% Hispanic/Latino; 83% reported ≥1 prior COVID-19 infections or SARS-CoV-2 vaccines. There were no deaths. Overall, 96 (3.2%) reported COVID-19 symptoms on day 90, 101 (3.4%) on day 120, and 79 (2.6%) on day 180. The covariate-adjusted risk of PASCD on day 180 was lower in the metformin group (-0.008; 95% credible interval [CrI] -0.022 to 0.006; posterior probability of efficacy [PPE] 0.83), compared with the placebo group with an adjusted risk ratio of 0.79 (95% CrI 0.474 to 1.230). The risk of clinician diagnosis of long COVID (secondary outcome) on day 180 was lower in the metformin group (-0.007; 95% CrI -0.015 to 0.001; PPE 0.96), with a relative risk of 0.495 (95% CrI 0.155 to 0.995).

Conclusions: The posterior probability of efficacy for metformin preventing the primary endpoint did not exceed the prespecified threshold of 0.975 for declaring efficacy. Secondary outcomes were numerically better with metformin.

Summary

- None of the RCTs have shown efficacy
- Many more with results in 2026-2027
- Prevention is key – vaccination, masking, Paxlovid, metformin

Thank you!

Questions / Comments? Email: angela.Cheung@uhn.ca