

Detailed overview of the 2025 PAIS Therapeutic Research Landscape

This dataset reflects a comprehensive 2025 audit of global clinical registries including ClinicalTrials.gov, the EU Clinical Trials Register (CTIS/EudraCT), and the ISRCTN. It specifically integrates the latest protocol data from major international PAIS platform trials, including the NIH RECOVER initiative (USA), STIMULATE-ICP (UK), and the RECLAIM platforms (Canada and Netherlands/EU).

The selection process rigorously prioritized the top 100 therapeutic interventions with a **defined biological mechanism of action targeting PAIS pathology**, based on three key pillars:

- **Strong biological rationale:** interventions targeting specific root causes like viral persistence or neuro-inflammation.
- **Active status:** isolating verified, ongoing interventional trials and expert-validated protocols (*including 3 failed phase 2 studies, as next steps have not yet been communicated or the intervention is on market in other indications*).
- **Strategic relevance:** prioritizing distinct, high-impact mechanisms that fill specific voids in the treatment landscape rather than supportive care.

The overview **encompasses Long COVID, ME/CFS, POTS, Fibromyalgia and Lyme**, and is structured to highlight the **key assets, mechanisms, target population, status, sponsors** ("Academic/Health Authority" includes government-funded platforms like RECOVER, RECLAIM, and STIMULATE-ICP) and other players involved.

Interventions are color-coded according to three asset categories: **Innovative** (Pipeline / Novel – Green), **On Market** (Repurposed Brand – Yellow), and **Generic** (Off-Label / Old – Blue). Within each category, projects are ordered by clinical maturity, with more advanced trials appearing higher in the list.

The resulting "Top-100" interventions (Categories I-VII), alongside key diagnostic platforms (Category VIII) may serve as a **competitive map for investigators and industry stakeholders to identify high-value collaborators and market opportunities in a specific segment**.

I. Pathogen Persistence & Reactivation

Targeting deep-tissue viral reservoirs and controlling immune-driven viral reactivation.

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
INNOVATIVE	<i>(Pipeline / Novel)</i>		
VYD2311 (Next-Gen mAb)	Neutralizing mAb Engineered backbone of Pemivibart. Designed for broader variant neutralization and easier IM administration to clear deep-tissue viral reservoirs and spike protein.	Long COVID or post vaccine injury POM: Safety, translational biology, and exploratory clinical efficacy vs. placebo	Active Phase 2 (Commencing Mid-2026) Study: SPEAR Study Protocol  Invivyd / SPEAR study Group
AER002 (Neutralizing mAb)	Neutralizing mAb Designed to neutralize Spike protein reservoirs in patients with weakened immune clearance. <i>Status Note: outSMART-LC trial failed to meet primary endpoint. Investigators emphasize future trials require better biomarker-driven patient selection rather than dismissing the mAb mechanism</i>	Long COVID (General) POM: PROMIS- 29	Phase 2 Completed (Failed POM; NIH RECOVER deferred; next steps pending) Study: outSMART-LC [NCT05877508]  Invivyd (Biotech)  UCSF
Sipavibart (AZD3152)	Neutralizing mAb Long-acting antibody designed to neutralize Spike protein reservoirs in patients with weakened immune clearance.	Long COVID + ME/CFS POM: PROMIS- 29	Active Phase 2 Study: PASC-mAb [NCT07021794]  AstraZeneca (Pharma)  Nova Southeastern
Temelimab (GNC-501)	Anti-HERV-W mAb Neutralizes the pathogenic envelope protein of Endogenous Retrovirus-W, a dormant virus triggered by SARS-CoV-2.	Long COVID (Neuro- Psychiatric) POM: PROMIS Fatigue SF 7a	Completed Phase 2 (Failed) Study: Proba-MSTS [NCT05497089]  GeNeuro (Biotech)

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Rintatolimod (Ampligen)	TLR3 Agonist Activates the innate immune system (NK cells) to seek and destroy intracellular viral reservoirs.	Long COVID + ME/CFS POM: PROMIS Fatigue SF 7a	Completed Phase 2 (Missed PE, new study planned in moderate / severe) Study: AMP-518 [NCT05592418]  AIM ImmunoTech (Biotech)
IMC-1 (Famciclovir + Celecoxib)	Antiviral Combination Synergistic inhibition of Herpesvirus reactivation (COX-2 + DNA polymerase blockade). Novel fixed-dose.	Fibromyalgia POM: NRS pain score	Phase 3 Ready (Ph2 positive in Tx-naïve subgroup) Study: FORTRESS [NCT04748705]  Virios Therapeutics (Biotech) - now Dogwood Therapeutics
IMC-2 (Valacyclovir + Celecoxib) + Paxlovid Triple Antiviral Regimen	Antiviral Combination Dual mechanism: IMC-2 suppresses Herpesvirus reactivation, while Paxlovid neutralizes persistent SARS-CoV-2. <i>Status Note: the previous ph2 VICI-Trial (NCT06316843) tested IMC-2 alone. The new SHIELD trial tests this aggressive 3-drug combination based on highly successful pilot data.</i>	Long COVID (General) POM: Fatigue, Dysautonomia, and Brain Fog	Active Phase 2 (Starting Q1 2026) Study: SHIELD (NCT Pending)  PridCor Therapeutics  Mount Sinai (Putrino / Proal)
Hygromycin A (FP-100)	Selective Spirochete Antibiotic First-in-class narrow-spectrum antibiotic that selectively targets Borrelia (Lyme) while preserving the gut microbiome.	Lyme Disease	Active Phase 1 (First human dosing May 2024) Study: FP-100-101  Flightpath Biosciences

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
ON MARKET	<i>(Repurposed Brand / Patent Protected)</i>		
Nirmatrelvir / Ritonavir (Paxlovid) 1/2	Mpro Inhibitor Extended 15-25 day course to penetrate deep-tissue "sanctuary sites" (gut/CNS).	Long COVID (General) POM: PROMIS Cognitive Function 8a; OHQ; DSQ- PEM	Active Phase 2 Study: RECOVER- VITAL [NCT05595369]  NIH RECOVER  Pfizer (Supplier)
Nirmatrelvir / Ritonavir (Paxlovid) 2/2	Mpro Inhibitor Evaluation of antiviral efficacy in specific European cohorts.	Long COVID (General) POM: EQ-5D-5L	Active Phase 2 Study: PROLIFIC [NCT05823896]  Karolinska Institutet  Pfizer (Supplier)
Ensitrelvir (Xocova)	3CL Protease Inhibitor Next-gen antiviral. Approved in Japan (2022)	Long COVID (General) POM: PROMIS- 29	Active Phase 2 Study: PREVAIL-LC [NCT06161688]  Shionogi (Pharma)  NIH RECOVER
Remdesivir (Veklury)	RNA Polymerase Inhibitor IV antiviral. Investigated for clearing persistent viral reservoirs in deep tissue.	Long COVID (General)	Completed Feasibility Study Study: ERASE-LC [NCT05911906]  Univ. Derby / Exeter
COVID-19 Vaccine (Various Boosters)	Immune Clearance Investigates whether booster doses trigger the immune system to eliminate residual viral reservoirs ("therapeutic vaccination").	Long COVID (General) POM: Overall Health +/-	Active Observational Study: Yale Recovery [NCT04895189]  Yale University

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
GENERIC	<i>(Off-Label / Old / Multi-Source)</i>		
Valganciclovir (Valcyte)	Viral DNA Polymerase Inhibitor Suppresses replication of reactivated Herpesviruses (EBV/HHV-6). Generics available.	ME/CFS (HHV-6/EBV Reactivation)	Completed Phase 2 (Positive Signal for neuro-cognitive function) Study: VAT [NCT00478465] 🏛️ Stanford (Montoya Lab)
Tenofovir / Emtricitabine (Truvada)	Reverse Transcriptase Inhibitor Originally for HIV. Investigated to block HERVs.	Long COVID (General) POM: EQ-5D-5L; VAS	Active Phase 2 Study: TEMPO [NCT06511063] 🏛️ Mt Sinai / PolyBio 🧬 Gilead (Supplier)
Maraviroc (Selzentry)	CCR5 Antagonist Blocks the CCR5 receptor to prevent inflammatory cells (monocytes/T-cells) from migrating into tissues. Investigated here specifically for Viral Persistence (reducing the reservoir size).	Long COVID (General) POM: EQ-5D-5L; VAS	Active Phase 2 Study: TEMPO [NCT06511063] 🏛️ Mt Sinai / PolyBio (Academic)

II. Chronic Inflammation & Immune Dysregulation

Breaking the cycle of systemic inflammation, cytokine storms, and glial activation.

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
INNOVATIVE	<i>(Pipeline / Novel)</i>		
Zofin (Organicell Flow)	Amniotic Exosomes / Biologic Acellular therapeutic derived from amniotic fluid. Contains cytokines / chemokines / growth factors to modulate inflammation and induce tissue repair.	Long COVID (general) POM: Safety, FSS	Phase 3 Ready (Phase 1/2 Positive Safety & Efficacy Signal) Study: [NCT05228899]  Organicell (Biotech) now ZEO ScientifiX
HB-adMSC (Mesenchymal Stem Cells)	Cellular Immunomodulation Allogeneic "living drug" that secretes paracrine factors to switch macrophages (M1→M2) and dampen systemic inflammation (IL-6/CRP reduction).	Long COVID (neurological symptoms) POM: VAS Neurological Symptoms	Completed Phase 2 (Positive Signal on Fatigue) Study: [NCT05126563]  Hope Biosciences (Biotech)
Bezisterim (NE3107)	Inflammation Modulator Selectively inhibits NF- kappa B and ERK to target neuroinflammation without broad immunosuppression.	Long COVID (Fatigue and Brain Fog) POM: Cogstate Cognition battery	Active Phase 2 Study: ADDRESS-LC [NCT06847191]  BioVie Inc. (Biotech)
Vidofludimus Calcium (IMU-838)	DHODH Inhibitor Dual mechanism: activates antiviral host factors and inhibits IL- 17/IFN-γ release.	Long COVID (General) POM: SF-36-PF	Active Phase 2 Study: RAPID_REVIVE [EudraCT number: 2024- 511628-16-00]  Goethe Univ. / Immunic

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
LAU-7b	Resolution Agonist Stimulates lipid metabolism to actively <i>resolve</i> inflammation.	Long COVID (General) POM: SF-36	Completed Phase 2/3 (Results Pending) Study: ESSOR [NCT04417257]  Laurent Pharma (Biotech)
Genistein (BIO 300)	Estrogen Receptor Agonist Anti-fibrotic nanoparticle formulation.	Long COVID (Pulmonary Fibrosis) POM: DLCO	Active Phase 2 Study: BIO-300 Trial [NCT04482595]  Humanetics (Biotech)
IFX-LC001, Tonabersat (Xiflam)	Connexin 43 Blocker Inhibits pathological Cx43 hemichannels to stop ATP leakage. Prevents activation of the NLRP3 inflammasome and breaks the cycle of chronic neuro-vascular inflammation.	Long COVID (general) POM: Multi-system VAS	Active Phase 2 Study: InflammX [NCT06437223]  InflammX (Biotech)
ON MARKET	<i>(Repurposed Brand / Patent Protected)</i>		
Upadacitinib (Rinvoq)	Selective JAK1 Inhibitor Potently inhibits the JAK-STAT pathway to block downstream signaling of key inflammatory cytokines (IL-6, Interferons).	Long COVID (General) POM: 5 SSBQ Subscales	Active Phase 3 Study: LC-REVITALIZE [NCT06928272]  Western Univ. / SILC (Schmidt Initiative)
Baricitinib (Olumiant)	JAK1/2 Inhibitor Blocks cytokine signaling to correct the "Interferon-Itaconate Shunt".	Long COVID (General) POM: CNS-Vital Signs Global Cognitive Index	Active Phase 3 Study: REVERSE-LC [NCT06631287]  Emory Univ. / PolyBio
Abrocitinib (Cibingo)	Selective JAK1 Inhibitor Highly specific cytokine blockade to reduce fatigue.	Long COVID (General) POM: FACIT-Fatigue Scale	Active Phase 2 Study: JAK-Fatigue [NCT06597396]  Beth Israel Deaconess

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Nogapendekin alfa (Anktiva)	IL-15 Agonist Activates NK/CD8+ T-cells. FDA Approved (Apr 2024).	Long COVID (General) POM: Safety, PROMIS-29	Active Phase 2 Study: INTERRUPT_LC [NCT07108036]  ImmunityBio (Biotech)
Tocilizumab (Actemra)	IL-6 Receptor Antagonist Inhibits IL-6, the master driver of the inflammatory loop. Targeted at patients who have persistently elevated CRP / inflammatory markers months after infection.	Long COVID (High Inflammatory Markers) POM: EQ5D	Active Phase 2 Study: PHOSP-I [ISRCTN46454974]  Univ. Leicester / Roche
Anakinra (Kineret)	IL-1 Receptor Antagonist Blocks IL-1a/b to halt the "cytokine storm".	Long COVID (pro-inflammatory respiratory phenotype) POM: a score for progression	Active Phase 2/3 Study: PRECISION [NCT05926505]  Sobi / Hellenic Inst.
GENERIC	<i>(Off-Label / Old / Multi-Source)</i>		
Loratadine + Famotidine	H1/H2 Receptor Blockade Dual antihistamine therapy (H1 + H2 blockers) that stabilizes Mast Cells and reduces histamine-mediated neuro-inflammation and immune dysregulation.	Long COVID (General) POM: Fatigue Assessment Scale	Phase 3 (Recruitment Completed - Results Pending 2025) Study: STIMULATE-ICP [ISRCTN10665760]  UCL / NIHR (UK Govt)

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Colchicine	NLRP3 Inflammasome Inhibitor Potent anti-inflammatory that inhibits microtubule polymerization and blocks the NLRP3 Inflammasome. Targets pericarditis/pleuritis symptoms and systemic cytokine production.	Long COVID (General) POM: Fatigue Assessment Scale	Phase 3 (Recruitment Completed - Results Pending 2025) Study: STIMULATE-ICP [ISRCTN10665760]  UCL / NIHR (UK Govt)
Colchicine	NLRP3 Inflammasome Inhibitor Potent anti-inflammatory that inhibits microtubule polymerization and blocks the NLRP3 Inflammasome. Targets systemic inflammation and pericarditis-like symptoms.	Long COVID (Fatigue and/or PEM) POM: PROMIS-29 physical health summary score	Active Phase 3 (Started Feb 2025) Study: RECLAIM (Netherlands) [NCT07280572]  UMC Utrecht / ZonMw
Minocycline	Microglial Inhibitor Tetracycline antibiotic that crosses the blood-brain barrier to inhibit Microglial Activation and reduce neuro-inflammation (TNF- α /IL-6). Targets "Brain Fog" and neuro-cognitive deficits.	Long COVID (Fatigue and/or PEM) POM: PROMIS-29 physical health summary score	Active Phase 3 Platform (Minocycline Arm Starting Jan 2026) Study: RECLAIM (Netherlands) [NCT07280572]  UMC Utrecht / ZonMw
Sirolimus (Rapamune)	mTOR Inhibitor Induces autophagy ("cellular cleanup").	Long COVID (General) POM: EQ VAS	Active Phase 3 Study: Sirolimus-LC [NCT06960928]  PolyBio / Mount Sinai

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Fluvoxamine	SSRI (Sigma-1 Agonist) High-affinity Sigma-1 receptor agonist that reduces cytokine production in the brain. Investigated to treat Neuro-Inflammation ("Brain Fog") and cognitive dysfunction, distinct from its antidepressant effects.	Long COVID (Neuro-Cognitive / Brain Fog) POM: symptom score via the daily questionnaire	Active Phase 2/3 (Results expected May 2025) Study: Fluvoxamine for Long COVID [NCT05874037]  Washington Univ. St. Louis
Ibudilast (Ketas)	PDE4 & MIF Inhibitor / Glial Modulator Dual inhibitor of PDE4 and Macrophage Migration Inhibitory Factor (MIF). Crosses the BBB to dampen Microglial Activation, stopping the neuro-inflammatory loop that drives "Brain Fog" and central fatigue.	Long COVID (General) POM: SF-36 (PCS)	Active Phase 2/3 (Analyzing Phase 2 Data) Study: RECLAIM (Canada) [NCT05513560]  Univ. Health Network
Atorvastatin (Lipitor) + Maraviroc (Selzentry)	Fractalkine & CCR5 Blockade Dual mechanism: Atorvastatin lowers Fractalkine (CX3CL1) to stop monocyte adhesion, while Maraviroc blocks CCR5 to prevent vascular migration. Targets the "Monocyte-Endothelial" inflammation axis.	Long COVID (General) POM: Fatigue (FSS & PGI-S)	Active Phase 2/3 Study: IMPACT-LC [NCT06974084]  HealthBio (formerly IncellDx)/ Academic
N-Acetylcysteine (NAC Monotherapy)	Redox Modulator & NF-κB Inhibitor Replenishes intracellular glutathione to neutralize oxidative stress. Directly inhibits the NF-κB pathway to break the cycle of systemic inflammation, cytokine storms (IL-6), and glial activation.	Long COVID (Fatigue / Systemic Inflammation) POM: Fatigue Assessment Scale & Inflammatory markers	Active / Completed Phase 2 (Various Academic Protocols) Study: NAC in Post-COVID  Multiple Academic Centers

III. Coagulation & Endothelial Damage

Clearing microclots, restoring vascular perfusion, and repairing endothelial lining.

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
INNOVATIVE	<i>(Pipeline / Novel)</i>		
Hyperbaric Oxygen (HBOT)	Angiogenesis / Stem Cell Mobilization Triggers the release of CD34+ Stem Cells and HIF-1alpha. This physically repairs damaged endothelial lining, grows new capillaries, and reverses tissue hypoxia / neuro-inflammation.	Long COVID (PEM and/or Dysautonomia) POM: SF-36	Active Phase 3 Study: HBOT-LC [NCT06267300] RECLAIM (Netherlands)  Erasmus MC
Vilobelimab (Gohibic)	Anti-C5a Monoclonal Antibody Selectively blocks C5a (a potent inflammatory peptide) to stop neutrophil activation and endothelial damage. Breaks the "Thrombo-Inflammation" loop driven by complement, without fully suppressing the immune system.	Long COVID (Vascular Inflammation / Microclots)	Protocol in Development (Post-Acute Program Announced)  InflaRx (Biotech)
ON MARKET	<i>(Repurposed Brand / Patent Protected)</i>		
Rivaroxaban (Xarelto)	Factor Xa Inhibitor (Anticoagulant) Direct oral anticoagulant that prevents the formation of Microclots and reduces endothelial inflammation. Investigated to improve vascular perfusion and reduce fatigue.	Long COVID (General) POM: Fatigue Assessment Scale	Phase 3 (Recruitment Completed - Results Pending 2025) Study: STIMULATE-ICP [ISRCTN10665760]  UCL / NIHR (UK Govt)

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Sulodexide (Vessel Due F)	Glycosaminoglycan (Heparan Sulfate) Restores the Endothelial Glycocalyx (the protective lining of blood vessels) to reduce permeability and inflammation. Also has antithrombotic properties without high bleeding risk.	Long COVID (Endothelial Dysfunction) POM: Long-COVID-19 symptoms evolution	Successful Phase 2 (Published 2022) Study: TUN-EndCOV [PACTR20210286754 4936]  Alfasigma (Pharma)
Vericiguat (Verquvo)	sGC Stimulator Stimulates soluble Guanylate Cyclase (sGC) to increase cGMP. This relaxes smooth muscle and restores Microvascular Perfusion in patients with Endothelial Dysfunction.	Long COVID with ME/CFS POM: SF36	Active Phase 2 Study: VERI-LONG [NCT05697640]  Charité Berlin / Bayer
Lumbrokinase (Boluoke)	Fibrinolytic Enzyme Potent enzyme derived from earthworms that breaks down Fibrin (the mesh of microclots). Investigated to dissolve amyloid microclots and improve oxygen delivery. <i>Nutraceutical (On Market).</i>	Long COVID / Lyme / ME/CFS POM: EQ-VAS	Active Phase 2 Study: Lumbrokinase for Long COVID [NCT06511050]  Mount Sinai / PolyBio
GENERIC	<i>(Off-Label / Old / Multi-Source)</i>		
Pirfenidone (Esbriet)	Anti-fibrotic Inhibits Transforming Growth Factor-beta (TGF- β) to stop collagen synthesis and tissue scarring. Repurposed here to treat systemic fibrosis and "vascular remodeling" across 5 symptom domains.	Long COVID (General) POM: 5 SSBQ Subscales	Active Phase 3 Study: LC-REVITALIZE [NCT06928272]  Western Univ. / SILC (Schmidt Initiative)

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Pentoxifylline (Trental)	PDE Inhibitor & Hemorheologic Agent Improves Red Blood Cell (RBC) deformability to resolve microvascular hypoperfusion (viscosity). Also inhibits TNF-alpha to reduce systemic inflammation.	Long COVID (General) POM: SF-36 (PCS)	Active Phase 2/3 (Analyzing Phase 2 Data) Study: RECLAIM (Canada) [NCT05513560]  Univ. Health Network
Serrapeptase / Nattokinase (Fibrinolytic Enzymes)	Proteolytic Enzymes Degrade Fibrin (the mesh of microclots) and potentially hydrolyze the Spike protein. Use of Serrapeptase (in ImmunoSEB) showed significant reduction in Post-COVID Fatigue vs placebo.	Long COVID (Fatigue) POM: CFQ-11	Successful Phase 2 (Published RCT) Study: ImmunoSEB Trial [CTRI/2021/05/033576]  Entero Healthcare / Clinical Centers
Triple Therapy (Clopidogrel / Aspirin / Apixaban)	Dual Antiplatelet + Anticoagulant Aggressive combination to clear amyloid Fibrin Microclots and reverse platelet hyperactivation.	Long COVID (Confirmed Microclots)	Clinical Evidence (Observational Study Published 2022) Study: Microclot Resolution [HREC Ref: B21/03/001]  Stellenbosch Univ. (Pretorius Lab).
Therapeutic Apheresis (H.E.L.P.)	Heparin-Induced Extracorporeal Filtration Filters the blood to remove Fibrinogen, Lipids, and inflammatory cytokines. Mechanistically targets Microclots and hyper-coagulation.	Long COVID (Microclots / Vascular)	Clinical Practice (Observational Data Only) Study: Jaeger Case Series (Germany)  Private Clinics (Dr. Jaeger/Mulheim)

IV. Neuro-Autonomic & Neuroendocrine

Repairing autonomic function, HPA axis homeostasis, and cognitive circuitry.

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
INNOVATIVE	<i>(Pipeline / Novel)</i>		
AXS-14 (Esreboxetine)	Selective NRI Highly selective Norepinephrine Reuptake Inhibitor (SS-enantiomer). <i>Status Note: The previous Phase 3 (NCT00752505) was positive, but FDA requested a New Phase 3 (Fixed-Dose) in June 2025. Axsome launches this new trial in Q4 2025.</i>	Fibromyalgia	Active Phase 3 (Start Q4 2025 / NCT Pending) Study: AXS-14 New Protocol  Axsome Therapeutics
OSU-6162 (Monoamine Stabilizer)	Dopamine "Thermostat" Unique stabilizer that normalizes dopamine / serotonin levels (boosts if low, dampens if high). Specifically targets "Mental Fatigue" and sensory overload by restoring cortical signaling efficiency.	(ME/CFS / Brain Fog) POM: self-assessment questionnaire mental fatigue and concentration	Phase 3 ready Completed Phase 2 (Positive Signal for Mental Fatigue) + 2nd Open Label Phase 2 Study: EudraCT 2011-004357-82  Carlsson Research (Biotech)
CT38	CRF2 Agonist Peptide that stimulates Corticotropin-Releasing Factor Receptor 2 to "reset" the HPA Axis and autonomic nervous system. Hypothesized to permanently reverse the "limbic cross-wiring" in ME/CFS.	ME/CFS POM: TDSS	Completed Phase 1/2 (Positive Pilot Published 2021) Study: InTiME [NCT03613129]  Cortene Inc.

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
TNX-102 SL Sublingual Cyclobenzaprine (Tonmya)	Sleep Quality / Analgesic Novel sublingual formulation. Improves "non-restorative sleep" to reduce central sensitization, widespread pain, and fatigue.	Long COVID (Fibro Phenotype) POM: Diary Pain NRS	Completed Phase 2 (Positive Fatigue Signal) Study: PREVAIL [NCT05472090]  Tonix Pharmaceuticals
REGN7544 (NPR1 Antagonist)	NPR1 Antagonist Targeted monoclonal antibody designed to increase blood volume and pressure, addressing the hypovolemia seen in POTS.	POTS POM: Safety, tolerability, and change in heart rate / blood pressure	Active Phase 2 PINNACLE (Enrolling) Study: [NCT06593600]  Regeneron Pharmaceuticals
Lidocaine (SC) (Subcutaneous / Low Dose)	Sodium Channel Blocker & P2X7 Inhibitor Systemic desensitization via subcutaneous injection. Inhibits the P2X7 receptor to dampen Hyperinflammation and reset central pain/fatigue pathways.	Long COVID (Pain / Fatigue)	Published Evidence (Positive Observational Study 2025) Study: VU Amsterdam Lidocaine Study  Vrije Univ. Amsterdam / Excellent Care
ON MARKET	<i>(Repurposed Brand / Patent Protected)</i>		
Vortioxetine (Trintellix)	Multimodal Antidepressant Modulates serotonin receptors and reduces neuro-inflammation. <i>Improved cognition / depressive symptoms in patients with high CRP</i>	Long COVID (General) POM: DSST	Completed Phase 2 (Published 2023) Study: Vortioxetine for PCC [NCT05047952]  Brain & Cognition Fdn (Canada)

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Tirzepatide (Zepbound / Mounjaro)	Dual GLP-1/GIP Agonist Activates both GLP-1 and GIP receptors to potentially reduce Neuroinflammation (via microglia) and improve metabolic function. Scripps hypothesizes this dual-action is superior to GLP-1 alone for "Brain Fog" and fatigue.	Long COVID (General) POM: FSS	Active Phase 2 Study: LoCITT-T [NCT07128082]  Scripps (Eric Topol) / Eli Lilly
Ivabradine (Corlanor)	HCN Channel Blocker Selectively inhibits the sinus node to lower heart rate without lowering blood pressure (unlike beta-blockers). Targets the hyperadrenergic / POTS phenotype caused by autonomic dysfunction.	Long COVID (POTS Phenotype) POM: OHQ/OIQ scales (and Malmo, Compass31 etc.)	Active Phase 2 Study: RECOVER-AUTONOMIC [NCT06305806]  Duke Univ. / NIH RECOVER
Solriamfetol (Sunosi)	DNRI (Dopamine-NE Reuptake Inhibitor) Potent wakefulness promoter. Unlike amphetamines, it does not release monoamines but inhibits their reuptake. Alternative arm for patients who cannot tolerate Modafinil.	Long COVID (Hypersomnia) POM: PROMIS 8a SRI	Active Phase 2 Study: RECOVER-SLEEP (Hypersomnia) [NCT06404099]  NIH RECOVER
tVNS (Nurosylm) (Proprietary Vagal Stimulator)	Parasympathetic Neuromodulator Non-invasive proprietary vagal stimulator (CE-marked medical device). Activates the cholinergic anti-inflammatory pathway to target nociceptive/neuropathic pain and migraines.	Long COVID (Pain / Migraine Phenotype) POM: Reduction in pain intensity	Active Phase 2 Study: COLOSAT [NCT05205577]  AP-HP (Paris)

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Suzetrigine (Journavx / VX-548)	NaV1.8 Sodium Channel Blocker First-in-class, non-opioid pain signal inhibitor. Highly selective for NaV1.8 channels in the peripheral nervous system, blocking pain signals before they reach the brain.	Fibromyalgia / PAIS Pain (Peripheral Neuropathic Pain)	Approved for acute pain; academic groups are initiating Phase 2 trials for chronic PAIS pain phenotypes in 2025.  Vertex Pharmaceuticals
GENERIC	<i>(Off-Label / Old / Multi-Source)</i>		
Cannabidiol (Medical CBD)	Endocannabinoid Modulator High-dose pharmaceutical CBD (up to 50 mg). Modulates glial activation (neuro-inflammation) and pain pathways without the psychoactive effects of THC.	Fibromyalgia	Completed Phase 2 (Results Analysis 2025) Study: CANNFIB Trial [NCT04729179]  Danish Pain Research Center
Lithium Aspartate	GSK-3β Inhibitor Reduces neuro-inflammation and protects neurons. <i>Low dose (15 mg) FAILED in RCT. Follow-up showed benefit only at higher doses (40-45 mg) targeting serum levels >0.18 mEq/L.</i>	Long COVID (Fatigue / Brain Fog) POM: Fatigue Severity Scale; Brain Fog Severity Scale	Completed Phase 2 (Published 2024) Study: UB-LC [NCT05618587]  Univ. at Buffalo (Guttuso)

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Psilocybin	5-HT2A Agonist / Central Reset Induces neuroplasticity to "reboot" pain processing networks. Investigated to break the cycle of central sensitization.	Fibromyalgia	Active Phase 2 Study: Psilocybin for Chronic Pain [NCT05068791]  UAB (Univ. Alabama Birmingham)
Amantadine (Gocovri / Generic)	NMDA Antagonist & Dopamine Agonist Increases Dopamine and blocks glutamate toxicity. Targets "Brain Fog" and fatigue by stimulating the frontal cortex. <i>Rationale: A 2024 pilot study showed significant fatigue reduction vs placebo.</i>	Long COVID (Cognitive Deficits) POM: improvement cognitive symptoms	Active Phase 2 Study: Amantadine-LC [NCT06055244]  Ohio State Univ.Univ.
Ketamine (IV / Intranasal)	NMDA Receptor Modulator Rapidly modulates Glutamate (the brain's main excitatory neurotransmitter) to reduce neuro-inflammation and promote synaptic plasticity. Targets the "Brain Fog" and rigid depression loops seen in Neuro-COVID.	Long COVID (Fatigue or Cognitive dysfunction) POM: PROMIS SF v1.0 - Fatigue 8a; PROMIS SF v2.0 Cognitive Function 4a; BrainCheck Cognitive Battery	Active Phase 2 Study: Neuromodulatory Effect [NCT06821087]  UT Austin / WithPower
Mestinon + LDN (Pyridostigmine + Low Dose Naltrexone)	AChE Inhibitor + Glial Modulator Combination therapy: Mestinon increases acetylcholine to improve Venous Return (Preload Failure), while LDN reduces neuro-inflammation. Targets the root cause of "Exercise Intolerance" and POTS.	Long COVID or ME/CFS (both OI subtype) POM: FUNCAP55	Active Phase 2 Study: LIFT Trial [NCT06366724]  Brigham & Women's (Systrom)

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Low-Dose Naltrexone (LDN / 4.5 mg)	Glial Modulator / TRPM3 Blocks opioid receptors briefly to increase endogenous endorphins and reduce Neuro-Inflammation (microglial activation). Also restores TRPM3 ion channel function (Griffith data).	Long COVID (PCFS) POM: FSS	Active Phase 2 Study: LDN for Post-COVID Fatigue [NCT05430152] 🏛️ UBC / BC Women's Hospital
rTMS (Repetitive Transcranial Magnetic Stimulation)	Neuromodulation (10Hz) Uses magnetic pulses to stimulate the prefrontal cortex. Intended to reverse Hypometabolism (reduced brain activity) associated with severe fatigue and "Brain Fog."	Long COVID (Severe Fatigue) POM: fatigue subscale of the Checklist Individual Strength (CIS)	Active Phase 2 Study: MALIBU Trial [NCT07278206] 🏛️ Amsterdam UMC / ZonMw
tVNS (Auricular Vagus Nerve Stimulation)	Neuromodulation (Ear Clip) Stimulates the auricular branch of the Vagus Nerve (at the tragus) to increase parasympathetic tone. Targeted to treat Fatigue & PEM in patients meeting ME/CFS criteria.	Long COVID + ME/CFS POM: Chalder Fatigue Questionnaire (CFQ); SF36 etc.	Active Phase 2 Study: tVNS in Long COVID [NCT06585254] 🏛️ Mount Sinai (Natelson)
tVNS (Auricular Vagus Stimulation)	Parasympathetic Neuromodulator Non-invasive vagal stimulator. Specifically tests the hypothesis that activating the cholinergic anti-inflammatory pathway suppresses muscarinic autoantibodies driving POTS.	POTS (Autoimmunity) POM: Heart rate variability	Active Phase 2 (Completed) Study: [NCT05043051] 🏛️ University of Oklahoma

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
tDCS (Transcranial Direct Current Stimulation)	Prefrontal Neuromodulation Delivers low-intensity current (2 mA) to the left dorsolateral prefrontal cortex to increase neuronal excitability and synaptic plasticity. Targets dysexecutive syndrome and "brain fog."	Long COVID (Brain Fog / Cognitive Deficits) POM: Change in executive function scores	Active Phase 2 Study: [NCT05092516]  Massachusetts General Hospital / Harvard
tDCS (Motor Cortex Stimulation)	Motor Cortex Neuromodulation Applies current over the primary motor and sensory cortex (M1/S1) to alter spontaneous neuronal firing rates. Corrects central fatigue loops seen in post-viral patients.	Long COVID (Central Fatigue) POM: Fatigue severity scale	Active Phase 2 Study: [NCT04876417]  University of Iowa
Modafinil (Provigil)	Dopamine Reuptake Inhibitor Wakefulness-promoting agent. Improves alertness by increasing synaptic dopamine. First- line intervention in the RECOVER platform for Hypersomnia.	Long COVID (Hypersomnia) POM: PROMIS 8a SRI	Active Phase 2 Study: RECOVER- SLEEP (Hypersomnia) [NCT06404099]  NIH RECOVER
Melatonin (High Dose / Guided)	Chronobiotic & Antioxidant Regulates the circadian Sleep-Wake Cycle and reduces oxidative stress. Used in combination with Light Therapy to reset circadian rhythm dysfunction.	Long COVID (CPSD) POM: PROMIS 8b SD	Active Phase 2 Study: RECOVER- SLEEP (CPSD) [NCT06404112]  NIH RECOVER

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Moxonidine (Central Sympatholytic)	Central Imidazoline Agonist Antihypertensive generic. Precision treatment targeting the "hyperadrenergic" POTS phenotype. Lowers excessive central sympathetic nerve activity to reduce paradoxical upright tachycardia.	(Hyperadrenergic) POTS POM: Difference in heart rate change from supine to upright postures (delta HR)	Active Phase 1/2 (Completed) Study: [NCT04050410]  Vanderbilt University Medical Center
Stellate Ganglion Block (SGB / Dual Sympathetic Reset)	Sympathetic Nerve Block Injection of local anesthetic to "reboot" the autonomic nervous system. <i>While the WashU trial (NCT06253806) failed for Parosmia, a 2025 pilot confirmed significant benefit for Fatigue, PEM, and Dysautonomia (Autonomic Reset).</i>	Long COVID / ME/CFS (Dysautonomia / Fatigue / PEM)	Clinical Evidence (Published Pilot 2025) Study: SolveME / Duricka Pilot  Neuroversion / SolveME  Washington Univ. St. Louis

V. Autoimmunity & Humoral Response

Neutralizing or removing functional autoantibodies (AABs).

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
INNOVATIVE	<i>(Pipeline / Novel)</i>		
BC 007 (Rovunaptabin)	DNA Aptamer Binds to and neutralizes functional GPCR Autoantibodies (fAAb) that disrupt blood flow and heart function. <i>The "Berlin Cures" trial FAILED (broad criteria), but the academic Erlangen "reCOVer" Trial was POSITIVE (showing significant fatigue reduction in fAAb+ patients).</i>	Long COVID with POTS (GPCR AAB Positive)	Active (New Entity) Study: Phase 2 Planning  APTA Therapeutics (formerly Berlin Cures)
RSLV-132 (RNase-Fc Fusion)	Auto-Autoantibody Digestion Digests circulating RNA-containing immune complexes.	Long COVID (Fatigue) POM: PROMIS Fatigue SF 7a T-score	Completed Phase 2 (Negative Results 2024) Study: RESOLVE-LC [NCT04944121]  Resolve Therapeutics
ON MARKET	<i>(Repurposed Brand / Patent Protected)</i>		
Daratumumab (Darzalex)	Anti-CD38 mAb Depletes long-lived Plasma Cells (which produce autoantibodies). <i>A 2025 pilot showed 60% of patients had dramatic remission. Targets the "Root Cause" of antibody production better than Rituximab (which missed plasma cells).</i>	ME/CFS (Autoimmune phenotype)	Active Phase 2 Study: ResetME Trial [EU CTIS 2024-520094-13]  Haukeland Univ. (Fluge & Mella)

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
Isatuximab (Sarclisa)	Anti-CD38 mAb Depletes Long-Lived Plasma Cells (the "factories" producing GPCR autoantibodies). Targets the specific immune cells that survive Rituximab (CD20) therapy.	ME/CFS, Long COVID (Autoimmune / GPCR AAB+)	Protocol in Development (Planned Investigator-Initiated Trial) 🏥 Charité Berlin (Scheibebogen) / Sanofi
Rituximab (Rituxan)	Depletes B-cells to stop autoantibody production. <i>Earlier Norwegian trials failed in the general population. This new Japanese trial targets a specific B-Cell Receptor (BCR) Skewed subgroup.</i>	ME/CFS (Stratified B-Cell Subset)	Active Phase 2 Study: NCNP Rituximab Trial [NCT06952413] 🏥 NCNP (Japan) / Dr. Wakiro Sato
Efgartigimod (Vyvgart)	FcRn Blocker Blocks the Neonatal Fc Receptor (FcRn), which normally acts as a "recycling pump" to save IgG from destruction. <i>The trial patients were not screened for autoantibodies first. Since ~40-50% of POTS patients may be seronegative, the drug likely worked mechanically but had no target to hit in half the patients, diluting the efficacy signal.</i>	Long COVID with POTS (AAB Non-stratified) POM: COMPASS 31; Malmö POTS Symptom Score (MaPS)	Failed Phase 2 (Lack of AAB screening) 🚫 Argenx (Biotech)
IVIG (Gamunex-C)	Immune Decoy / Immunomodulator Pool of donor antibodies that neutralizes Autoantibodies (e.g., GPCR antibodies) and modulates immune signaling. Targets the immune-mediated driver of POTS and Small Fiber Neuropathy.	Long COVID (POTS Phenotype) POM: OHQ/OIQ scales (and Malmö, Compass31 etc.	Active Phase 2 Study: RECOVER-AUTONOMIC [NCT06305793] 🏥 Duke Univ. / NIH RECOVER

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
IVIG (High dose)	Passive Immunity / Immune Modulation Broad-spectrum antibodies. Neutralizes autoantibodies, downregulates macrophage activation, and clears viral reservoirs. The "Heavy Hitter" for immune dysfunction.	Long COVID (Neurological symptoms) POM: Health Utilities Index Mark 3 (HUI3)	Active Phase 2 Study: NIH Neuro-IVIG [NCT05350774]  NIH Clinical Center (Avindra Nath)
HYQVIA	Immune Replacement Facilitated subcutaneous immunoglobulin.	ME/CFS (IgG Deficiency) POM: Chalder fatigue scale	Active Phase 2 (PoC) Study: EudraCT 2016-002370-12  Charité / Takeda
GENERIC	<i>(Off-Label / Old / Multi-Source)</i>		
Immuno-adsorption	Apheresis Procedure Column-based filtration that selectively removes Autoantibodies (IgG) against GPCRs (adrenergic / muscarinic receptors). Targets the autoimmune driver of POTS and fatigue.	Long COVID + ME/CFS or ME/CFS (Severe Autoimmune Phenotype) POM: Chalder Fatigue Scale	Active Phase 2 (Sham-Controlled RCT) Study: IA-PACS-CFS [NCT05710770]  Charité Berlin / BMBF (German Govt)
Cyclophosphamide (Cytoxan / IV Pulse)	Broad Cytotoxic Immune Reset Potent chemotherapy agent that depletes B-cells, T-cells, and naive lymphocytes ("rebooting" the immune system).	ME/CFS (Severe / Refractory) POM: Selfreported Fatigue score	Clinical Evidence (Positive Phase 2 + 6-Year Follow-Up) Study: CycloME Trial [NCT02444091]  Haukeland Univ. (Fluge & Mella)

VI. Metabolic & Energy Dysfunction

Restoring mitochondrial function and correcting metabolic traps.

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
INNOVATIVE	<i>(Pipeline / Novel)</i>		
KH176 (Sonlicromanol)	Redox Modulator & ROS Scavenger Unique brain-penetrant small molecule reducing Reactive Oxygen Species (ROS) inside mitochondria and modulates the inflammatory redox network. Targets the "Bioenergetic Failure" in Post-COVID fatigue.	Long COVID (General)	Active Phase 2 (Recruiting Q1 2025) Study: Sonlicromanol in Post-COVID [ZonMw 11080022420008]  Khondrion / Amsterdam UMC
MDC002	Ion Exchange Modulator (NCLX) Small molecule that stimulates the Na ⁺ /K ⁺ Pump and mitochondrial Na ⁺ /Ca ²⁺ Exchanger. Fixes the "Sodium Overload" that causes Ca-toxicity in mitochondria during exertion (PEM).	ME/CFS & Long COVID (PEM Symptoms)	Pre-Clinical (Phase 1 Planning) Study: Mitodicure Pipeline  Mitodicure GmbH (Germany)
IDO2 Modulator (Metabolic Trap Breaker)	Kynurenine Pathway Reset Targets the "Metabolic Trap" where the IDO2 enzyme is stuck (or overactive), disrupting the conversion of Tryptophan to Kynurenine / Serotonin (the Dutch biotech Oncolines launched a screening assay for this in late 2024).	ME/CFS & Long COVID (Tryptophan Trap / Kynurenine Dysfunction)	ZonMw Grant 2024 Study: ME/CFS Lines (Genetics & Metabolomics) [ZonMw Grant: 09120012010063]  Erasmus MC / ZonMw / Oncolines

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
ON MARKET	<i>(Repurposed Brand / Patent Protected)</i>		
Dapagliflozin (Farxiga)	SGLT2 Inhibitor / mTOR Induces a metabolic "fasting state" (mild ketosis) that reduces oxidative stress and inhibits NLRP3 inflammasome activation. Targets mitochondrial dysfunction and endothelial inflammation.	Long COVID (General) POM: EQ-5D	Active Phase 3 Study: DALCO [NCT06907251]  Ottawa Heart Institute
GENERIC	<i>(Off-Label / Old / Multi-Source)</i>		
Metformin	mTOR & AMPK Activator Anti-diabetic drug that suppresses mTOR (anti-viral) and activates AMPK (mitochondrial repair/autophagy). <i>The COVID-OUT prevention trial (Completed 2023) proved Metformin reduced Long COVID risk by 41%. This new trial tests if it works as a Treatment for established symptoms.</i>	Long COVID (Fatigue and/or PEM) POM: PROMIS-29 physical health summary score	Active Phase 3 (Started Feb 2025) Study: RECLAIM (Netherlands) [NCT07280572]  UMC Utrecht
Oxaloacetate (Oxalax)	Energy Metabolite & Glutamate Scavenger Krebs Cycle intermediate. Increases mitochondrial biogenesis and scavenges excess brain glutamate.  <i>Note: This is a Supplement/Medical Food, not a prescription drug.</i>	Long COVID / ME/CFS (Fatigue / Brain Fog)	Completed Phase 2 RCTs (Published 2025) Study 1 (LC): REGAIN [NCT05840237] Study 2 (ME): RESTORE ME [NCT05273372]  Terra Biologicals / Bateman Horne Center
Taurine (High Dose)	Mitochondrial Neuroprotection Sulfur-containing amino acid that restores Mitochondrial Membrane Potential and acts as an antioxidant. Reduces neuro-inflammation and protects against spike-protein induced metabolic stress.	Long COVID (General) POM: Trail-Making Tests A & B; MFIS	Active Phase 2/3 Study: RECLAIM-TaurineLC [NCT06721949] RECLAIM (Canada)  Univ. Alberta

VII. Microbiome & Gut-Brain Axis

Restoring gut integrity to reduce systemic inflammation and neuro-symptoms.

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
INNOVATIVE	<i>(Pipeline / Novel)</i>		
LIMIT Synbiotics (Butyrate Producers)	Gut-Lung Axis Modulation Specific synbiotic formula (Vitakruid) designed to increase Butyrate-producing bacteria. Targets the "Gut-Lung Axis" to reduce pulmonary inflammation and systemic immune dysregulation.	Long COVID (General)	Active Phase 2 (Recruiting Late 2025) Study: P4O2 LIMIT Project [Dutch P4O2-04]  UMCG / Amsterdam UMC / Vitakruid
Larazotide Acetate (AT-1001)	Zonulin Inhibitor Closes intestinal "tight junctions" (zips them shut). Prevents the leakage of viral antigens (Spike) and toxins from the gut into the bloodstream ("Leaky Gut"), stopping systemic inflammation at the source.	Long COVID (General) POM: SBQ-LC	Active Phase 2 Study: MIS-C/LC [NCT05747534]  Mass General / 9 Meters <i>The company (9 Meters) failed, but Mass General Hospital is keeping the trial alive with grant funding.</i>
ON MARKET	<i>(Repurposed Brand / Patent Protected)</i>		
SIM01 (G-NiiB Formula)	Specific formulation derived from Chinese microbiome data. Restores gut barrier and increases Short Chain Fatty Acids (SCFAs).	Long COVID (General)	Positive Phase 2 (Published) Study: RECOVERY-SIM01 [NCT04950803]  GenieBiome (G-NiiB) / CUHK

Intervention (Asset Name)	Mechanism & Rationale	Population & Primary Outcome Measure (POM)	Current Status & Sponsor
GENERIC	<i>(Off-Label / Old / Multi-Source)</i>		
Rifaximin (Xifaxan / Zaxine)	Non-Systemic Antibiotic Reduces bacterial overgrowth (SIBO). Generics available (200mg).	Long COVID / ME/CFS (GI / SIBO Phenotype)	Clinical Recommendation Study: Standard of Care (ACGs)  Clinical Practice
FMT	Fecal Transplant Complete ecosystem replacement. <i>Open-label Pilot showed significantly improved Insomnia (Remission: 37.9% vs 10%), Anxiety, and Fatigue compared to controls.</i>	Long COVID (General) POM: Insomnia Severity Index (ISI)	Clinical Evidence (Positive Pilot 2024) Study: FMT-PACS (CUHK) [NCT05556733]  Chinese Univ. Hong Kong (Siew Ng)

VIII. Diagnostics & Precision Medicine

Biomarkers for PAIS patient stratification (Endotyping)

Platform / Test	Technology & Rationale	Target Biomarker	Status & Developer
Biolab Microclots	Fluorescence Microscopy Detects amyloid fibrin microclots.	Microclots	Commercial  Biocode Technologies
CellTrend Panels	ELISA Detects functional autoantibodies (GPCR, ACE2).	Functional Autoantibodies	Commercial  CellTrend
IncellKINE MetX	AI / Flow Cytometry Scores cytokine signatures and S1 Protein.	Cytokine Signature	Commercial  IncellDx
HIFIBIO Profiling	Single-Cell Analysis Deep immune profiling.	Immune Cell Subsets	Active R&D  HIFIBIO
Corneal Confocal Microscopy	Ophthalmic Imaging Non-invasive scan of corneal nerves.	Small Fiber Neuropathy	Clinical / Research  Weill Cornell
Nailfold Capillaroscopy	Microscopy Visualizes capillaries to detect damage.	Microvascular Damage	Clinical / Research  Academic
Sublingual Microscopy	Vital Microscopy Real-time imaging of glycocalyx.	Glycocalyx	Active Research  MicroVision Medical
EndoPAT	Peripheral Arterial Tonometry Measures endothelial vasodilator function.	Endothelial Dysfunction	Commercial  Itamar Medical
CoverScan	Multi-parametric MRI Single-scan assessment of multi-organ damage.	Multi-organ Damage	Commercial / Research  Perspectrum
TSPO-PET	Nuclear Imaging Radiotracers visualize activated microglia.	Neuro-Inflammation	Active Research  Imaging Centers
Invasive CPET	Cardiopulmonary Testing Diagnose Preload Failure.	Preload Failure	Active Clinical  Brigham & Women's

Platform / Test	Technology & Rationale	Target Biomarker	Status & Developer
2-Day CPET	Serial CPET Objectively verifies Post-Exertional Malaise.	PEM / Metabolic Dysfunction	Standard of Care  Workwell Foundation
Extracranial Doppler	Ultrasound Measures cerebral blood flow volume during tilt.	Cerebral Hypoperfusion	Clinical Validation  Expert Centers
7 Tesla MRI	Ultra-High Field MRI Visualizes brainstem atrophy.	Brainstem Injury	Academic Validation  Cambridge / NIH
Skin Biopsy (IENFD)	Tissue Histology Counts nerve fibers for SFN.	Small Fiber Neuropathy	Standard of Care  Neurology Clinics
Retinal OCT-A	Angiography Measures retinal vessel density.	Microcirculation	Active Research  Northwestern
Sodium MRI	Magnetic Resonance Measures elevated tissue sodium.	Muscle Pathology	Active Research  Charité Berlin
Dynamic HRV Recovery	Autonomic Monitoring Tracks recovery curve after exertion.	PEM Threshold	Clinical Research  VU Amsterdam
Muscle Ultrastructure	Electron Microscopy Measures capillary basement membrane thickening.	Diffusion Barrier	Definitive Proof  VU Amsterdam
Single-Cell Multi-Omics	AI Proteomics Identifies distinct patient clusters.	Molecular Subtypes	Active Mapping  KU Leuven
VIPER Algorithm	In Silico Systems Biology Reverse-engineers "Master Regulators".	Master Regulators	Academic Research  Columbia Univ.
mitoPO2	Cellular Bioenergetics Measures mitochondrial oxygen tension.	Mitochondrial Function	Active Research  UMC Groningen
suPAR	Blood Biomarker Inflammatory marker for Anakinra.	Inflammation	Validated  Radboud UMC

Platform / Test	Technology & Rationale	Target Biomarker	Status & Developer
Kynurenine Metabolites	Mass Spectrometry Measures Tryptophan/Kynurenine ratio.	Metabolic Trap	Active Research  ZonMw
Neurofilament Light	Simoa Assay Measures axonal injury.	Axonal Injury	Active Research  Quanterix
Mitochondrial EVs	Liquid Biopsy Detects mitochondrial proteins.	Mitochondrial Dysfunction	Active Research  NIH / Cornell
Circulating RNA-Complexes	Molecular Assay Detects immune complexes.	RNA	Active Research  Resolve Therapeutics
Nanoneedle Bioimpedance	Nano-electronics Measures cellular electrical response to stress.	Metabolic Stress	Prototype R&D  Stanford
Breath Biopsy	VOC Analysis Detects Volatile Organic Compounds.	Metabolic Dysregulation	Active R&D  Owlstone Medical

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