New treatments for PH, clinical trials and drugs in development

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afph
ALLIANCE FOR PULMONARY HYPERTENSION

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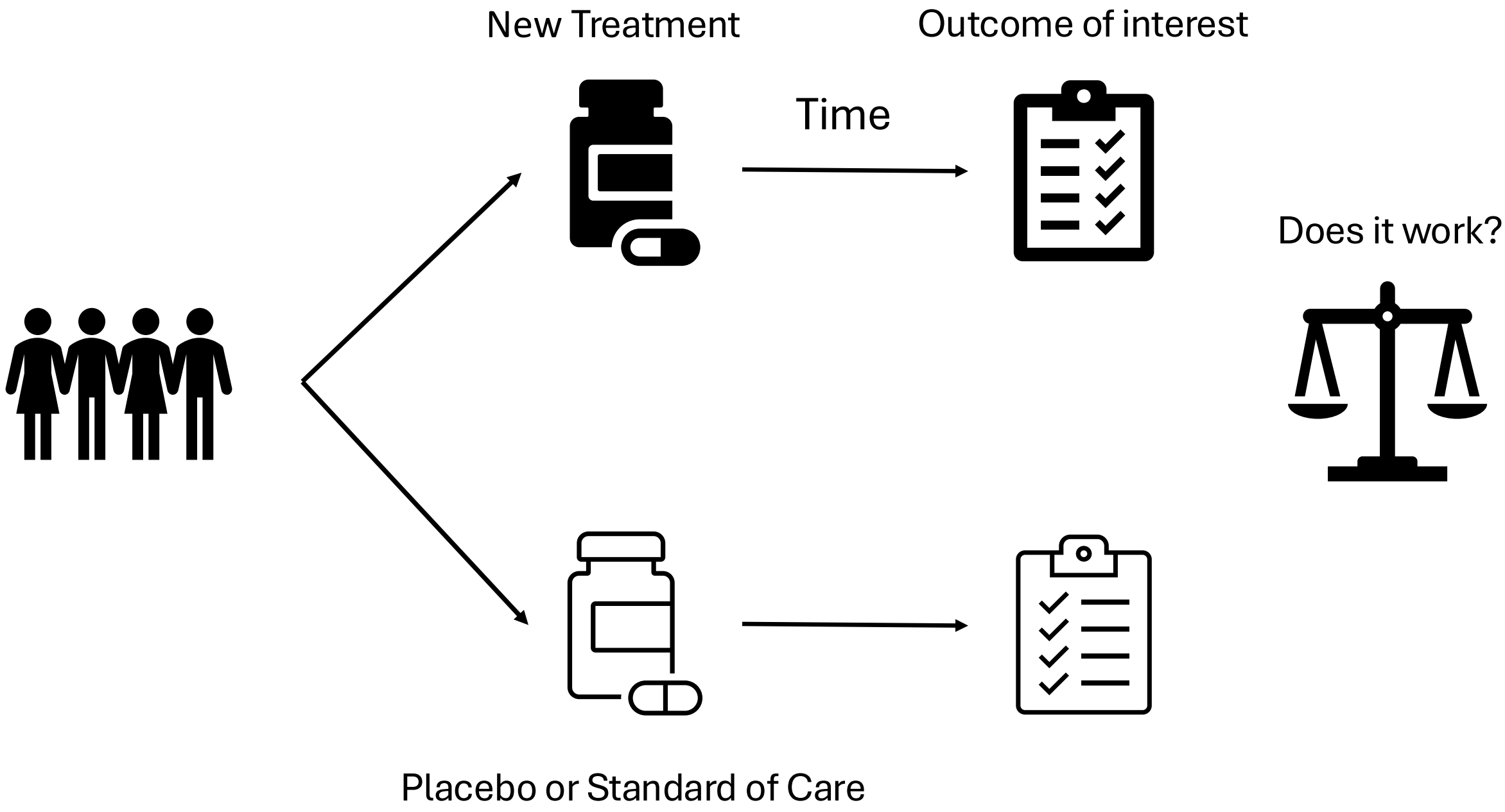
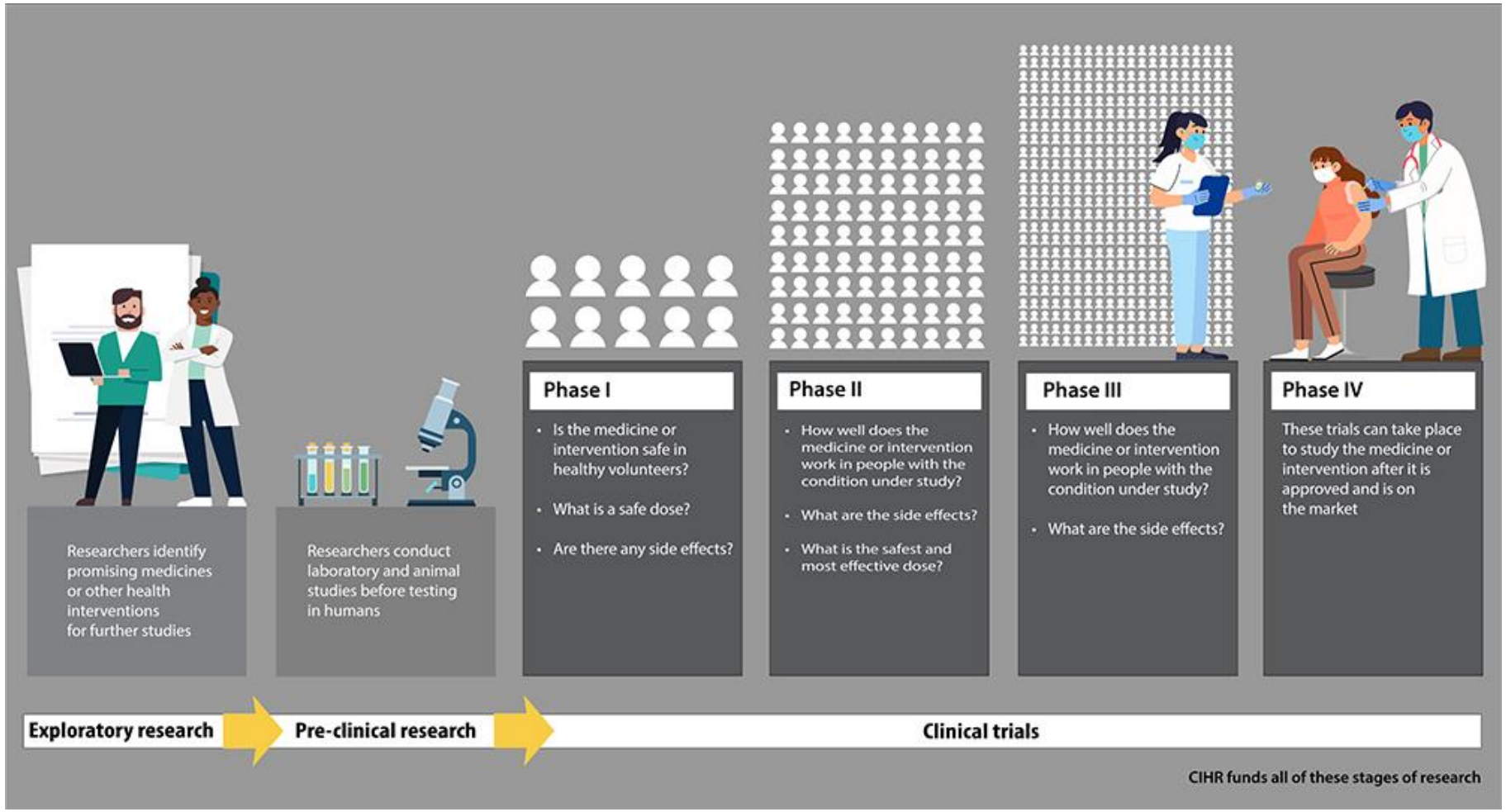
What are clinical trials?

- Type of research study
- One or more participants
- Prospectively assigned to 1 or more interventions
- Test the effect on health-related or behavioral outcome


New Treatment
Outcome of interest
Time
Does it work?
Placebo or Standard of Care

What are the phases of clinical trials?



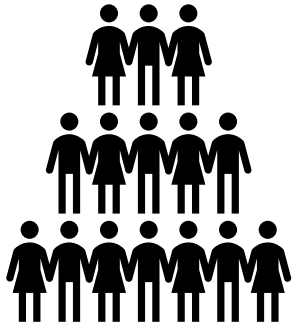
https://cihr-irsc.gc.ca/e/52988.html

Why do we need clinical trials?

Is it safe?

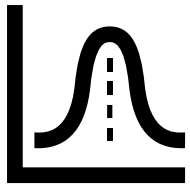
Is it effective?

Advance knowledge and care

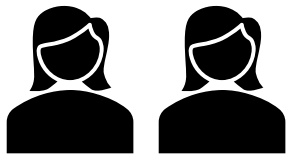


Who benefits?

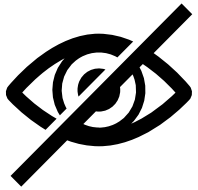
Key Features of Phase 3 Clinical Trials for New Pharmaceutical Therapies



Randomization – eliminates 'confounders'.
Ensures the groups are the same so that only treatment is different between groups



Controls – need to compare a treatment to something.
E.g. Standard of care, placebo. Otherwise there's no way to know what would have happened without the treatment



Blinding – patients and researchers shouldn't know.
Not always possible to do (e.g. surgery trial). Without blinding patients might be treated differently, they might quit the trial or perform/report outcomes differently → *Introduces Bias*

Complete Follow-up – drop-outs undermine the results and introduce bias.
What if drop-outs are all do to side effects? Analyzing only people without side effects would make a drug look better than it actually is.

Endpoints in Pulmonary Hypertension Trials: What do we measure to know that something works?

Phase 1 Trials

Safety & tolerability
Drug levels

Phase 2 Trials

Safety & tolerability
Hemodynamics – Heart Catheters
Exercise capacity

Phase 3 Trials

"Feels, Functions, Survives"

Symptoms – WHO functional class
Patient reported outcomes – surveys
6-minute walk distance
Hospitalizations, clinical worsening, survival
Safety & tolerability

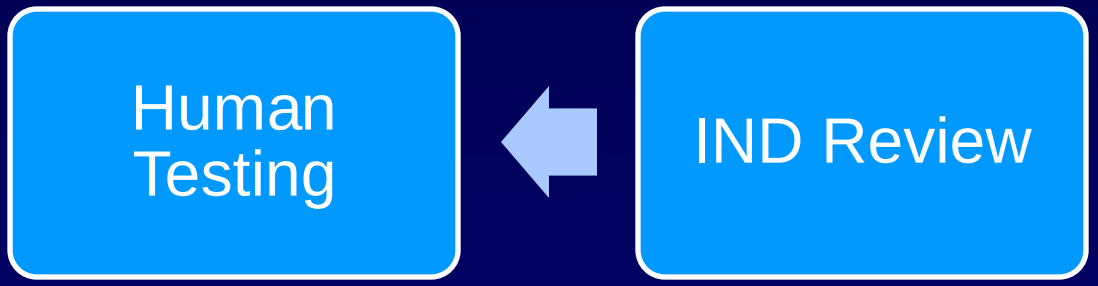
Number of patients needed in the trial

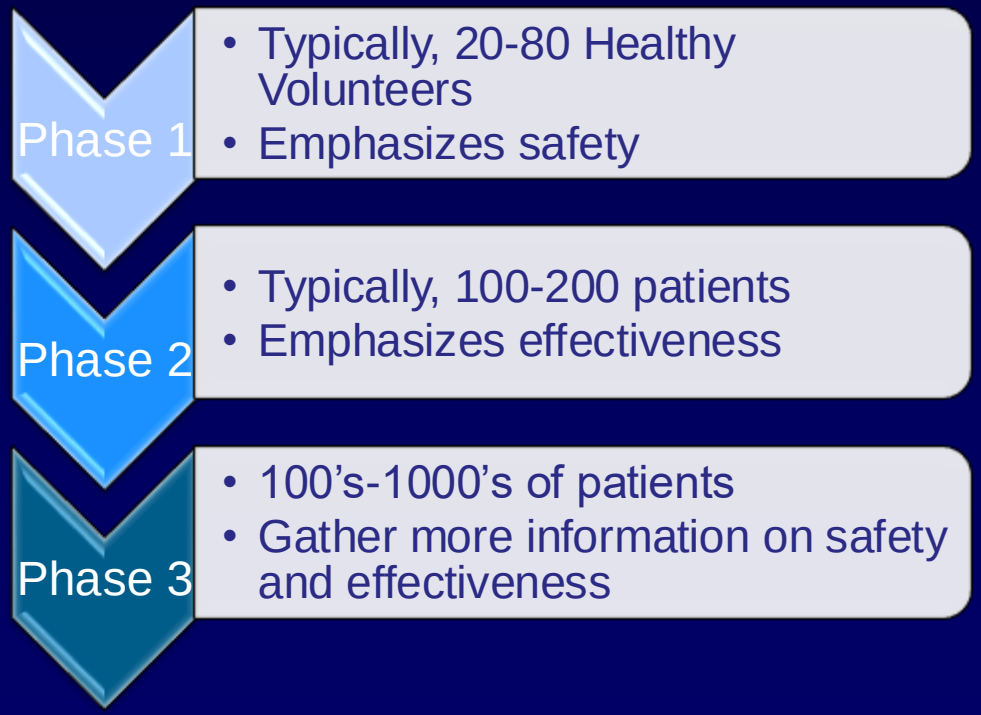
10-20 | **30-100** | **100-2000**

Clinical trial process

Clinical Trials

Investigational drugs go through many steps before they can be approved by the FDA.





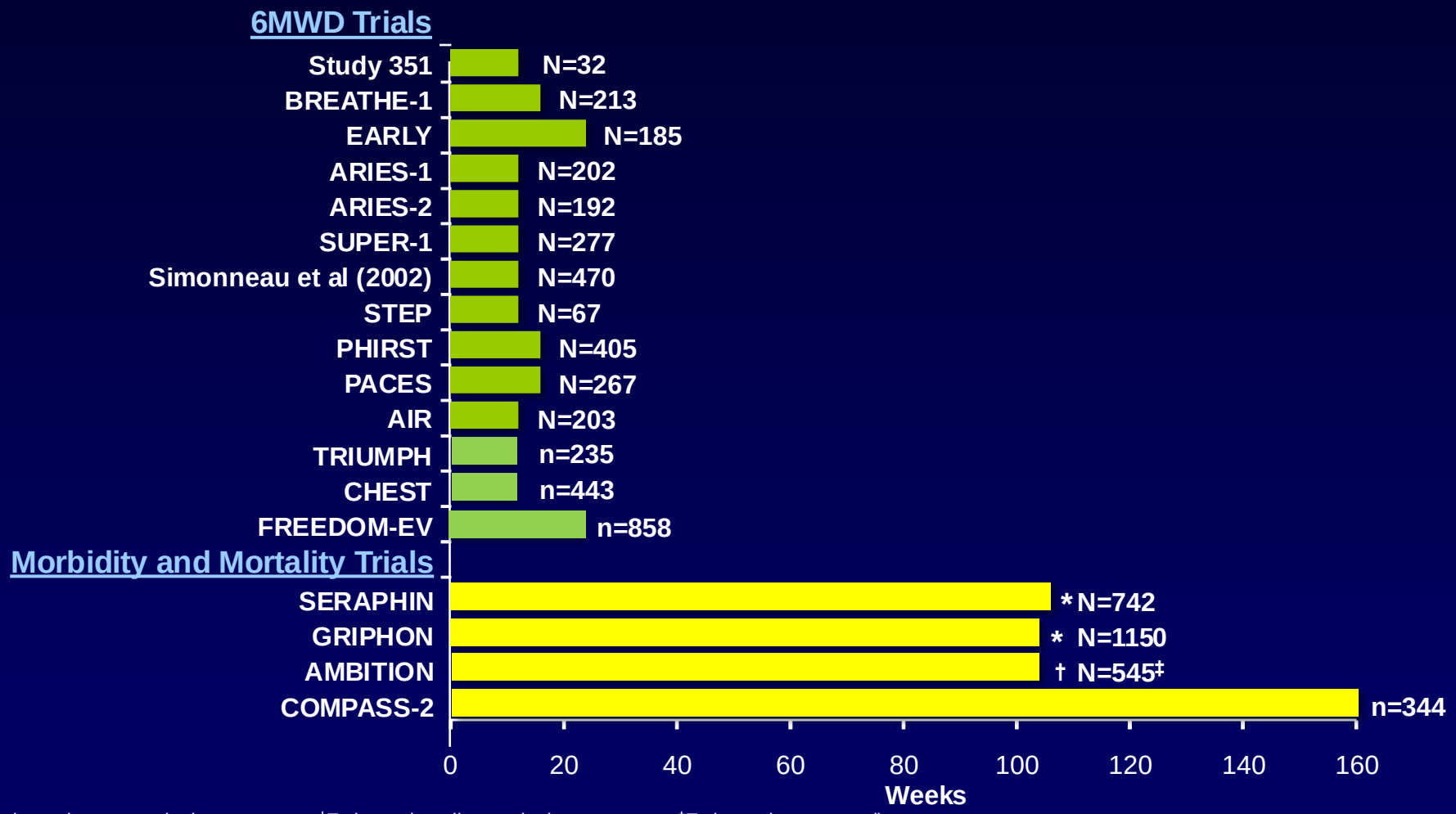
Regulatory Process

- Protocol developed by sponsor, often with advice of a steering committee
- Reviewed with regulatory agencies
- Sites chosen for participation, local or central IRB review
- Contracts and budget negotiation and approval
- Informed consent
- Training and monitoring of each site

What to expect

- Study participation is completely voluntary
- Frequent study visits
  - Hotel Stays
  - Mileage Reimbursement
  - Stipends
- Medical Assessments
  - Clinic visits, Blood draws, Hall walks, ECG’s, Echo’s, Right Heart Catheterizations, Questionnaires
- All Study related assessments are paid for

Trial Durations Vary



*Estimated mean study drug exposure. †Estimated median study drug exposure. ‡Estimated target enrollment.
PAH=pulmonary arterial hypertension; RCT=randomized controlled trial.

Channick RN et al. *Lancet.* 2001;358:1119-1123. Rubin LJ et al. *N Engl J Med.* 2002;346:896-903. Galiè N et al. *Lancet.* 2008;371:2093-2100. Galiè N et al. *Circulation.* 2008;117:3010-3019. Galiè N et al. *N Engl J Med.* 2005;353:2148-2157. Simonneau G et al. *Am J Respir Crit Care Med.* 2002;165:800-804. McLaughlin VV et al. *Am J Respir Crit Care Med.* 2006;174:1257-1263. Galiè N et al. *Circulation.* 2009;119:2894-2903. Simonneau G et al. *Ann Intern Med.* 2008;149:521-530. Olschewski H et al. *N Engl J Med*. 2002;347:322-329. Pulido T et al. *N Engl J Med*. 2013;369:809-818. Sitbon O et al. *N Engl J Med*. 2015;373:2522-33. Galiè N et al. *N Engl J Med*. 2015;373:834-44. McLaughlin VV et al. *Eur Respir J.* 2015;46:405–413

Benefits and Risks

- Potential Benefits
  - Closer monitoring of your symptoms
  - Clinical improvement
  - Play a more active role in your care
  - Earlier access to effective therapy
  - Greater good, helping the PH community
- Potential Risks
  - Side effects
  - Reproductive risks
  - Symptoms may not improve or may worsen
  - Loss of confidentiality or privacy
  - Unforeseen risks

Trial Completion

- Data queried and cleaned
- Database lock
- Results available
  - Phase 2, go or no go on phase 3, decisions regarding dose
  - Phase 3, plan for regulatory submission to health authorities, which can take 6-12 months

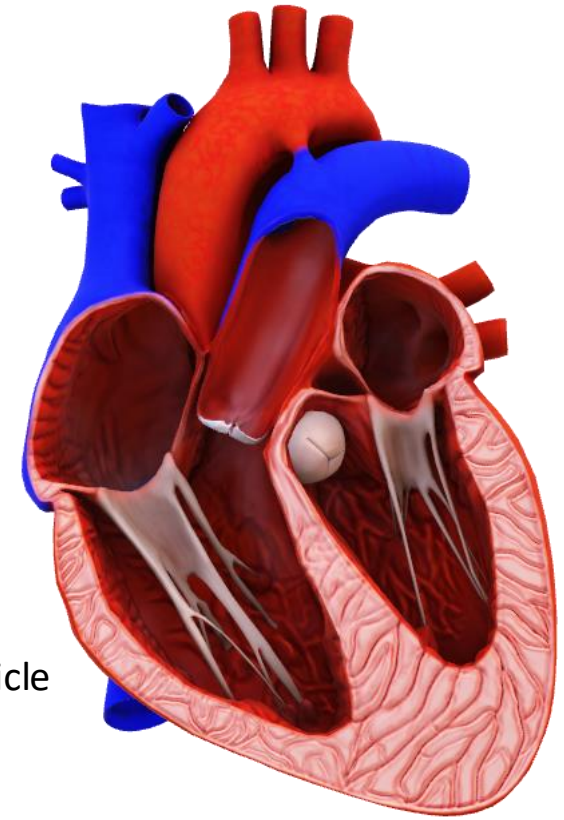
Approval Process

- US FDA, NDA, 6 months for priority review, 10 months for standard review
- EMEA, 150-210 days
  - Price negotiations and drug availability are then country specific

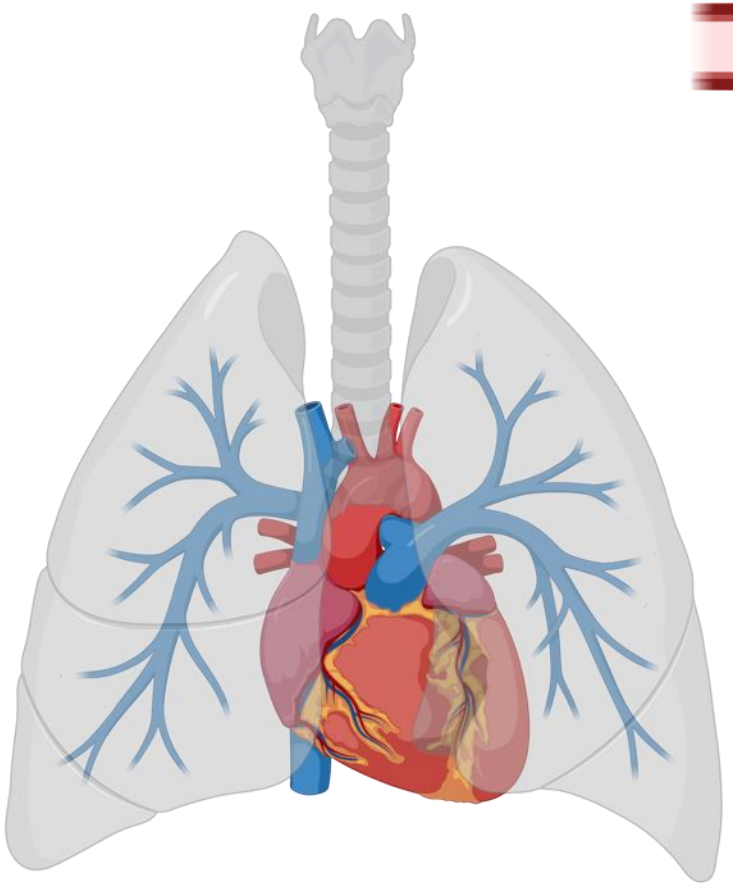
How to find out about trials

- Your PH care team
- ClinicalTrials.gov
- Patient associations

New Treatments for PAH: what are the possible targets?

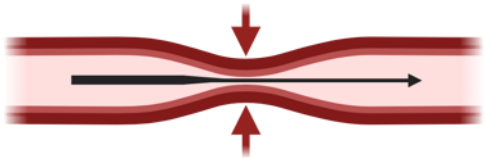


Right ventricle

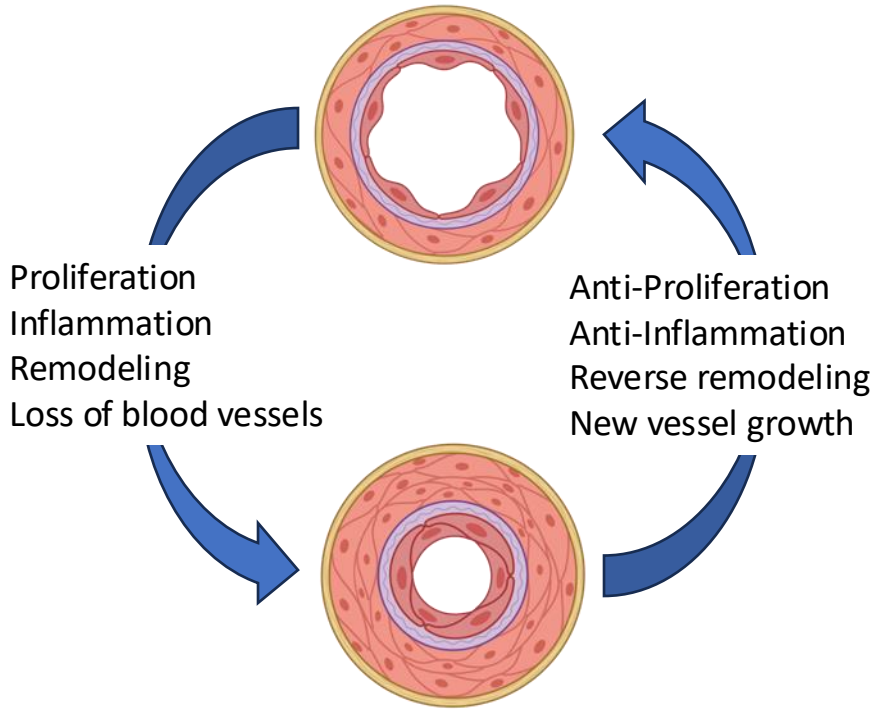


Blood vessel constriction

Vasodilation

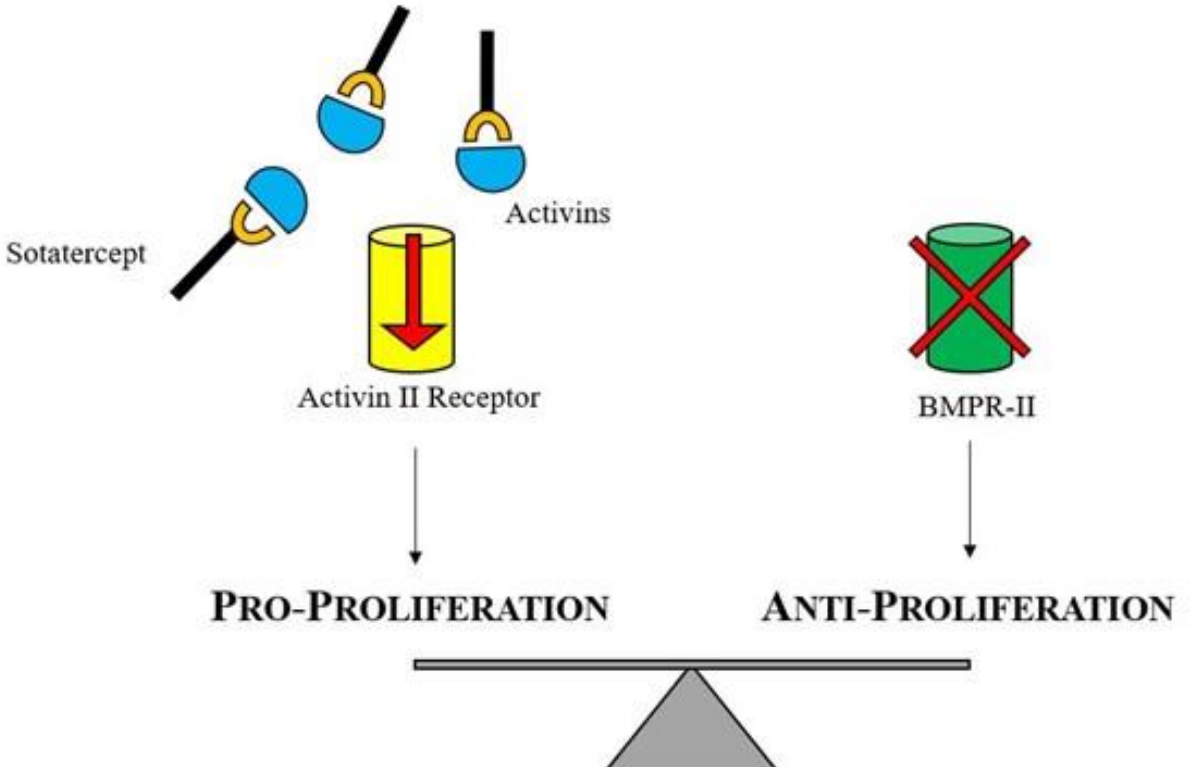


Normal lung artery



PAH artery

Sotatercept



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

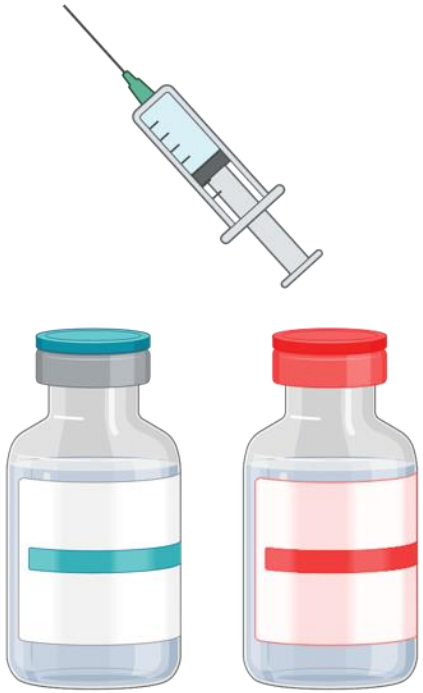
M.M. Hoeper, D.B. Badesch, H.A. Ghofrani, J.S.R. Gibbs, M. Gomberg-Maitland, V.V. McLaughlin, I.R. Preston, R. Souza, A.B. Waxman, E. Grünig, G. Kopeć, G. Meyer, K.M. Olsson, S. Rosenkranz, Y. Xu, B. Miller, M. Fowler, J. Butler, J. Koglin, J. de Oliveira Pena, and M. Humbert, for the STELLAR Trial Investigators*

FDA approves new drug that may help stop a rare, fatal condition that doctors call a ‘ticking time bomb’

By Brenda Goodman, CNN

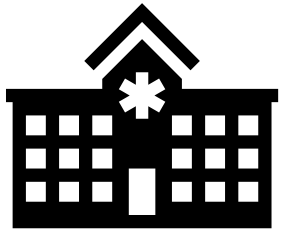
11 minute read · Updated 1:37 PM EDT, Wed March 27, 2024

Sotatercept: The STELLAR Trial

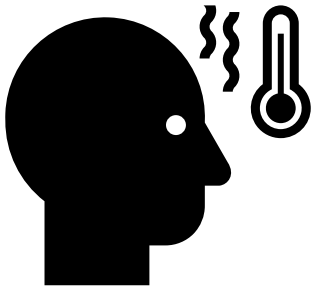


Sotatercept or Placebo
Injection every 3 weeks

40 m increase in 6-minute walk distance



84% reduction in risk of death or clinical worsening

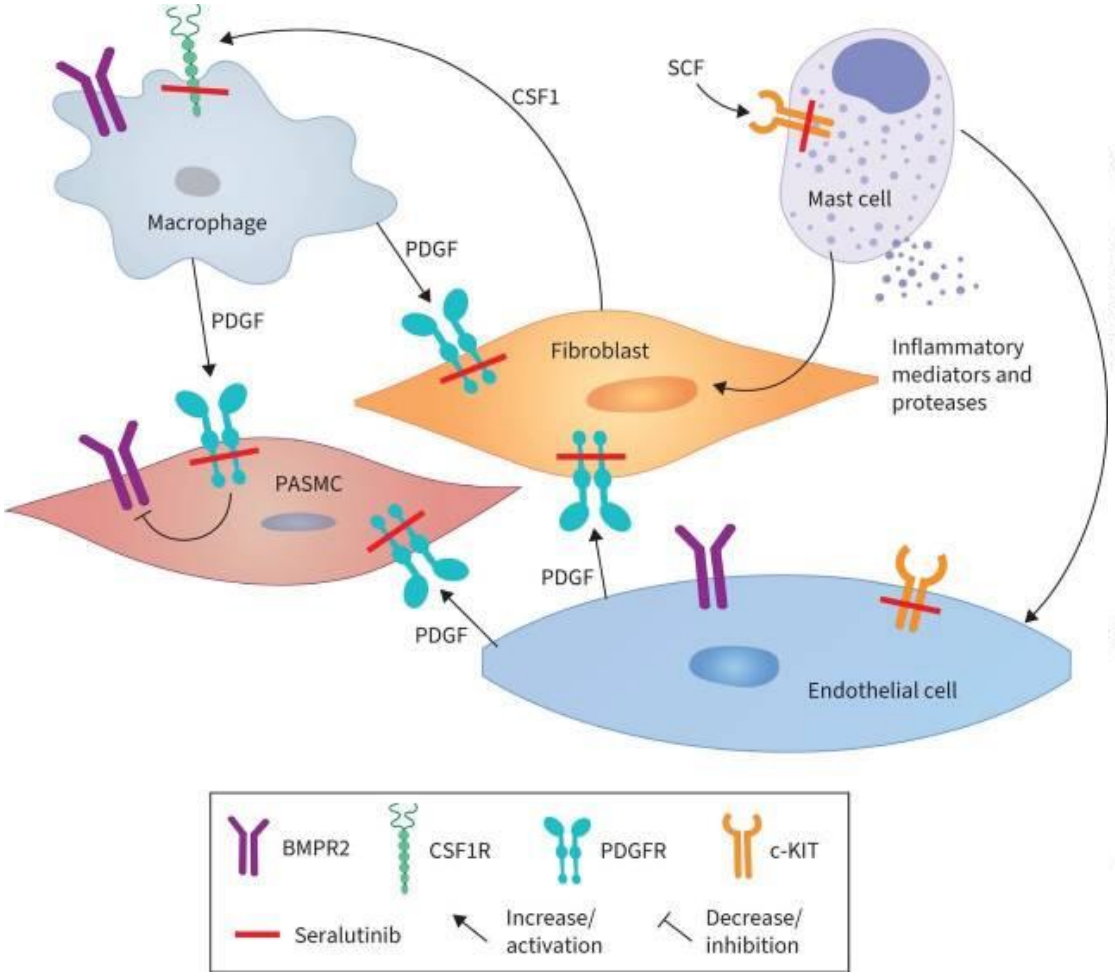


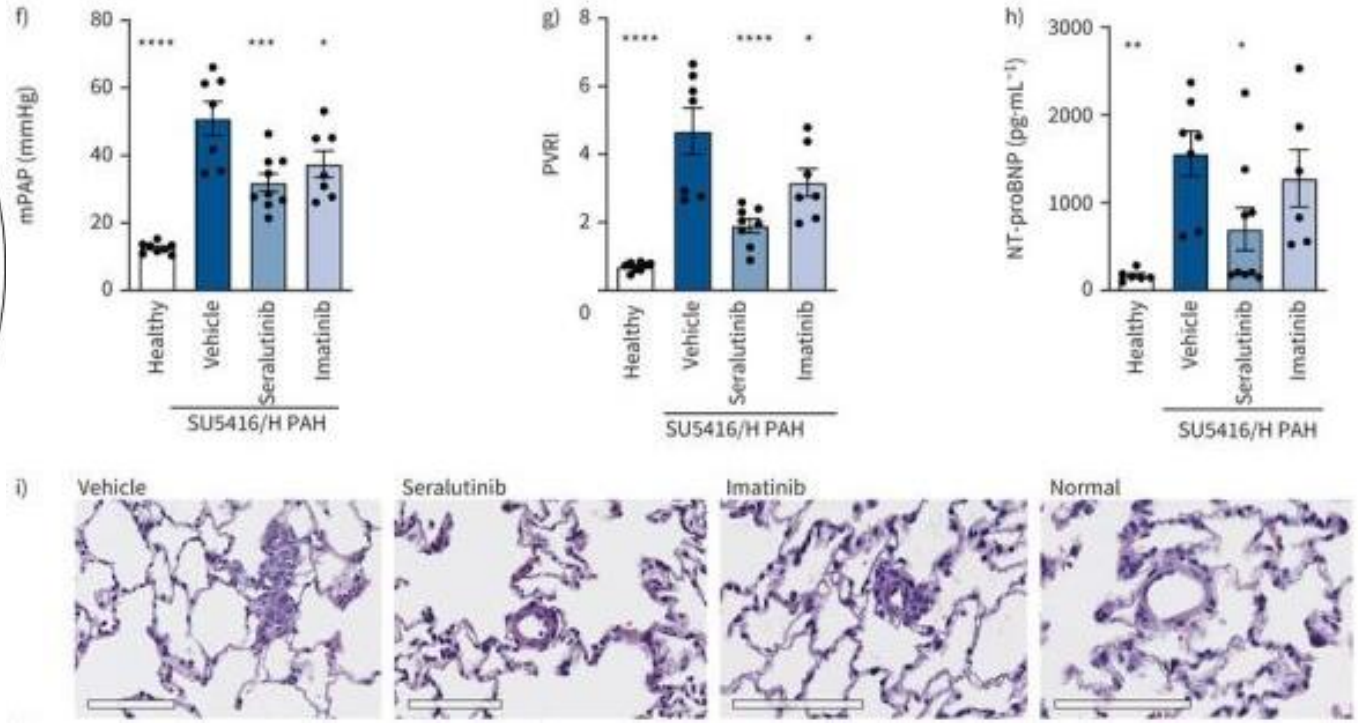
Serious adverse events 14%
Quit sotatercept 1.8%
Bleeding 21%
Telangiectasias 10%

Unanswered questions about sotatercept

1. Will the effect wear off over time?
2. Are there rare or long-term side effects?
3. Does it work in more severe PAH patients?
4. Does it work as well in patients with a high burden of comorbidities?
5. Does it work for patients who are recently diagnosed?
6. Does it work in other types of PH?
7. Can patients who respond safely stop other PAH meds?

Seralutinib



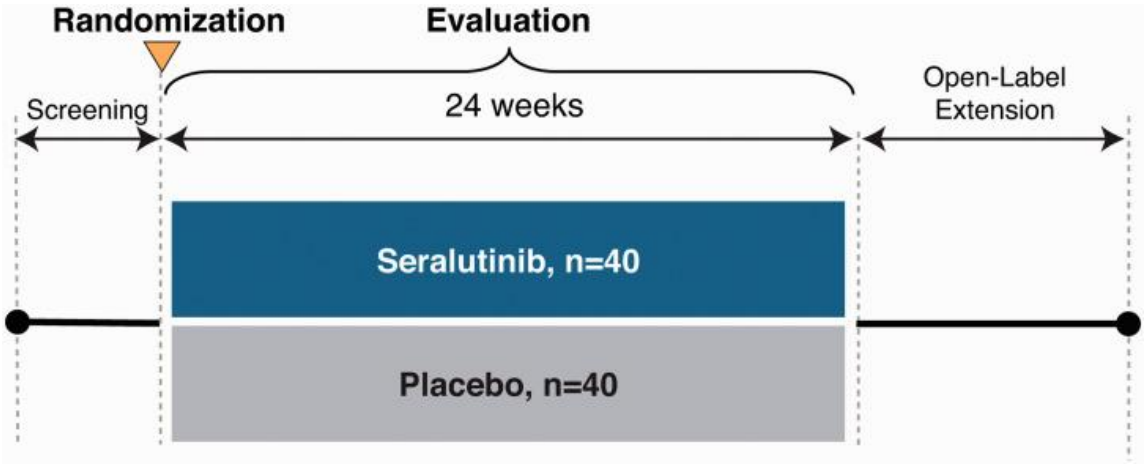


https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/35680144/

Galkin A, et al. Eur Respir J. 2022 Dec 1;60(6):2102356.

Seralutinib

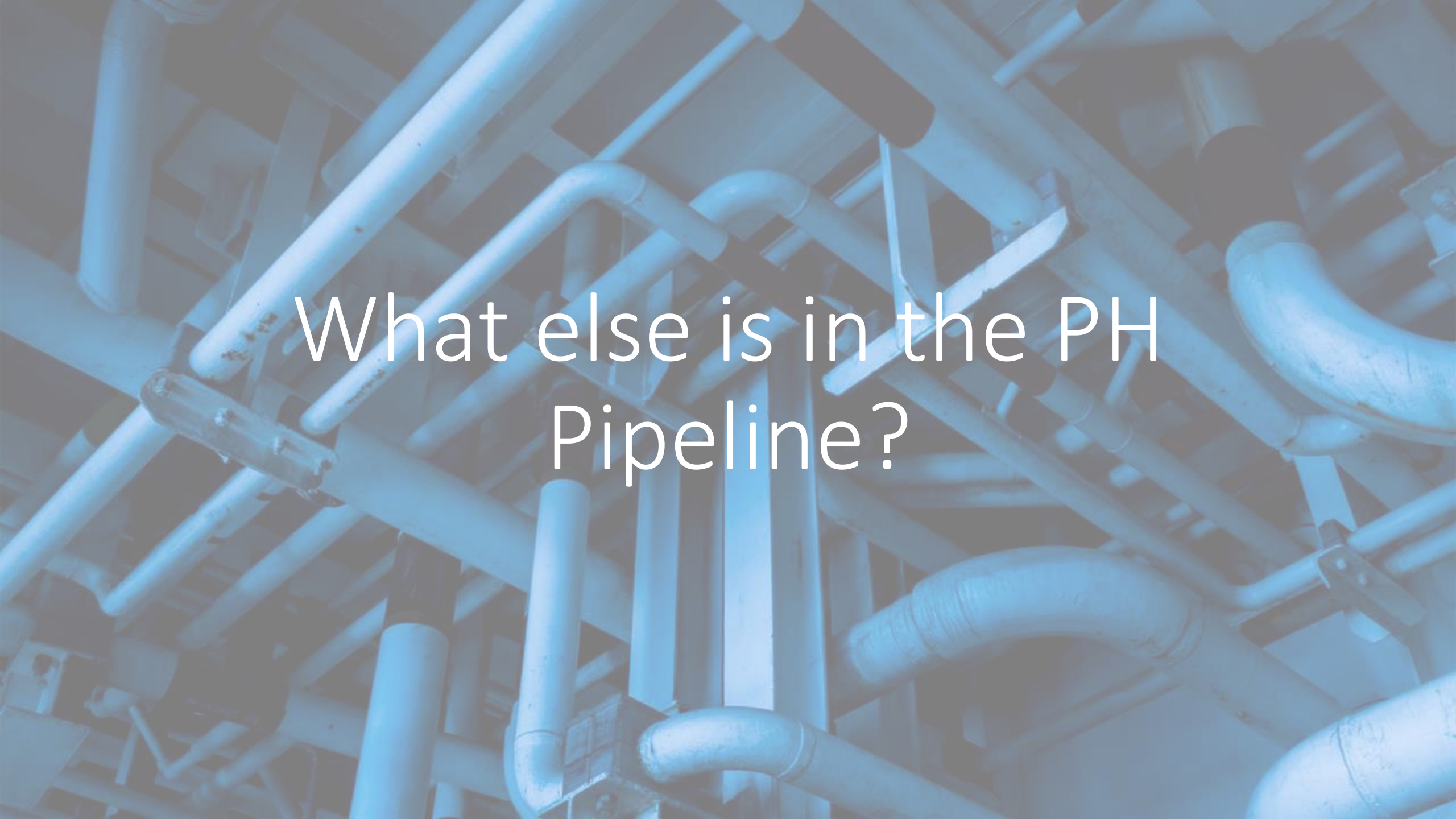
TORREY STUDY



Frantz et al. Lancet Respir Med 2024; 12: 523-534

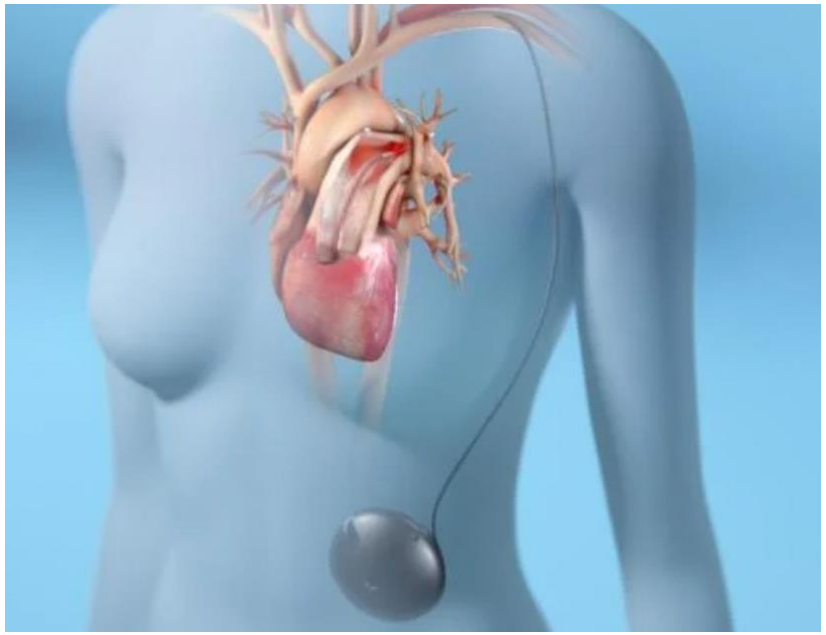
PROSERA STUDY

Phase 3 PROSERA Trial now running

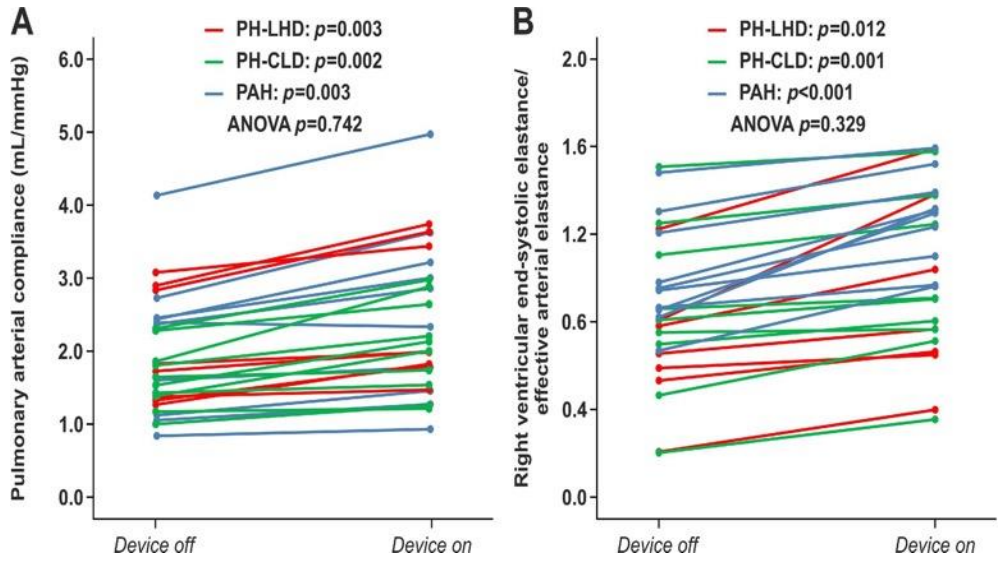


What else is in the PH Pipeline?

ARIA device



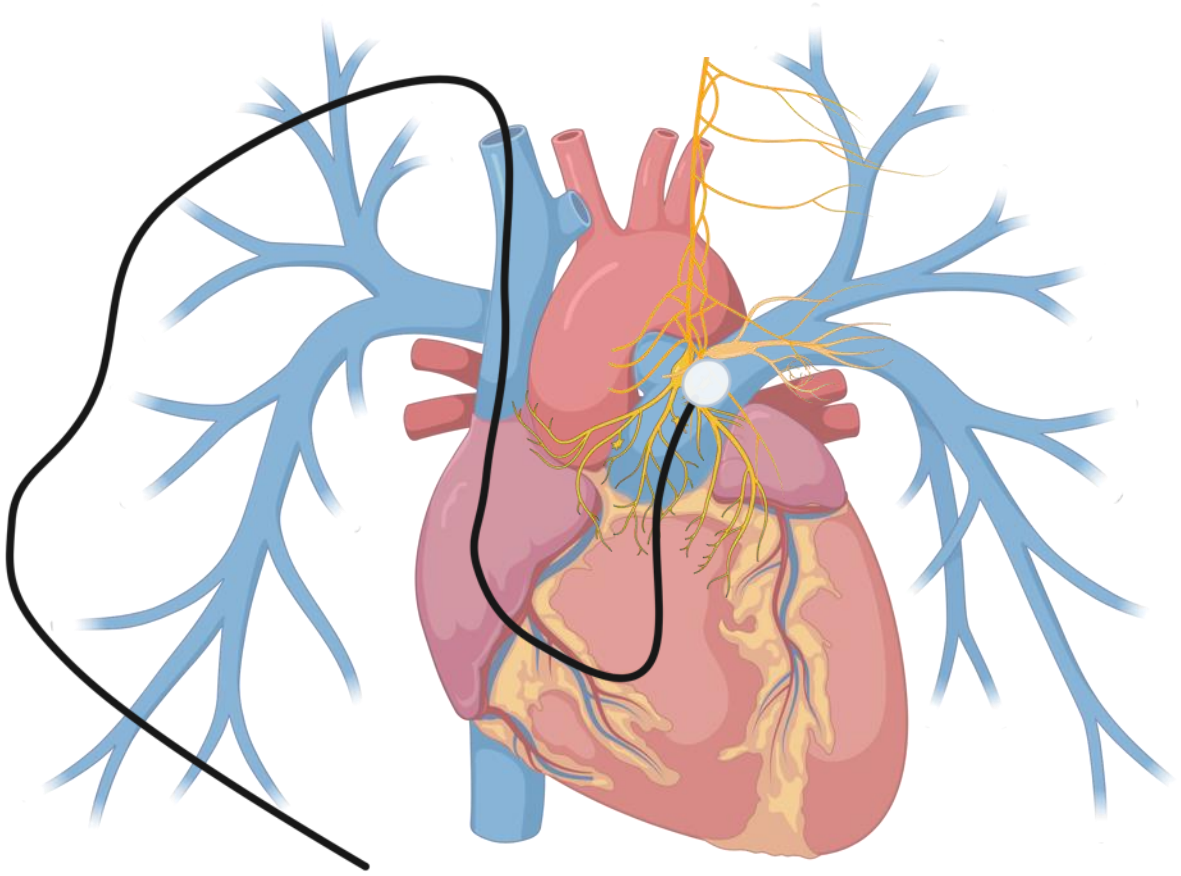
Phase 1b Pilot Study – 18 Patients

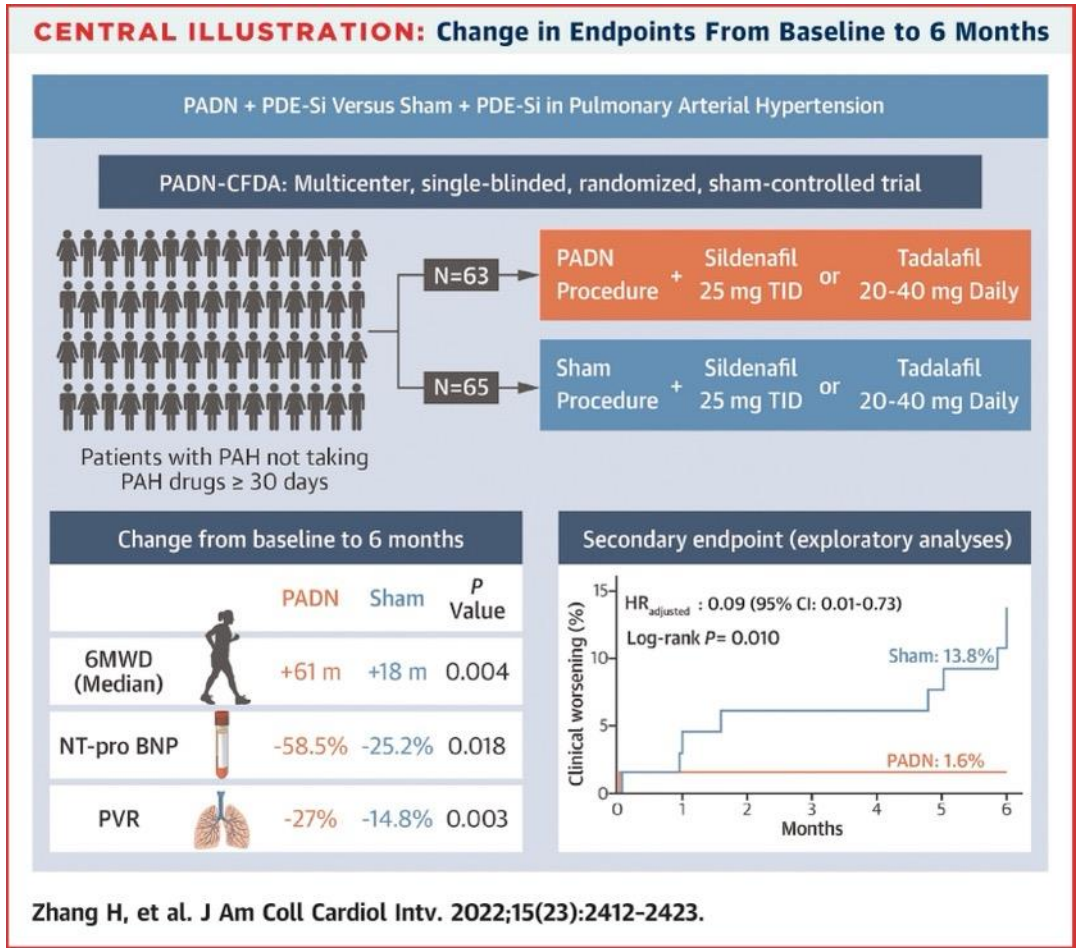


ariacv.com

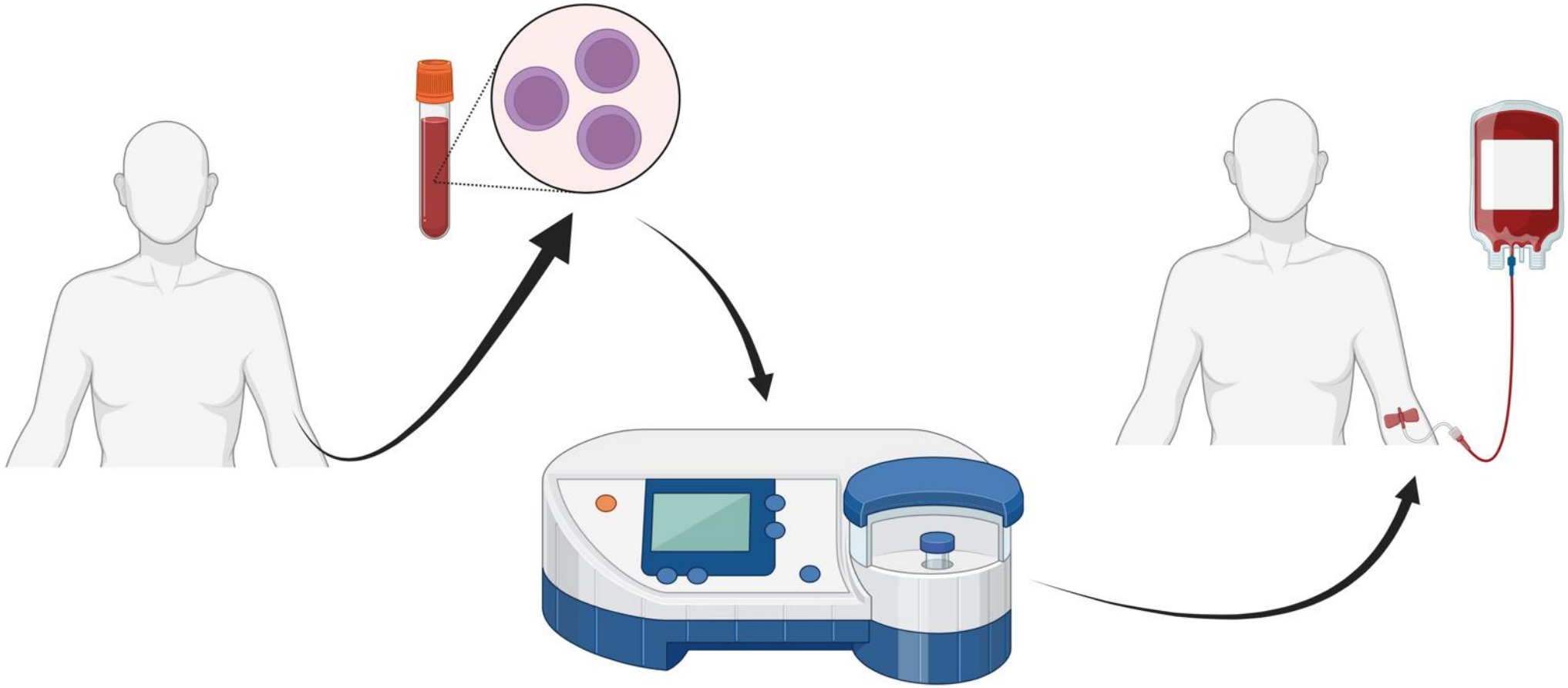
Gerges C, et al. Eur J Heart Fail. 2024 Mar;26(3):686-694.

Pulmonary artery denervation



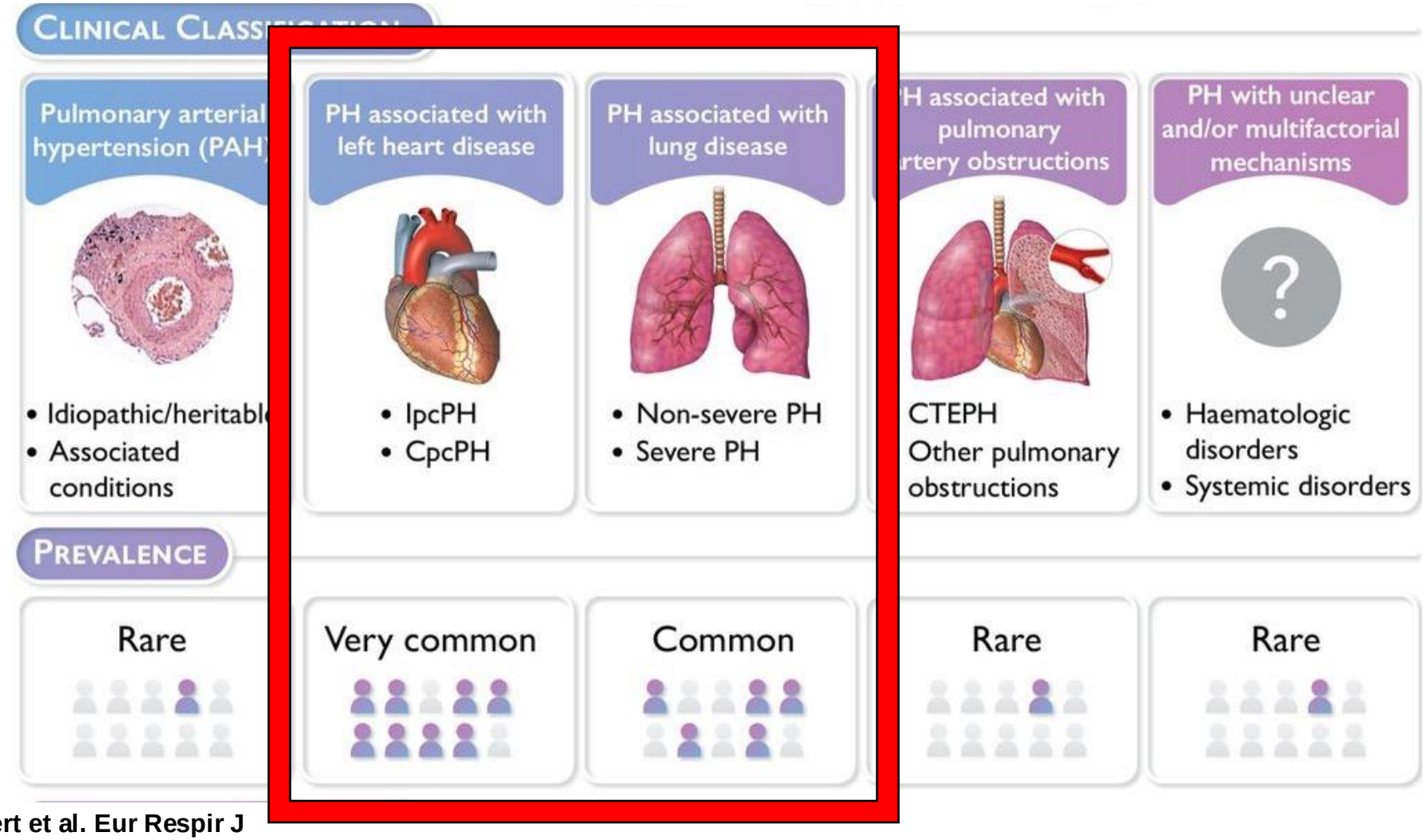


Stem Cells



SAPHHIRE Trial – Phase 2 trial of autologous endothelial progenitor cells

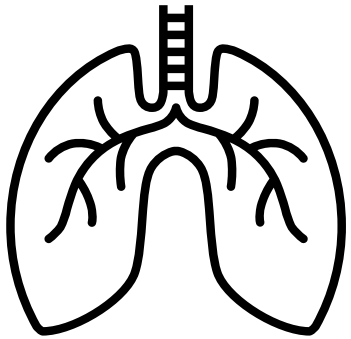
Clinical Trials in Other Types of PH



Marc Humbert et al. Eur Respir J
doi:10.1183/13993003.00879-2022

Ongoing Trials for PH Due to Left Heart Failure

Trial	Treatment	Phase	Status
CADENCE	Sotatercept	2	Recruiting
Re-PHIRE	AZD3427	2	Recruiting
PADN-HF-PF	PADN	3	Recruiting
PreVail-PH2 Study	PADN	2	Recruiting
Level	Levosimendan	3	Recruiting



Ongoing Trials for PH Due to Lung Disease

Trial	Treatment	Phase	Status
NCT04691154	L606	3	Recruiting
SAPPHIRE	Inhaled Treprostinil	2	Recruiting
INSIGNIA-PH-COPD	MK-5475	2	Recruiting
ERASE-PH-COPD	Tadalafil	3	Recruiting

Summary

- Clinical trials are how new treatments for PH can be proven to work
- Clinical trials of new treatments are tightly regulated to ensure they are rigorously conducted and so the results are valid.
- Ongoing clinical trials in PAH are aiming to:
    1. Improve upon existing treatments that target blood vessel dilation
    2. Reverse the abnormal thickening and obstructed blood vessels
    3. Target abnormal nervous system function
    4. Improve the function of the right heart and it’s connection to the lung circulation
- There are many ongoing clinical trials aiming to treat other types of PH such as PH due to heart or lung disease