PVRI Drug discovery and development

Session 1: New standards of care

Global perspective on regulatory approval of Sotatercept

1. *Illiana Meurs – CBG-MEB (Dutch Medicine Evaluation Board)*

EMA

A 24-week placebo-controlled trial followed by a 72-week extension showed the treatment significantly improved **six-minute walk distance** (+41 meters) in PAH patients (WHO FC 2–3), supported by secondary measures like **PVR**, **NT-proBNP**, and **functional class**. The treatment was **generally well-tolerated**, with manageable side effects (e.g., thrombocytopenia, increased hemoglobin).

Regulatory concerns included the **exclusion of patients with low platelets** and the need for **post-marketing safety data**, particularly regarding cardiovascular effects. The **final approved indication** was narrowed to improving **exercise capacity only**, removing all references to secondary endpoints, and requiring **combination use** with other PAH therapies.

Next Steps:

- Conduct post-marketing cardiovascular safety analysis
- Restrict indication wording to exercise capacity only
- Clarify combination therapy use in the label

2. *Mitchell Psotka - FDA*

FDA

The discussion centered on how **substantial evidence of effectiveness** is established for new therapies like **sotatercept** in **pulmonary arterial hypertension (PAH)**. Regulatory standards typically require **two adequate and well-controlled trials**, though **one trial with strong confirmatory evidence** may suffice. The **primary endpoint**, a **41-meter improvement in six-minute walk distance**, was statistically and clinically significant. Several **secondary endpoints** (e.g., functional class, clinical worsening) also showed benefit but were **selectively included** in the final label.

The **final indication** stated that sotatercept is for **improving exercise capacity and functional class** in PAH. Additional findings—like reductions in **PVR** and **NT-proBNP**—were noted in the **clinical pharmacology** section, not the main indication. Due to too few events, **mortality and hospitalization outcomes** did not meet the threshold for label inclusion.

How sotatercept will change the treatment algorithm

Luke Howard – Imperial college London

The discussion focused on updates to pulmonary arterial hypertension (PAH) treatment strategies, highlighting the potential of **sotatercept**, a remodeling drug, to reshape outcomes. New thinking moves beyond symptom control, aiming instead at **remission** and **disease modification**, although current guidelines don't yet include these terms. Sotatercept has demonstrated rapid clinical benefits and is now positioned within **intermediate and high-risk** treatment categories. There's also growing interest in **treatment de-escalation**—reducing or withdrawing therapies once patients reach remission-like states.

The conversation underscored the importance of **hemodynamic normalization**, **right ventricular (RV) function**, and **health economics** in guiding personalized, cost-effective care. Future research will further clarify **quadruple therapy**, **initiation timing**, and **withdrawal criteria**, especially in high-risk patients.

Next Steps:

- Define **remission** in PAH using robust **hemodynamic and clinical criteria**.
- Continue research to refine where and how **sotatercept** fits into treatment algorithms.
- Develop tools for identifying **likely responders** using risk stratification and clustering analysis.

Implications of a new background therapy for drug development

Marion Delcroix – UZ Leuven

Prof Delcroix explored the current challenges and innovations in **pulmonary arterial hypertension (PAH)** treatment. Despite active treatment, PAH still carries an **8–10% annual mortality rate** and a **30% event rate** in clinical trials. A new treatment approach approved in **2024** (referring to **sotatercept**) shows promising improvements and is positioned **after traditional combination therapy** in treatment algorithms.

She emphasized that **future trials** must demonstrate **superior or additive effects** to the standard of care, using **larger sample sizes**, **biomarker-based endpoints**, and a focus on **right ventricular function**. The role of **precision medicine** is growing.

The conversation also focused on the strategic importance of **clinical trial networks**, especially in rare diseases, to accelerate patient access, improve data quality, and reduce costs. The **need for collaboration across stakeholders**, better **predictive markers**, and **refined patient selection** was a recurring theme.

Session 2: Disease modification

How to define or prove disease modification

Mark Toshner – University of Cambridge

What does it truly means for a drug to be **disease-modifying**, emphasizing the need for **longitudinal, patient-centric outcomes** rather than just symptom relief. A poll revealed **low consensus**, with only 30% of participants viewing **immunomodulatory drugs** as disease-modifying—compared to higher agreement on **anti-retrovirals** and **insulin**.

Using **rheumatoid arthritis** and **Alzheimer's disease** as case studies, highlighted how the definition has evolved to include **pathobiological change**, **functional improvement**, and **sustained effects after treatment stops**. **Withdrawal studies** and **staggered-start trials** were cited as essential tools to validate these effects, though they raise **ethical and practical concerns**.

Patients must be involved in defining disease modification—particularly regarding **quality of life**, **daily function**, and **personal definitions of remission**. A truly meaningful definition of disease modification should reflect both **biological impact** and **what matters most to patients**.

Next Steps:

- **Deepen patient engagement** in defining goals and outcomes that reflect **real-world, lived experiences**.
- **Re-evaluate the requirement** of drug withdrawal in the definition—can **long-term benefit without withdrawal** qualify as disease modification?
- **Develop clearer biomarkers** to distinguish between **clinical response** and **true disease modification**.
- **Integrate quality-of-life metrics** more systematically in clinical trials and regulatory frameworks.

The role of imaging in establishing disease modifyingeffects of a trial drug

Sudarshan Rajagopal – Duke University School of Medicine

This discussion explored how **imaging technologies**—especially **cardiac MRI (CMR)** and **echocardiography**—can support the assessment of **disease modification** in **pulmonary arterial hypertension (PAH)**. While imaging plays a crucial role in evaluating **right ventricular (RV) function and size**, **cardiac MRI was highlighted as superior** to echo for predictive accuracy.

Limitations remain, including the **inability to visualize small pulmonary arteries** and the current **disconnect between imaging results and patient symptoms or outcomes**. Innovative methods like **hyperpolarized Xenon MRI** and **DLNO (diffusing capacity of the lung for nitric oxide)** offer promise in **assessing gas exchange** and **microvascular changes**, but further validation is needed.

The discussion also covered the potential of **AI in pattern recognition**, helping extract features from MRI to predict mortality and define new imaging-based endpoints. Despite advances, imaging is **not yet recognized by regulators as a validated marker** of disease modification—highlighting a need for stronger **evidence and correlation with clinical outcomes**.

Next Steps:

- **Advance AI-based image analysis** to identify novel RV and lung features correlated with **clinical outcomes**.
- **Continue research into imaging biomarkers** that more directly reflect **pathobiological change and functional improvement**.

Session 3: Diversity and inclusion

Addressing sex differences in treatment decisions and drug development

Deimante Hoppenot – LithuanianUniversity of Health Sciences

The discussion addressed the critical role of **sex differences in pulmonary arterial hypertension (PAH)**, particularly focusing on **pathophysiology, treatment response, and drug development**. Although **females are more frequently affected by PAH**, especially in WHO Groups 1 and 2, **they have better survival rates than males**, who tend to experience more severe disease and higher mortality. This disparity is attributed in part to **hormonal influences**, particularly **estrogens**, which affect pulmonary vascular resistance and right ventricular function.

Despite clear evidence from registries and studies (e.g., the French network, CTEPH registries), **sex is not currently considered in PAH treatment guidelines**. Clinical trials targeting hormone pathways (e.g., anastrozole, fulvestrant) have so far shown **limited success**, underscoring the need for **more targeted research and sex-specific approaches**.

Next Steps

- **Identify and explore new therapeutic targets** tailored to sex-related differences in PAH pathophysiology.

- **Integrate sex as a variable** in both research design and clinical guidelines for PAH management.

How to include underrepresented patient into cardiovascular clinical trials

Cati Brown -Johnson – Stanford university School of medicine

Cati presented the **TOTAL trial**, a collaborative project with Morehouse and funded by the American Heart Association, aimed at increasing **racial and ethnic diversity** in **cardio-metabolic clinical trials**, including pulmonary hypertension (PH). The trial randomizes studies to **test specific diversity-enhancing recruitment strategies** like community ambassadors, registries, and social media outreach.

The data shows that **Black Americans are significantly underrepresented (3.2%)**, while **Asian Americans are overrepresented (19.3%)** in PH clinical trials. Barriers to inclusion include **systemic racism, mistrust, socioeconomic limitations**, and rigid trial protocols. The TOTAL trial employs a **learning clinical trial model**, adapting strategies in real-time and emphasizing trust-building and localized outreach.

Findings indicate that while **community ambassadors** and **social media (with tailored ads)** can improve outreach, these methods require **centralized funding, staff support**, and **culturally sensitive protocols**. There's also a need for **more flexible eligibility criteria** to avoid excluding underserved populations.

Session 4: Global aspects of drug development and availability

Using GoDeep Regsitry to prioritise & facilitate global drug trials

Werner Seeger – Justus Liebig University Giessen

The **Go Deep registry** is a global pulmonary hypertension (PH) data initiative with participation from **47 centers** (32 actively contributing), gathering **clinical, imaging, and genomic data**. It enables deep phenotyping and survival analysis across PH subgroups, revealing significant patterns in **risk scores, sex differences**, and **comorbidities**.

Key findings include:

- **Better survival in females**, independent of PH group or comorbidities.
- **Mild PAH and COPD-PH patients** show survival benefits when treated with **sildenafil**.
- A surprising **"systemic arterial hypertension paradox"** emerged: PH patients with **systemic hypertension** had **lower hazard ratios**, possibly due to higher cardiac output and lower pulmonary artery pressures.

The registry has strong potential for **optimizing clinical trial design**, particularly by refining **inclusion/exclusion criteria**, conducting **real-world sample size calculations**, and validating **digital biomarkers**. Longitudinal data may also support **AI-driven modeling**, outcome predictions, and **cost-effectiveness analyses**.

Pro/Con debate: it is Big Pharma's responsibility to prioritise drug availability over drug discovery

Pro: Anna Hemnes – Vanderbilt University Medical Center
Con: Ardeschir Ghofrani – University Hospital Giessen

Pro:
Anna argues that **drug availability must take precedence over discovery**, as even the best treatments are useless if patients can't access them. Barriers like **cost, geography, regulation, and administration** limit access—even in wealthy countries. A case in India showed that recommended treatments weren't practically available, despite being listed.

Solutions include lowering **generic entry barriers**, stopping **patent evergreening**, enabling **cross-country approvals**, and using **precision medicine** to match drugs to patients.

Conclusion: Innovation is vital, but without access, it has no impact—**availability is what ultimately saves lives**.

Con:
Ardeschir argues that **drug discovery must remain a top priority**, as **innovation is essential for the future of medicine**. While drug availability is important, **without ongoing research, the pipeline dries up**, and progress halts—especially for diseases like **pulmonary hypertension**, where cures remain elusive and many subgroups lack effective therapies.

Key points:

- **Discovery fuels access**, not the other way around.
- Diseases evolve, new phenotypes emerge, and resistance develops—**only innovation can keep up**.
- Many PAH drugs (e.g. sildenafil, prostacyclins) were **repurposed thanks to early academic research**, later picked up by pharma.
- **New classes**, like anti-proliferative and tyrosine kinase inhibitors (e.g. sotatercept, inhaled agents), show promise for **remission**, not just symptom control.
- Innovation requires **economic viability** for pharma, while **availability is a shared responsibility** (governments, payers, regulators, NGOs).

Conclusion: Innovation and access are **not opposing goals**—they are **twins**. Focusing solely on availability risks halting future breakthroughs. **We must support original research to give patients better, safer treatments tomorrow.**

Session 5: Innovations in trial designs

How to use risk scores (enrichment, endpoints)

Athenais Boucly – Paris Saclay University

The session examined how **risk scores**, such as **REVEAL 2.0** and **European models**, are used in **clinical trials** to guide treatment strategies and patient selection. These multi-variable tools, which include factors like **functional class**, **NT-proBNP**, and **systolic blood pressure**, help assess prognosis at **baseline and follow-up**. Recent trials like **Zenith** and **Prosera** used risk scores to enrich for high-risk patients, resulting in significant outcome improvements. However, **risk scores are not yet validated surrogate endpoints**—a recent meta-analysis found weak mediation effects—though they hold promise for future use.

Next Steps

- **Analyze** how treatment affects risk score changes and their link to clinical outcomes.
- **Explore** using risk score changes as surrogate endpoints in future PH trials.
- **Incorporate imaging and biomarker data** to refine risk assessment tools.
- **Validate** risk score changes through meta-analyses and prospective trial design.

How to use imaging endpoints reflecting the pulmonay circulation & RV

David Kiely – University of Sheffield

The discussion focused on the growing role of **imaging as a surrogate endpoint** in clinical trials for pulmonary hypertension. Tools like **echocardiography** and **cardiac magnetic resonance (cMRI)** are being explored for estimating **cardiac output** and **pulmonary artery pressure**. A meta-analysis of 20 studies (2,000 patients) confirmed cMRI's predictive value for **mortality and clinical worsening**. Innovations like **AI-enhanced imaging** and **multi-modal techniques** (e.g., CT, implantable devices) offer detailed patient profiling and quicker, cost-effective measurements. Despite historical underuse, imaging is emerging as a valuable, non-invasive method to evaluate treatment impact and improve trial design.

Next Steps

- Engage the **imaging community** to integrate novel imaging endpoints into clinical trial design.
- Investigate **multi-modality imaging** (e.g., implantable monitors, CT) in **early-phase trials**.
- Develop a **PVRI imaging repository** to standardize imaging data and support trial readiness.

N=1 trials& randomised withdrawal studies

Martin Wilkins – Imperial College London

The presentation highlighted the limitations of using averages in medicine, drawing from a 1940s Air Force study that found no pilot fit the "average" body type. This concept was applied to healthcare, advocating for **n-of-one (N1) studies**—individualized trials that monitor patient-specific responses to treatment. Using technologies like **implantable devices** and **remote monitoring**, N1 studies can optimize treatment in diseases like pulmonary arterial hypertension. A case study using **Imatinib** demonstrated the feasibility of this approach. The method promises more precise, personalized care, especially in early drug development, though challenges remain around implementation and scalability.

Novel statistical approaches : Bayesian statistics , use of win ratio

Alex Rothman – University of Sheffield

The presentation addressed the shortcomings of traditional trial methods that rely on single or composite endpoints. It advocated for **Bayesian statistics** and **hierarchical endpoint analysis** to better capture treatment effects and individual variability. Examples showed how **continuous data, withdrawal/re-challenge designs**, and **personalized models** (using imaging and device data) can enhance understanding of drug efficacy and guide individualized treatment in diseases like pulmonary hypertension. The **win ratio** method was also discussed, with caution about its limitations in certain datasets.

Practical and ethical aspects around OLE (Open Label Extension) studies

Harm Jan Bogaard – Amsterdam UMC

Open-label extension (OLE) studies are commonly used after pulmonary hypertension trials to collect long-term safety and efficacy data. They offer ethical benefits—such as continued access to treatment—and can support patient recruitment. However, they also raise concerns: violating clinical equipoise, introducing selection bias, limiting patient availability for future trials, and creating ethical challenges around informed consent. Alternatives like early access programs and delayed-start analyses may offer similar benefits with fewer drawbacks. The speaker emphasized the need for careful evaluation of whether OLEs are appropriate on a trial-by-trial basis.

Next Steps:

- Critically assess the value of OLEs in future pulmonary hypertension trials.
- Consider alternatives like early access programs or real-world data approaches to gather long-term safety/efficacy data.

- Address ethical concerns about unblinding, informed consent, and trial duration in dialogue with institutional review boards (IRBs).

Climate impact of drug development

Frances Varian – University of Sheffield

The presentation emphasized the urgent need to reduce the carbon footprint of clinical trials, which collectively emit ~100 million tons of CO_2 annually. Climate change is already impacting health, with heat causing 60,000 premature deaths in Europe in 2022. Digitization and decentralized trial designs can cut emissions by 20–30% while improving patient retention. A five-step method was shared to calculate a trial's footprint, and studies like PHOENIX highlighted how patient travel is a major emissions source. Remote monitoring and sustainable design were advocated to minimize environmental and health burdens.

Session 6 Novel drug & device therapies

Spermine-mediated-metabolic reprogramming in puilmonary vascular remodeling and innovative drug discovery

Zhi-Cheng Jing – Guangdong Provincial People's Hospital

Researchers found that a molecule called **spermine** is higher in people with **pulmonary arterial hypertension (PAH)** and is linked to how severe the disease is. Spermine seems to encourage the growth and movement of cells that narrow the lung's blood vessels, making the disease worse. The team created a compound, **M2**, that blocks this effect.

In lab and animal studies, M2 helped **reduce high blood pressure in the lungs**, **improve heart function**, and **slow disease progression**. This discovery opens the door to **a new possible treatment for PAH** by targeting how cells in the lungs behave abnormally. More studies are planned to understand how M2 works in the body and to move closer to human trials.

Elaphin

Rohan Zamainian – Vera Moulton Wall Center and Stanford

This presentation introduced a new potential treatment for **pulmonary arterial hypertension (PAH)** called **Elephin (Prilostat)**, a drug that blocks a harmful enzyme called **neutrophil elastase**. In PAH, this enzyme breaks down **elastin**, a key protein that keeps blood vessels in the lungs flexible. When elastin is lost, blood vessels become stiff and narrow, making it harder for the heart to pump blood through the lungs.

In lab and animal studies, Elephin helped **lower lung blood pressure** and **improve heart function**. It also appeared to reduce inflammation and help damaged blood vessels heal. Early human trials showed Elephin was **safe at different doses**, with no serious side effects.

The next step is a **larger clinical trial**, called the **Athena study**, where 90 people with PAH will receive Elephin or a placebo. Researchers will measure how well it reduces lung pressure, improves walking distance, and enhances quality of life over 28 weeks. The goal is to see if Elephin can **slow or even reverse the disease**—not just manage symptoms.

Aria Device

Marc Pritzker – University of Minnesota

This presentation introduced two new technologies that may help people with **pulmonary arterial hypertension (PAH)**—a serious condition where blood pressure in the lungs is too high, putting strain on the heart.

1. **Mechanical Device**:
   A special implantable device has been developed to help the blood vessels in the lungs expand and contract more like they should. This helps the heart pump blood more easily. In early tests, it:
   - Improved heart function
   - Increased how far patients could walk in six minutes by about **47 meters**
   - Made people feel better and improved their quality of life
     The device is simple to maintain and designed to slowly help **remodel blood vessels** over six months, making lasting improvements. A small study is already underway in patients.
2. **Neuromodulation Device**:
   Another approach uses a device that stimulates the **vagus nerve**—a nerve that helps control the immune system—through the **spleen**. Originally tested for COVID-19, this method may also help reduce harmful inflammation in PAH. Early studies in animals and humans have shown **promising results**.

Together, these devices may **enhance drug treatments** by targeting both the **physical strain on the heart** and the **inflammation** seen in PAH, offering hope for better long-term outcomes.

New drugs to modify TGF-Beta receptor signaling

Paul Yu – Harvard Medical School

This talk focused on a new way to treat **pulmonary arterial hypertension (PAH)** by targeting a protein called **BMP9**, which helps keep blood vessels in the lungs healthy.

Researchers have found that many genes involved in PAH affect a pathway called **BMP signaling**. One key protein in this pathway, **BMP9**, is important for controlling blood pressure in the lungs. In some people with PAH, BMP9 levels are lower than normal, which may contribute to disease development.

Animal studies have shown that giving BMP9 can **reverse signs of PAH**, such as high blood pressure in the lungs and thickened blood vessels. However, the story is complex: in some genetically modified mice, removing BMP9 actually **protected them from developing PAH**, raising questions about how and when BMP9 is helpful or harmful.

BMP9 also controls other genes that affect how blood vessels work, such as **CXCL12** and **endothelin-1**, both of which are known to worsen PAH when overactive. This makes BMP9 an important player in the disease.

Now, a **new medicine that blocks BMP9** (an anti-BMP9 antibody) is being tested in humans. It may help by calming down some of the harmful effects of the BMP9 pathway. Early safety tests have been completed, and a **phase 2 trial is underway**.

This research opens up the possibility of **a new treatment option** for PAH by fine-tuning how BMP9 works—potentially improving blood vessel health and reducing pressure in the lungs.

Seralutinib

Pilar Escribano Subias – Hospital Universitario 12 de Octubre

Dr. Pilar Escribano presented encouraging results about a new inhaled medicine called **Seralutinib**, being developed to treat **pulmonary arterial hypertension (PAH)**.

Seralutinib works by targeting several of the root causes of PAH, including **inflammation, abnormal cell growth, and blood vessel scarring**. In a clinical study of 74 patients, those who received Seralutinib had a **24% reduction in pressure in the lungs' blood vessels** after 24 weeks, compared to those who received a placebo. Importantly, there were **no serious side effects**.

The treatment also **improved how well the right side of the heart worked** and helped some patients **walk farther**, especially those with more advanced symptoms (WHO functional class III). Ongoing studies are tracking its long-term benefits, and early results suggest continued improvement over time.

This medicine is inhaled directly into the lungs, which means it works where it's needed most and **limits side effects** elsewhere in the body. Based on these promising results, a **larger phase 3 trial called Prosera** is being prepared to see if Seralutinib could become a **disease-modifying therapy**—a treatment that doesn't just manage symptoms but may actually slow or reverse PAH.

Overall, Seralutinib may offer **new hope for patients with PAH**, potentially improving both quality of life and long-term outcomes.

Mosliciguat

Ardecshir Ghofrani – University Hospital Giessen

Researchers are developing a new **inhaled drug called Mosliciguat** to treat **pulmonary hypertension (PH)**. This medicine works by improving a natural pathway in the body (called **sGC signaling**) that helps blood vessels relax and open up.

In a recent clinical study, Mosliciguat **reduced pressure in the lungs by 36–38%**, which is a big improvement, **without causing low blood pressure in the rest of the body**. The drug was inhaled directly into the lungs, allowing it to **work exactly where it's needed**, reducing side effects. It also helped some patients **breathe better and feel less fatigued**.

The treatment was well-tolerated. The most common side effects were mild and included **headache and tiredness**. Importantly, the effects of a single dose **lasted up to 24 hours**.

Because of these positive results, researchers are now planning a **larger Phase 2 trial**, especially focusing on people who have both **pulmonary hypertension and lung disease (PH-ILD)**. This inhaled drug may offer a **new, targeted way to improve breathing and quality of life** for people living with serious lung-related high blood pressure.

Pulmonary artery denervation

Alex Rothman – University of Sheffield

Lay Summary: Pulmonary Artery Denervation for Pulmonary Hypertension

Doctors are exploring a new, non-drug treatment for **pulmonary arterial hypertension (PAH).** This treatment is called **pulmonary artery denervation**.

In PAH, the **nervous system becomes overactive**, increasing stress signals (like adrenaline) that cause the blood vessels in the lungs to tighten. Researchers discovered that a large portion of these stress signals are produced right in the lungs, and this may contribute to the disease.

To counter this, doctors are using **catheters to deliver energy (radiofrequency or ultrasound)** to the walls of the pulmonary arteries. This process **disrupts the nerves** around the arteries—similar to turning off part of the "fight-or-flight" response in the lungs.

In a small study of **23 patients**, this procedure led to:

- **Lower pressure in the lung arteries**
- **Improved ability to exercise** (patients walked farther in a 6-minute test)
- **Better quality of life**
- **Reduced heart strain** and **lower levels of heart failure markers**

Larger studies are ongoing, including in patients with **pulmonary hypertension due to heart disease**. Early results are promising, showing that this technique could **help the heart work**

more efficiently and **reduce symptoms** for people with different forms of pulmonary hypertension.

This approach offers hope for a **non-medication-based therapy** that may improve outcomes in a challenging disease.

Summary fabricated using AI