

Innovations in drug delivery to improve patient experience

Hossein-Ardeschir Ghofrani

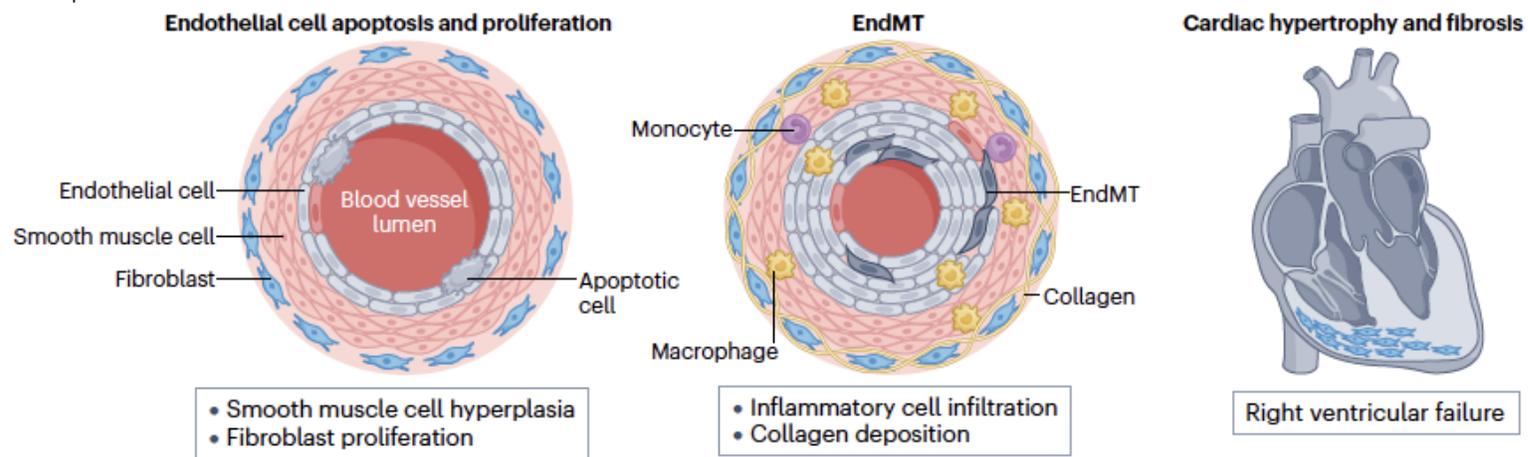
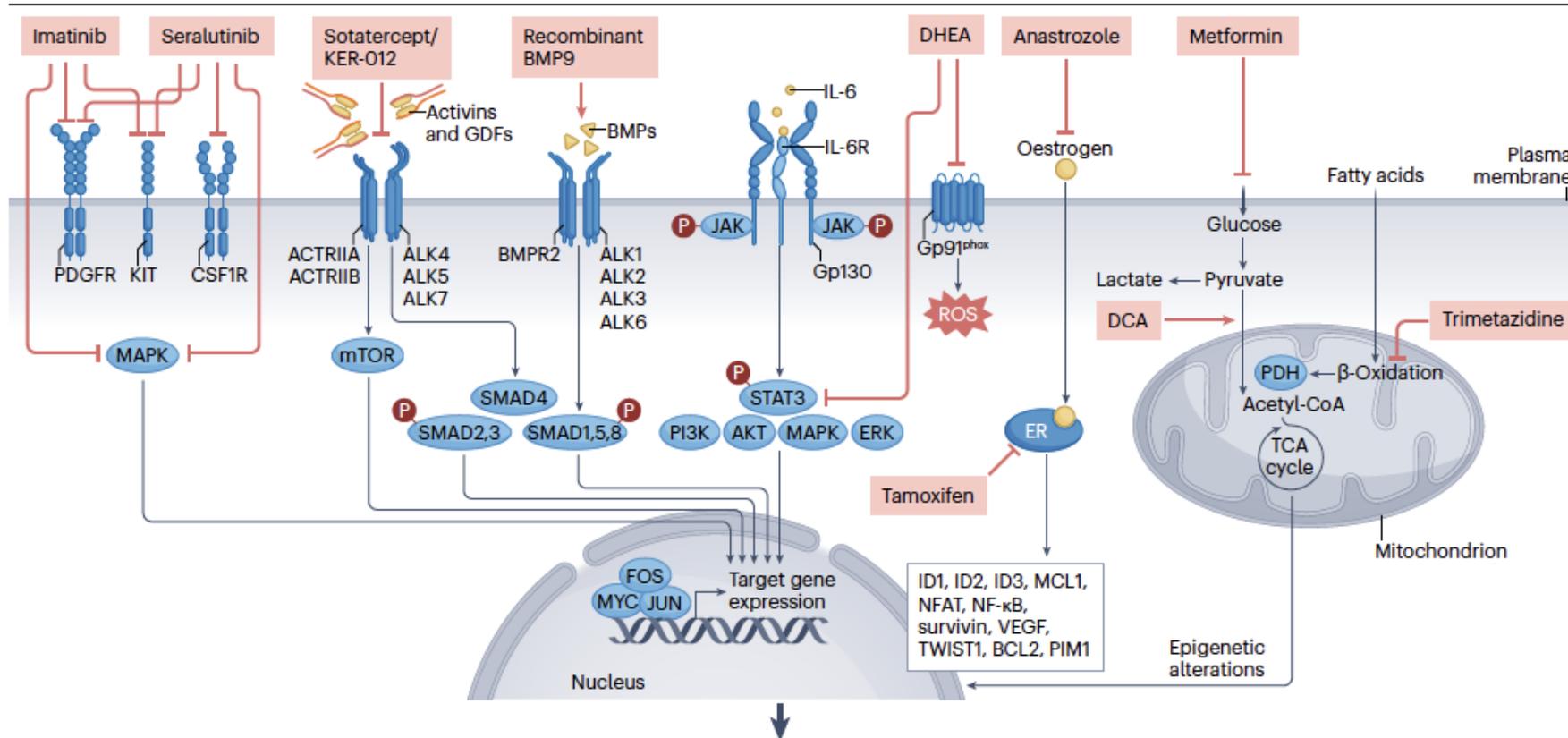
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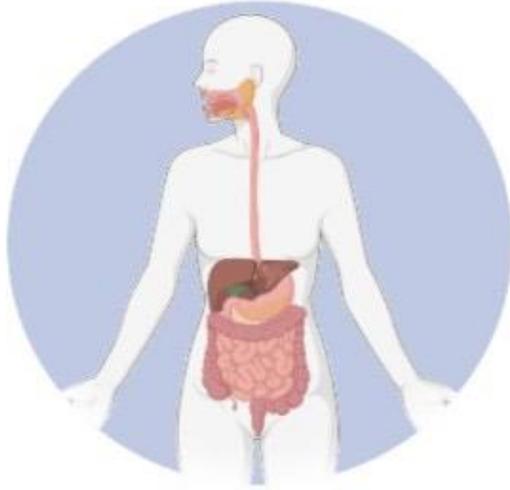
Disclosures

- Consultant fees from Gossamer Bio, Inc, Bayer AG, Attgeno, Janssen/Actelion, MSD/Acceleron, Pfizer, Liquidia, Morphic, Keros, Pulmovant, Inc.
- Payment or honoraria for lectures, presentations, or speaking from Bayer AG, Janssen/Actelion, Gossamer Bio, Inc, Keros, and MSD
- Serving as a steering committee member for Bayer AG, Attgeno, Janssen/Actelion, MSD/Acceleron, Pfizer, and Pulmovant, Inc.
- Serving as a data and safety monitoring board member for Insmed
- Spouse employment by Liquidia

Novel therapeutic targets

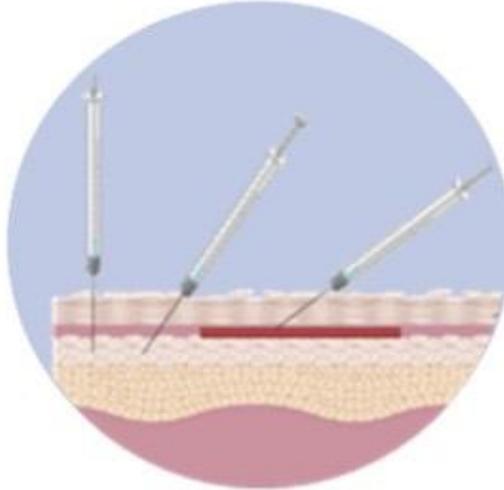


ROUTES OF DRUGS ADMINISTRATION



ENTERAL

Oral
Sublingual
Rectal



PARENTERAL

Intramuscular injection
Subcutaneous injection
Intravenous injection
Intradermal injection
Local injection



TOPICAL

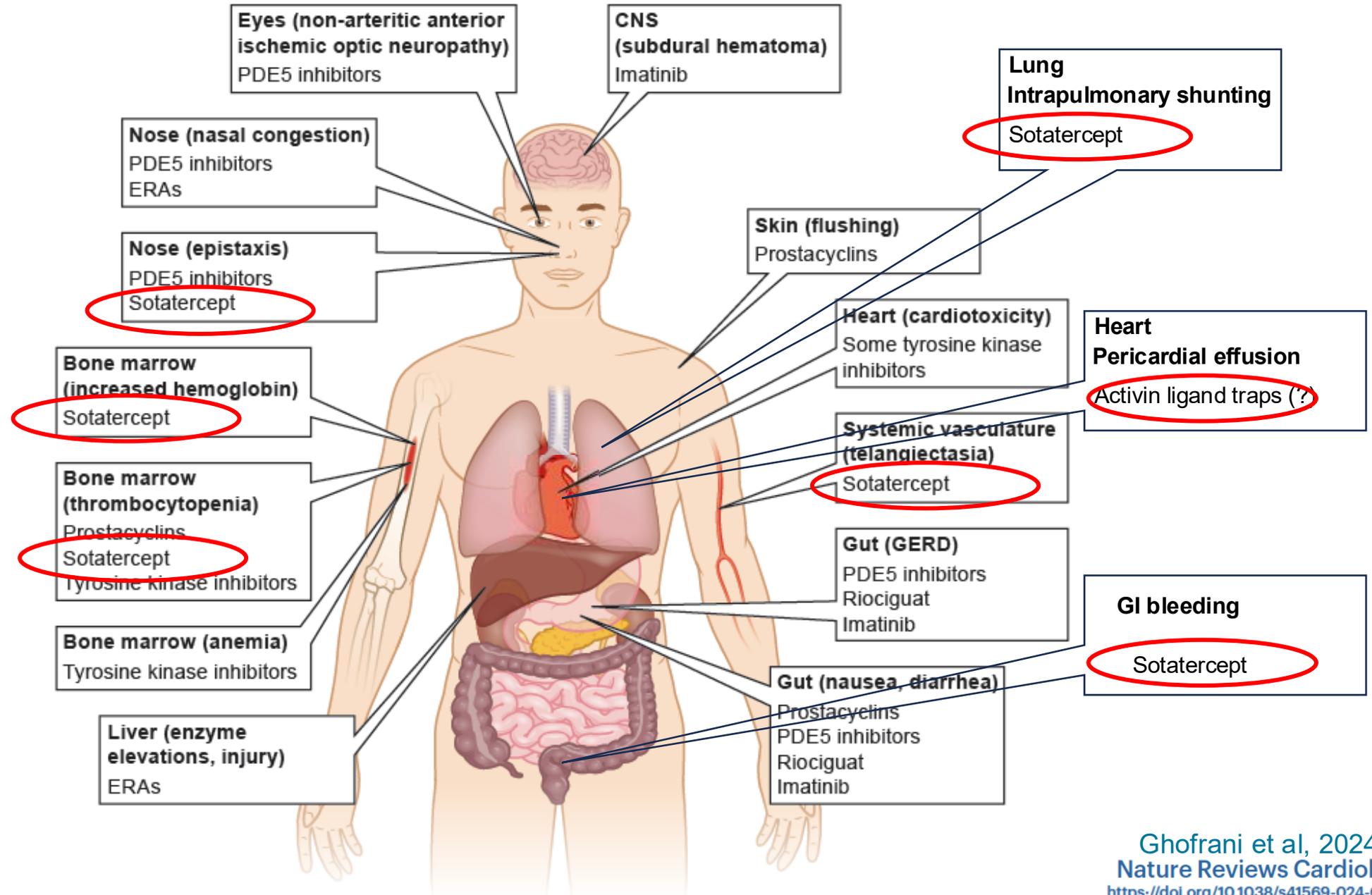
Epidermic
Instillation
Irrigation



INHALATION

Vaporization
Gas inhalation
Nebulization

Adverse event profile: Tolerability is also dependent on mode of delivery

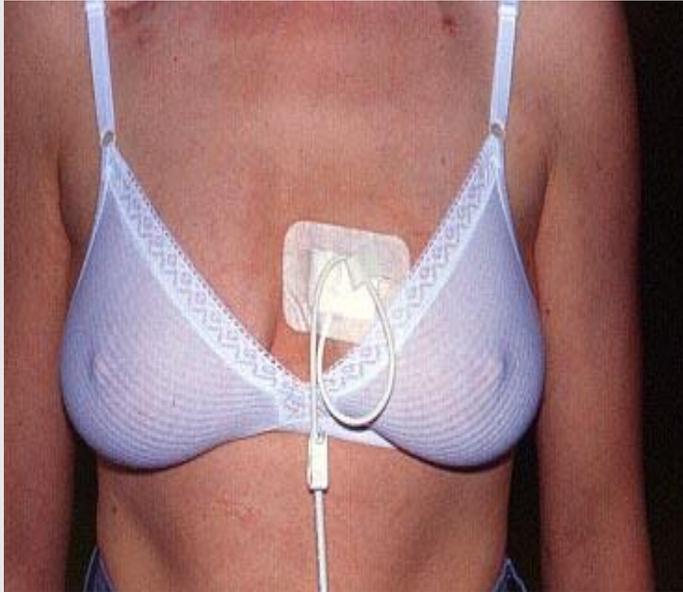


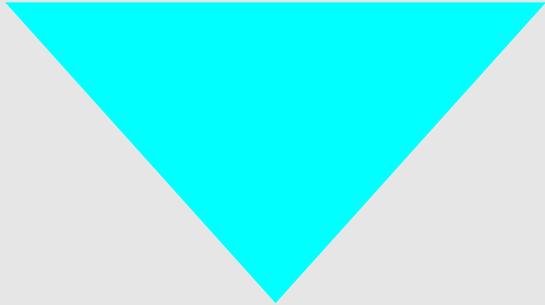
Oral PH medications

THERAPY	EXAMPLES	ADMINISTRATION	PH type
Endothelin receptor antagonists	<ul style="list-style-type: none"> • Letairis • Opsumit • Tracleer • Opsynvi (a dual class combination therapy) 	 <p>Oral</p>	PAH
Phosphodiesterase 5 inhibitors	<ul style="list-style-type: none"> • Adcirca • Revatio • Opsynvi (a dual class combination therapy) 	 <p>Oral</p>	PAH
Prostacyclin therapies	<ul style="list-style-type: none"> • Orenitram • Remodulin • Tyvaso • Yutrepia • Flolan • Veletri • Uptravi 	 <p>Oral Inhaled Subcutaneous or intravenous infusion</p>	PAH, PH-ILD
Soluble guanylate cyclase stimulators	<ul style="list-style-type: none"> • Adempas 	 <p>Oral</p>	PAH, CTEPH

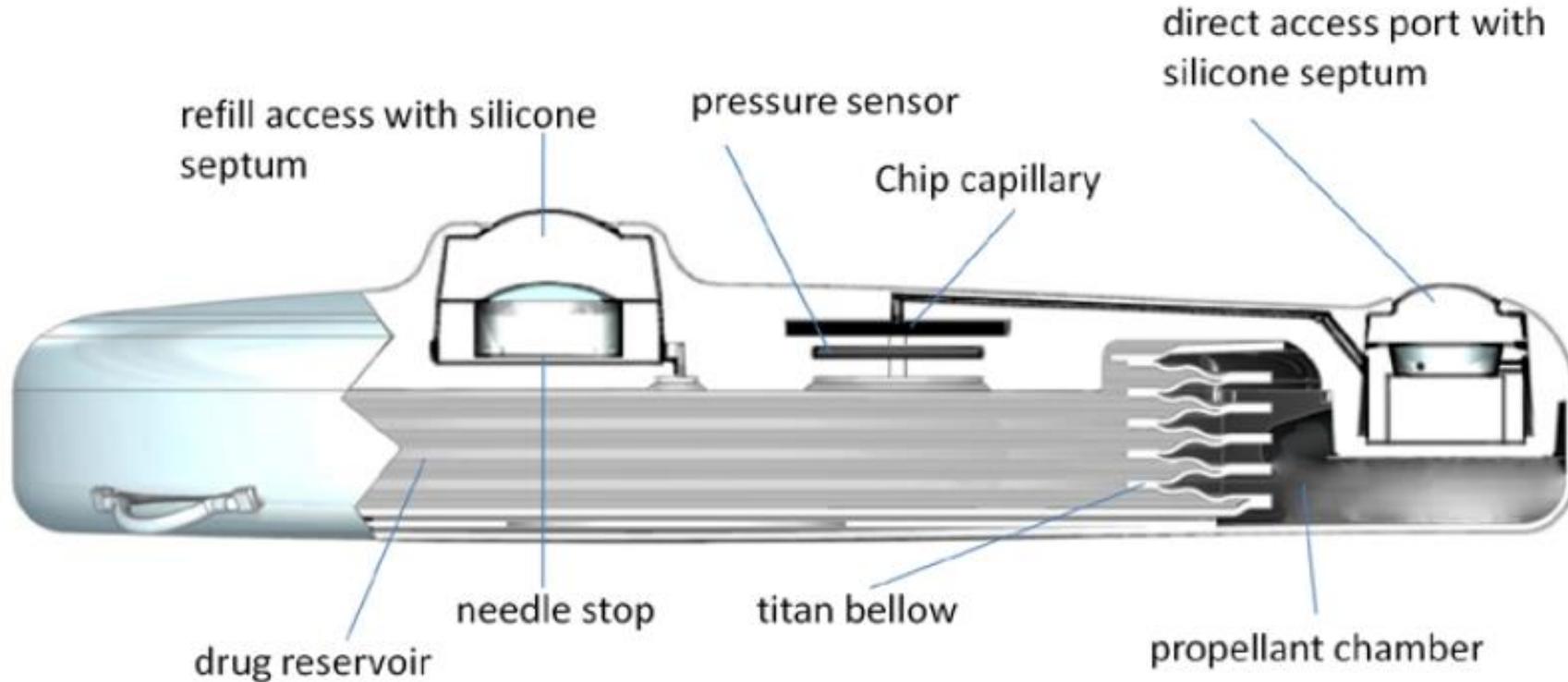
Therapies for PAH

Shortcomings of i.v. PGI₂



- 
- **Systemic side effects**
 - **Line-Infections**
 - **Thrombotic episodes**
 - **Catheter dislocation**
 - **Infusion-pump failure**
 - **Costs!**

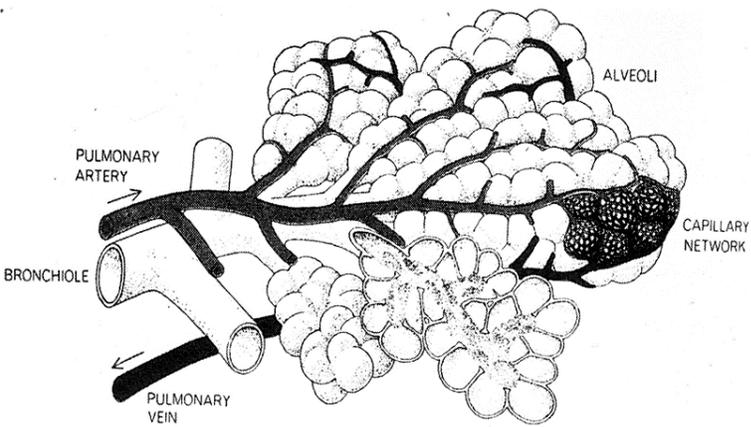
Implantable Pump for intravenous Prostanoid-therapy



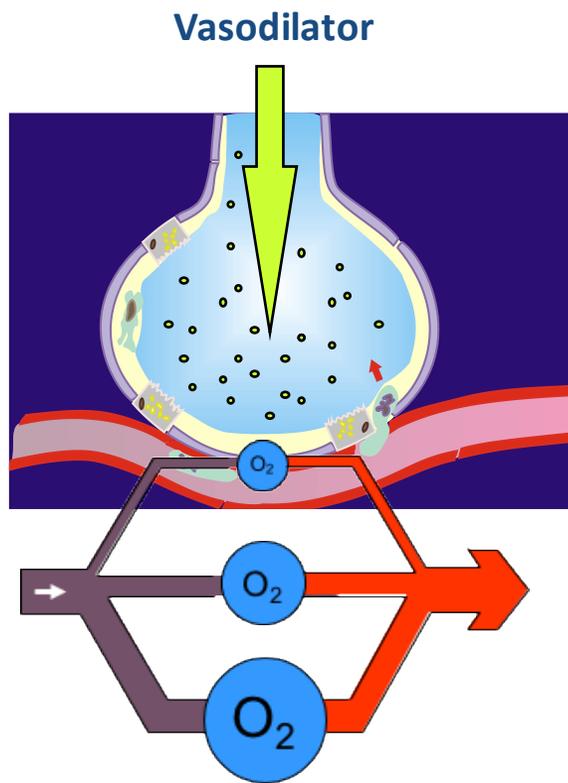
***An implantable pump for intravenous prostanoid therapy in patients with severe pulmonary hypertension**

Ralf Ewert¹, Michael Halank², Leonhard Bruch³, and Hossein Ardeschir Ghofrani^{4#}

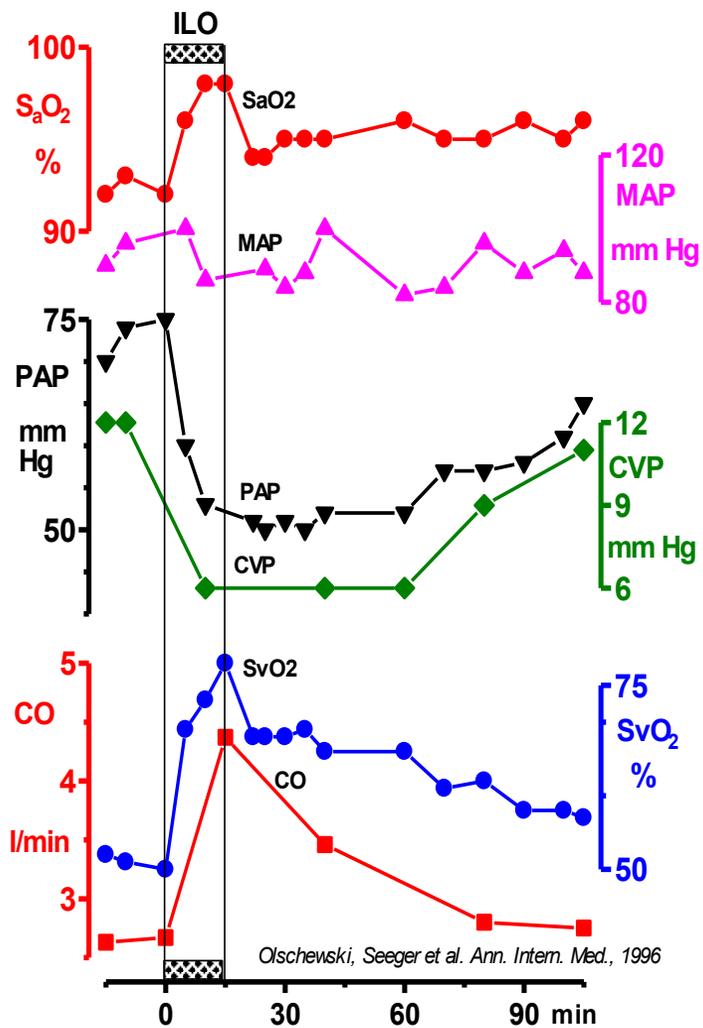
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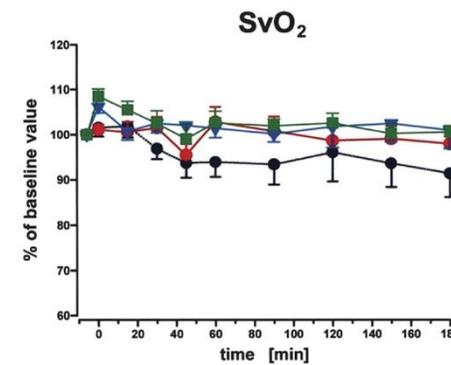
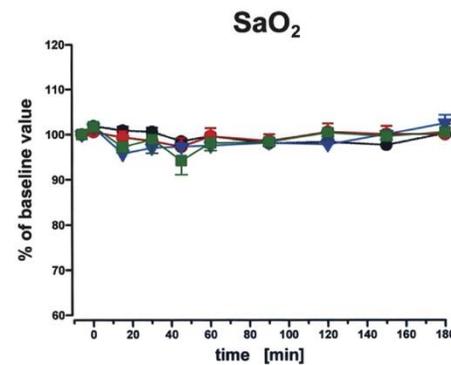
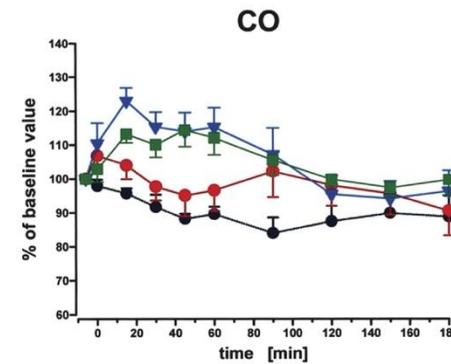
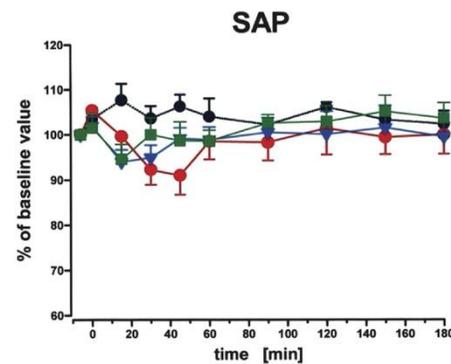
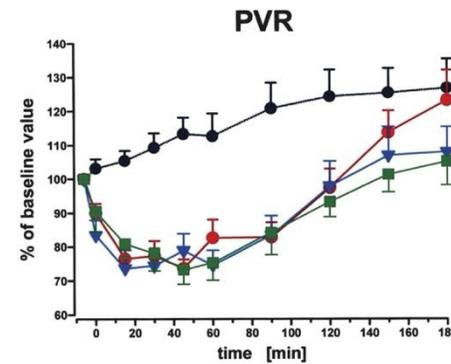
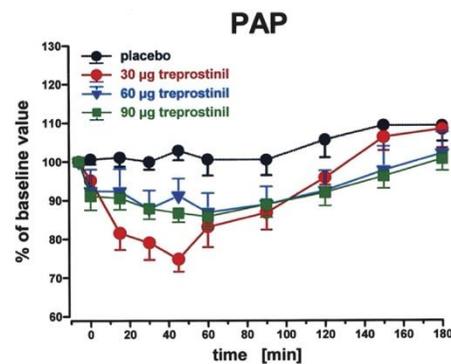
Concept of intrapulmonary Vasodilation



Ventilation/Perfusion



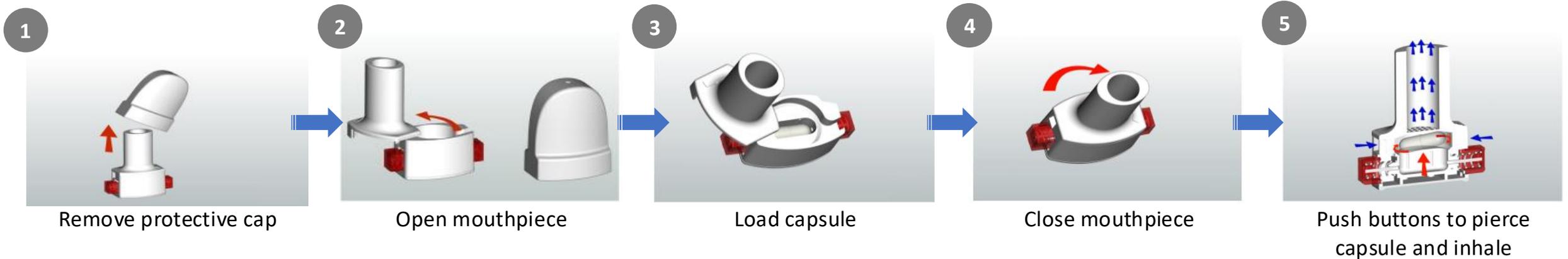
Olschewski, Seeger et al. Ann. Intern. Med., 1996





Mosliciguat is Administered Once-Daily via a Simple, Easy-to-use Device

Dry powder inhaler (DPI) is small and portable



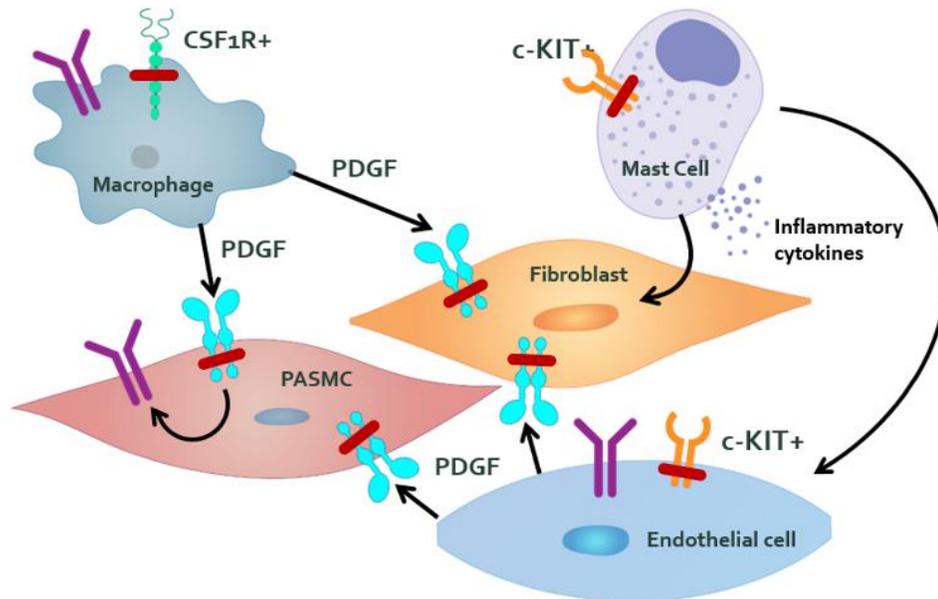
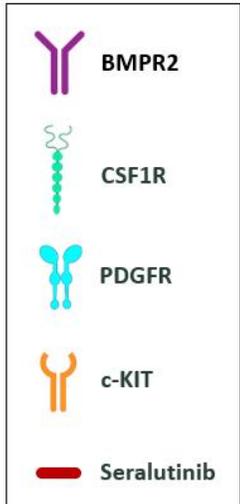
Device Type	Dosing Frequency	# capsules	Total Estimated Dosing Time
Dry Powder Inhaler (DPI)	1 puff/day	1 capsule/dose	Within seconds

TKI's beyond Imatinib: Seralutinib

Prof. Dr. Ardeschir Ghofrani

	GB002	Imatinib
PDGFR α IC ₅₀ (nM)	7	12
PDGFR β IC ₅₀ (nM)	6	74
Lung Exposure	++++	+++
Systemic Exposure	+	++

Dry Powder Inhaler From Plastiapipe

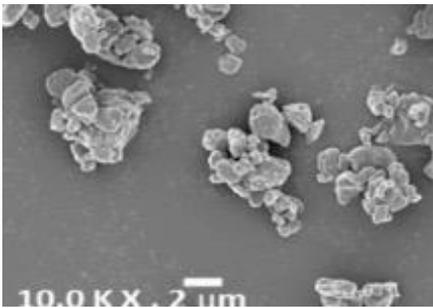


- **Seralutinib** (GB002) novel chemical entity; small molecule platelet-derived growth factor receptor (PDGFR) kinase inhibitor
- Equipotent against PDGFR α and β ; **10 fold more potent than imatinib against PDGFR β** in vitro; GB002 more potent in fibroblast assay.
- **In preclinical models**, inhaled administration results in **greater lung to systemic exposure**
- GB002 formulation and administration **via dry powder inhaler (DPI)** designed to reach areas of the deep lung

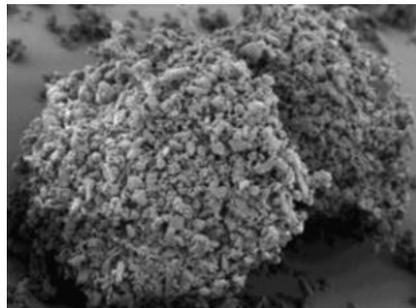
Traditional Dry Powder Formulations vs. Next Generation PRINT Designed Particles



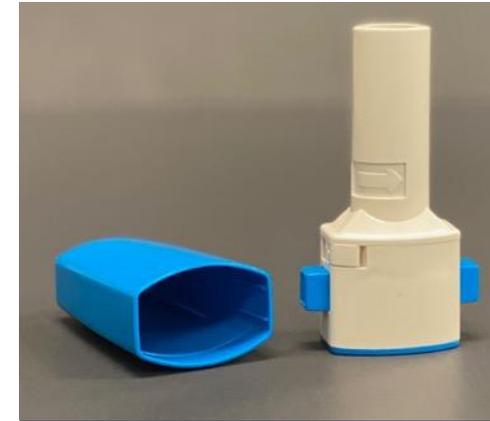
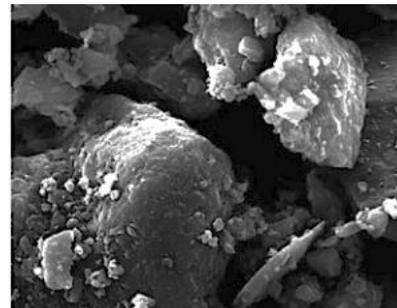
SPIRIVA®
HandiHaler
(Boehringer-Ingelheim)



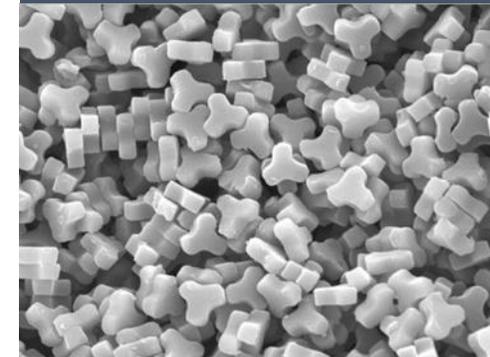
Pulmicort
Turbohaler®
(AstraZeneca)



Advair Diskus®
(GlaxoSmithKline)



**YUTREPIA™ &
Plastiape RS00**



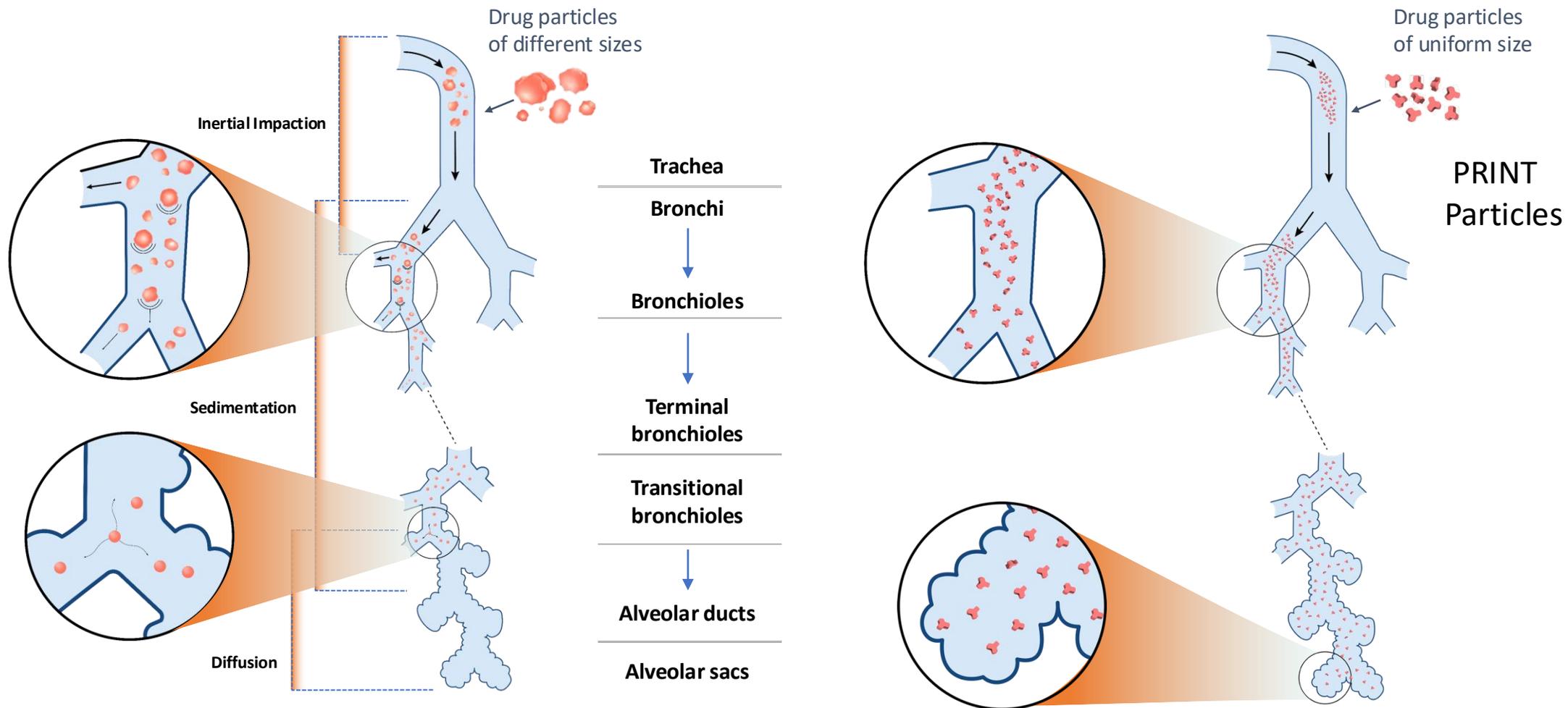
1. Muralidharan P, et al. Advanced design and development. RSC Adv. 2020 Nov 17;10(68):41846-41856.
2. Malamatarı M, et al. Spray Drying for the Preparation Processes. 2020; 8(7):788.
3. Image adapted from: <https://www.doktorabc.com/de/behandlungen/pulmicort-turbohaler>

4. M. Hoppentocht, et al. Technological and practical challenges, *Advanced Drug Delivery Reviews*, Volume 75, 2014, Pages 18-31.
5. Image adapted Kwon Y-B, et al, Preparation and Evaluation *Pharmaceutics*. 2022; 14(7):1409. <https://doi.org/10.3390/pharmaceutics14071409>
6. Image adapted from <https://www.healthnavigator.org.nz/medicines/t/tiotropium/>
*Spiriva® is a registered trademark of Boehringer Ingelheim Pharma KG Corporation
*Pulmicort® is a registered trademark of AstraZeneca AB Corp.
*Advair Diskus® is a registered trademark of Glaxo Group Limited



Traditional DPI Formulations require mechanical breakdown of particles by either high flowrates or high resistance DPI devices

**PRINT[®] Technology
DPI Formulations do not require further manipulation by devices**



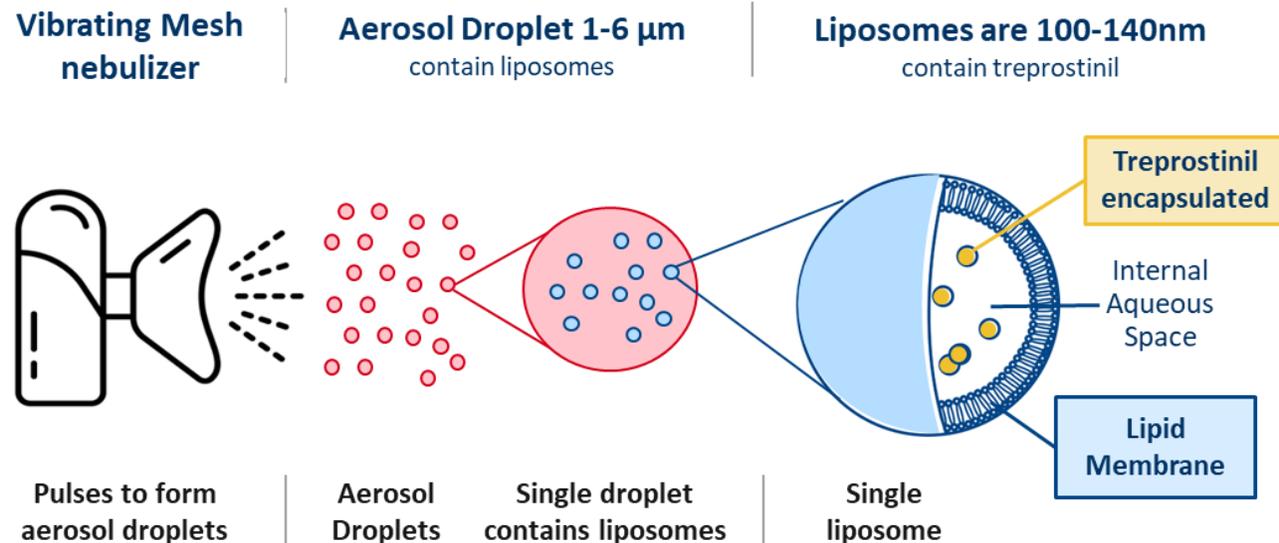
QOL= Quality of life 1. Humbert M, et al. Eur Heart J. 2022;43(38):3618-3731.



New formulation: L606 liposomal inhaled sustained release treprostinil being studied in a global phase 3 trial

Potential benefits to patients

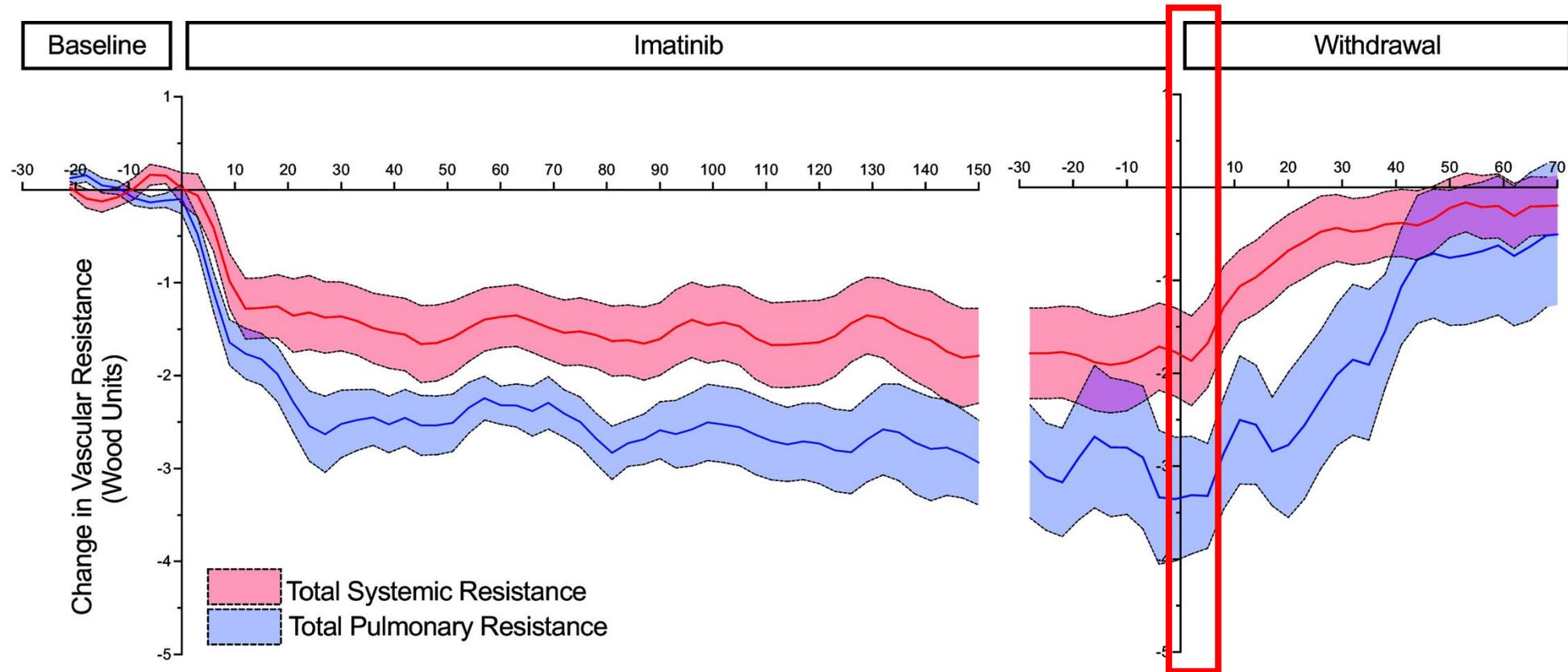
- Twice daily dosing
- Sustained drug exposure over 24 hours
- Improved tolerability with lower peak exposures
- Rapid delivery with next-generation nebulizer



- **Extended plasma PK up to 12 hours** as compared to 4 hours for Tyvaso® in Phase 1 trial^{1,2}
- **~7x lower Cmax** compared to Tyvaso with AUC being similar in Phase 1 trial¹
- Has been safely titrated to doses **comparable to 25 to 27 breaths of Tyvaso 4x daily** in POC study¹
- **Some patients dosed for more than 3 years**³
- **Less than 2-minute delivery** using **breath-actuated smart technology** and patients' normal breathing pattern³

1. Press Release: June 28, 2023 "Liquidia Corporation and Pharmosa Biopharm Announce Collaboration for Sustained-Release Inhaled Treprostinil Product in North America" Pharmacokinetic (PK), Maximum peak concentration (Cmax), Area Under the Curve (AUC), Proof of Concept (POC) Phase 1 study [NCT04691154](#); 2. Tully, J. et al, [POSTER] PVRI 2024 Annual Congress; 2024 Feb 2, London; Tyvaso® is a registered trademark of United Therapeutics. 3. Liquidia 2025. Data On File

Utilising implantables to measure PD



→ Plasma half-time: 15 hours → no circulating Imatinib after 1 week, but 8 weeks improvement = indicator for disease-modifying effect

10 PAH Patients

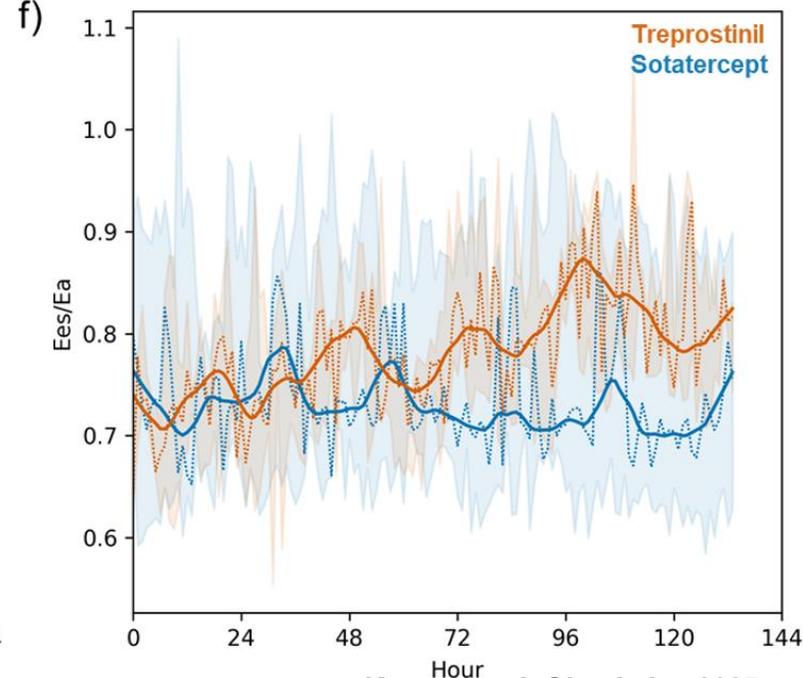
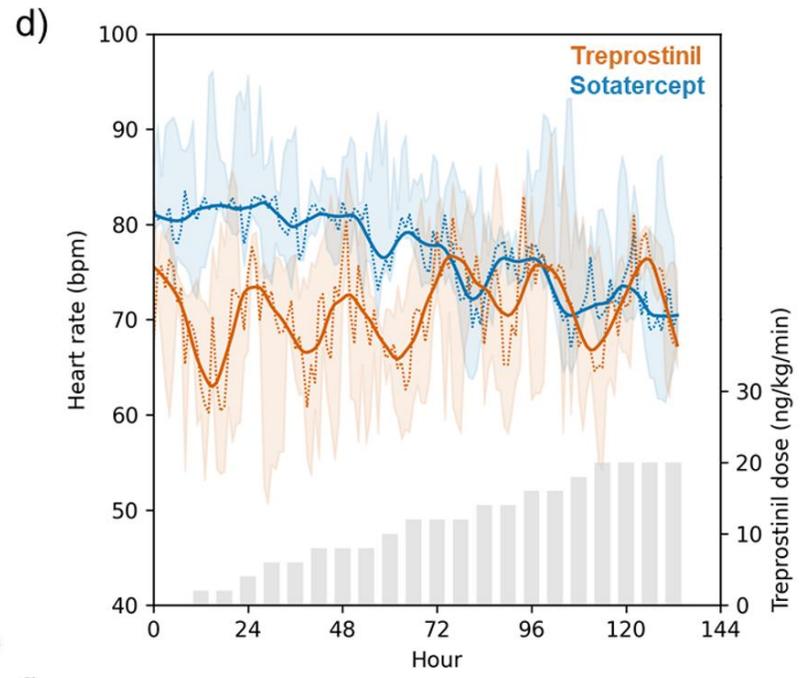
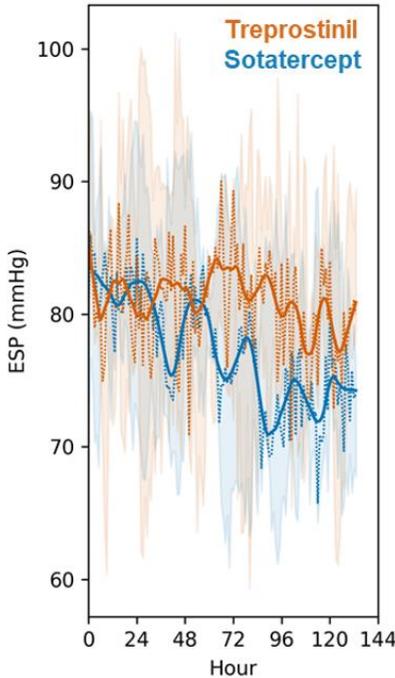
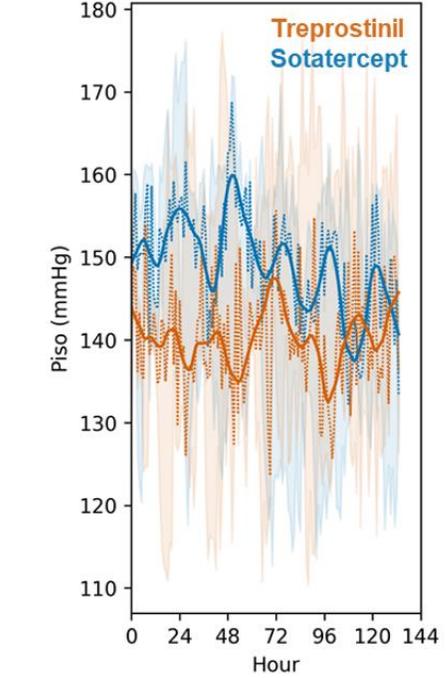
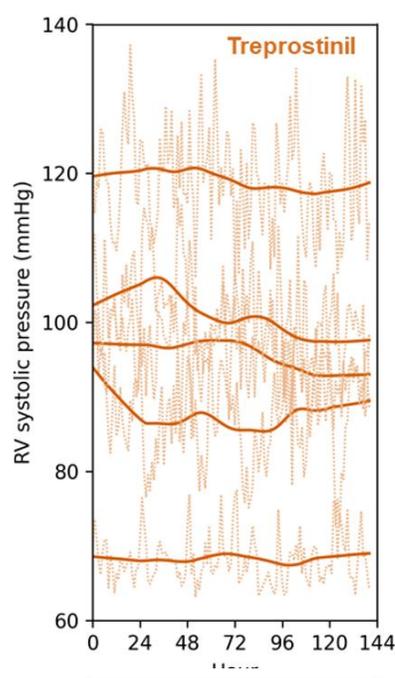
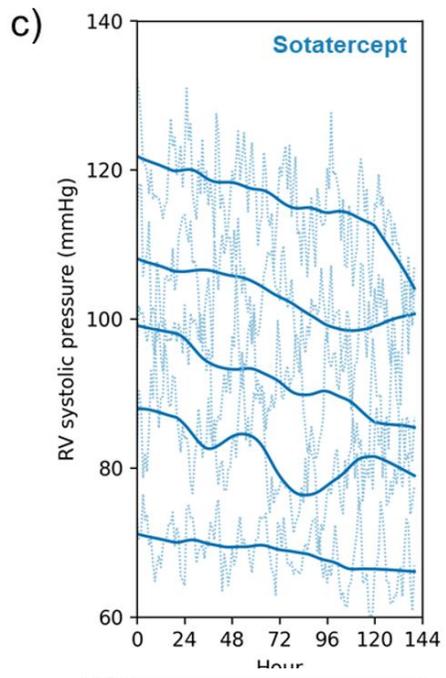
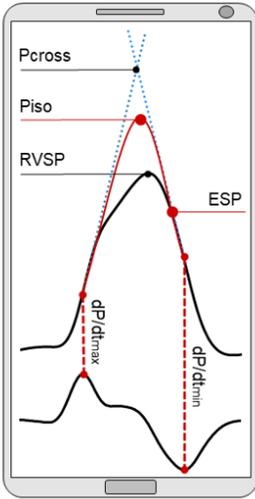
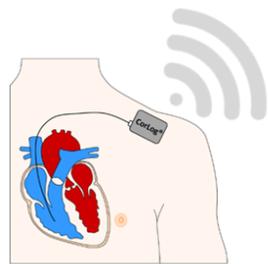
5 received first dose of Sotatercept (0.3mg/kg)

5 initiation of Treprostinil (target 20ng/kg/min at day 5)

Continuous monitoring of RV-Pressure for ~7 days

RV-PA coupling calculated as:

$$\frac{E_{es}}{E_a} = \left(\frac{P_{iso}}{ESP}\right) - 1$$



Conclusion

- **Classical routes of administration:** oral, i.v., s.c., i.m., inhal., transdermal
- **First approved PH drug i.v. epoprostenol**, drug related side-effects, adverse events related to route of administration
- **Oral PH medications major step forward**, drug specific side effects
- **Inhaled route ideal to deliver drugs to the region of interest**, reducing systemic exposure
- In future **combining lung-targeted therapies with online-pharmacodynamic monitoring** is key for individualised therapies
- Ultimately the goal is to **make treatments efficacious AND well tolerable** for patients

The DZL-Family Welcomes You to Join our Mission

