R&D DAY

September 30, 2020

Agenda

Section	Speakers
Welcome & Kick-off	**Will Lewis** *Chair & Chief Executive Officer*
Treprostinil Palmitil Inhalation Powder Opportunity	**Dr. Eugene Sullivan, M.D.** *Chief Product Strategy Officer* **Dr. Ronald J. Oudiz, M.D., FACP, FACC, FCCP** *Professor of Medicine and Interim Chief* *Harbor-UCLA Medical Center Division of Cardiology* *Lead Investigator for Planned Phase 2a Trial*
Brensocatib Development Program Update	**Dr. Kevin Mange, M.D., MSCE** *Head of Clinical Development* **Colleen Silk** *General Manager, Brensocatib*
ARIKAYCE Front Line and Global Expansion Update	**Dr. Kevin Mange, M.D., MSCE** *Head of Clinical Development* **Neil Hughes** *General Manager, Head of Europe, Middle East and Africa (EMEA) Commercial* **Roger Adsett** *Chief Operating Officer*
Financial Update **Closing Remarks**	**Sara Bonstein** *Chief Financial Officer*
Q&A Session	**Insmed Executive Team & Participants**

Forward Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. "Forward-looking statements," as that term is defined in the Private Securities Litigation Reform Act of 1995, are statements that are not historical facts and involve a number of risks and uncertainties. Words herein such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "intends," "potential," "continues," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) may identify forward-looking statements.

The forward-looking statements in this presentation are based upon the Company's current expectations and beliefs, and involve known and unknown risks, uncertainties and other factors, which may cause the Company's actual results, performance and achievements and the timing of certain events to differ materially from the results, performance, achievements or timing discussed, projected, anticipated or indicated in any forward-looking statements. Such risks, uncertainties and other factors include, among others, the following: the risk that brensocatib does not prove effective or safe for patients in the STOP-COVID19 study; business or economic disruptions due to catastrophes or other events, including natural disasters or public health crises; impact of the novel coronavirus (COVID-19) pandemic and efforts to reduce its spread on our business, employees, including key personnel, patients, partners and suppliers; failure to successfully commercialize or maintain U.S. approval for ARIKAYCE®, the Company's only approved product; uncertainties in the degree of market acceptance of ARIKAYCE by physicians, patients, third-party payors and others in the healthcare community; the Company's inability to obtain full approval of ARIKAYCE from the FDA, including the risk that the Company will not timely and successfully complete the study to validate a PRO tool and complete the confirmatory post-marketing study required for full approval of ARIKAYCE; inability of the Company, PARI or the Company's other third party manufacturers to comply with regulatory requirements related to ARIKAYCE or the Lamira® Nebulizer System; the Company's inability to obtain adequate reimbursement from government or third-party payors for ARIKAYCE or acceptable prices for ARIKAYCE; development of unexpected safety or efficacy concerns related to ARIKAYCE or brensocatib; inaccuracies in the Company's estimates of the size of the potential markets for ARIKAYCE or its product candidates or in data the Company has used to identify physicians; expected rates of patient uptake, duration of expected treatment, or expected patient adherence or discontinuation rates; the Company's inability to create an effective direct sales and marketing infrastructure or to partner with third parties that offer such an infrastructure for distribution of ARIKAYCE or any of the Company's product candidates that is approved in the future; failure to obtain regulatory approval to expand ARIKAYCE's indication to a broader patient population; failure to successfully conduct future clinical trials for ARIKAYCE, brensocatib and the Company's other product candidates, including due to the Company's limited experience in conducting preclinical development activities and clinical trials necessary for regulatory approval and the Company's inability to enroll or retain sufficient patients to conduct and complete the trials or generate data necessary for regulatory approval; risks that the Company's clinical studies will be delayed or that serious side effects will be identified during drug development; failure to obtain, or delays in obtaining, regulatory approvals for ARIKAYCE outside the U.S. or for the Company's product candidates in the U.S., Europe, Japan or other markets, including the United Kingdom as a result of its recent exit from the European Union; failure of third parties on which the Company is dependent to manufacture sufficient quantities of ARIKAYCE or the Company's product candidates for commercial or clinical needs, to conduct the Company's clinical trials, or to comply with laws and regulations that impact the Company's business or agreements with the Company; the Company's inability to attract and retain key personnel or to effectively manage the Company's growth; the Company's inability to adapt to its highly competitive and changing environment; the Company's inability to adequately protect its intellectual property rights or prevent disclosure of its trade secrets and other proprietary information and costs associated with litigation or other proceedings related to such matters; restrictions or other obligations imposed on the Company by its agreements related to ARIKAYCE or the Company's product candidates, including its license agreements with PARI and AstraZeneca AB, and failure of the Company to comply with its obligations under such agreements; the cost and potential reputational damage resulting from litigation to which the Company is or may become a party, including product liability claims; the Company's limited experience operating internationally; changes in laws and regulations applicable to the Company's business, including any pricing reform, and failure to comply with such laws and regulations; inability to repay the Company's existing indebtedness and uncertainties with respect to the Company's ability to access future capital; and delays in the execution of plans to build out an additional FDA-approved third-party manufacturing facility and unexpected expenses associated with those plans.

The Company may not actually achieve the results, plans, intentions or expectations indicated by the Company's forward-looking statements because, by their nature, forward-looking statements involve risks and uncertainties because they relate to events and depend on circumstances that may or may not occur in the future. For additional information about the risks and uncertainties that may affect the Company's business, please see the factors discussed in Item 1A, "Risk Factors," in the Company's Annual Report on Form 10-K for the year ended December 31, 2019, Quarterly Reports on Form 10-Q for the quarters ended March 31, 2020 and June 30, 2020, and any subsequent Company filings with the SEC.

The Company cautions readers not to place undue reliance on any such forward-looking statements, which speak only as of the date of this presentation. The Company disclaims any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

Will Lewis
Chair & CEO

Mission, Vision & Strategy

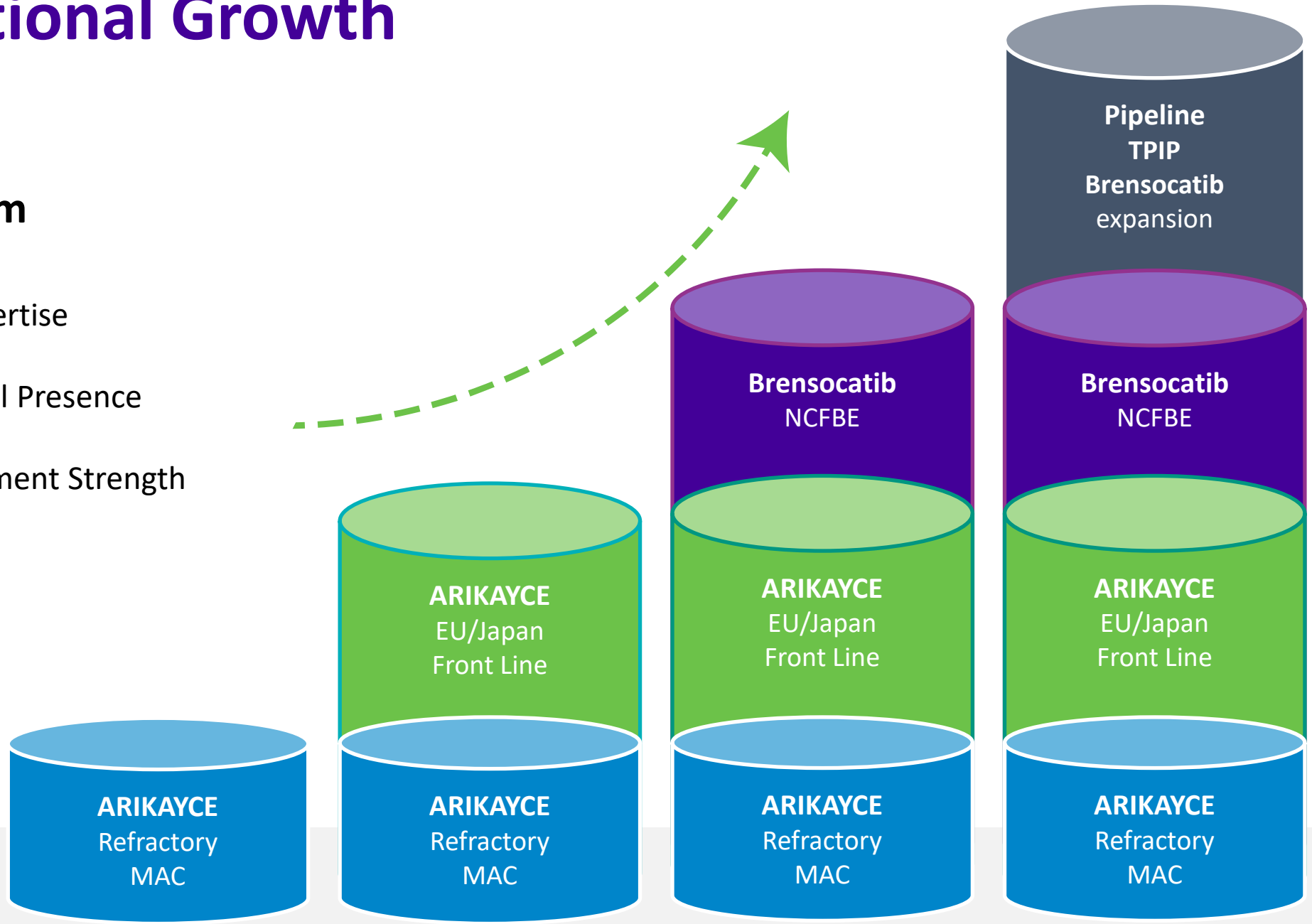
Transformational Growth Strategy

World Class Team

Research &
Development Expertise

Global Commercial Presence

Business Development Strength



Leadership Team

William H. Lewis J.D., M.B.A.

Chair & Chief Executive Officer

Roger Adsett, M.B.A.

Chief Operating Officer

Sara M. Bonstein, M.B.A.

Chief Financial Officer

Martina Flammer, M.D., M.B.A.

Chief Medical Officer

Christine Pellizzari, J.D.

Chief Legal Officer

John Soriano, J.D.

Chief Compliance Officer

Nicole Schaffer, M.B.A.

Chief People Strategy Officer

Eugene Sullivan, M.D.

Chief Product Strategy Officer

Neil Hughes, LL.B., M.B.A.

General Manager & Head EMEA

Kevin C. Mange, M.D., MSCE

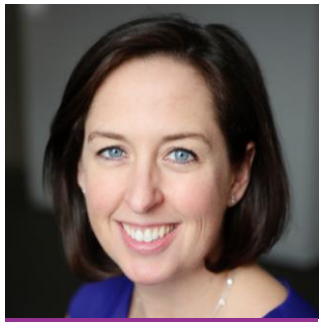
Head of Clinical Development

Yuji Orihara, M.B.A.

General Manager & Head of Japan

Walter Perkins, Ph.D.

Chief Technology Officer



Colleen Silk, M.B.A.

General Manager - Brensocatib

Andy Stautberg, M.B.A.

General Manager, Early Pipeline

Drayton Wise, M.B.A.

Head of U.S. & General Manager - ARIKAYCE

Dr. Eugene Sullivan, M.D.
Chief Product Strategy Officer

Dr. Ronald J. Oudiz, M.D., FACP, FACC, FCCP
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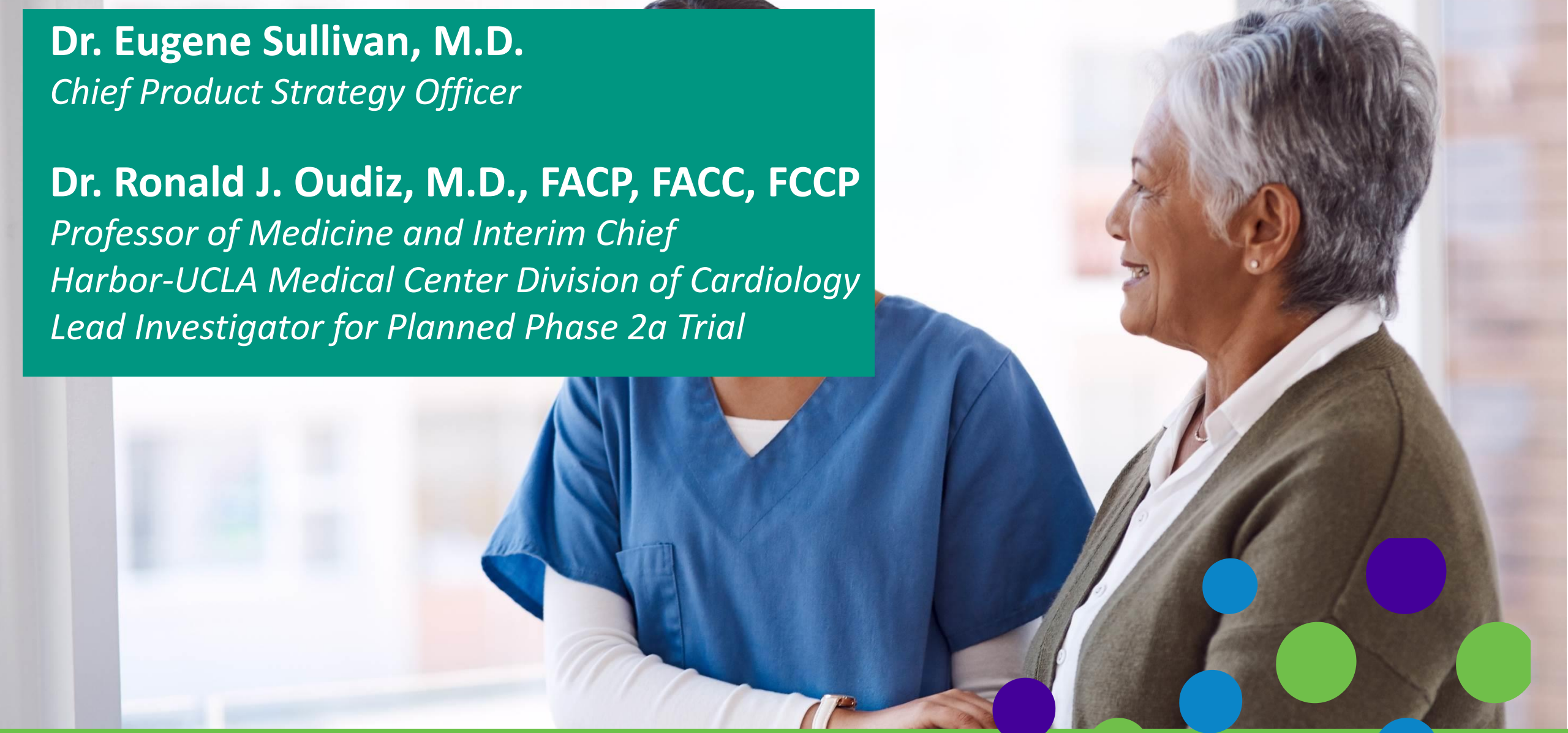


Treprostinil Palmitil

Development Update

Harnessing the Full Potential of the Prostanoid Pathway in Pulmonary Arterial Hypertension (PAH)

Prostanoids have long been considered the cornerstone therapy for PAH but clinical use has faced challenges related to rapid metabolism and tolerability issues

Treprostinil palmitil has the potential to address the shortcomings of the existing prostanoid therapies by:

- Potentially minimizing side effects, both local and systemic
- Potentially maximizing the vasodilatory activity, by maintaining high local concentrations in the lung
- Allowing for histologic disease-modifying effects of prostanoid therapy

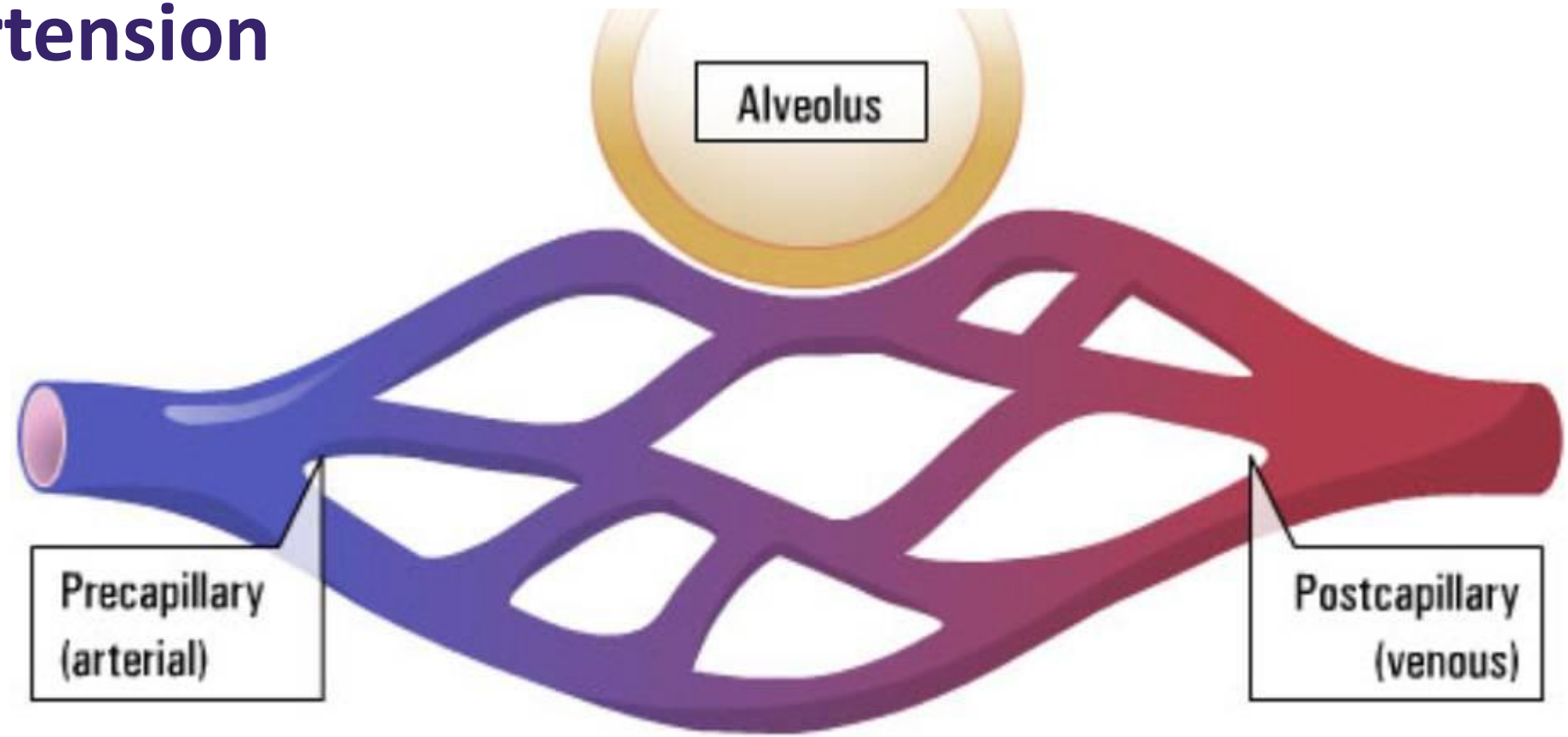
Agenda

1. Pulmonary Arterial Hypertension (PAH)
2. Treprostinil Palmitil Inhalation Powder (TPIP)
3. Highlights of Preclinical Data
4. Product Differentiation
5. Path Forward

Dr. Ronald J. Oudiz, M.D., FACP, FACC, FCCP
Professor of Medicine and Interim Chief
Harbor-UCLA Medical Center Division of Cardiology
Lead Investigator Planned Phase 2a Trial

Pulmonary Arterial Hypertension (PAH) Treatment Landscape

Types of Pulmonary Hypertension



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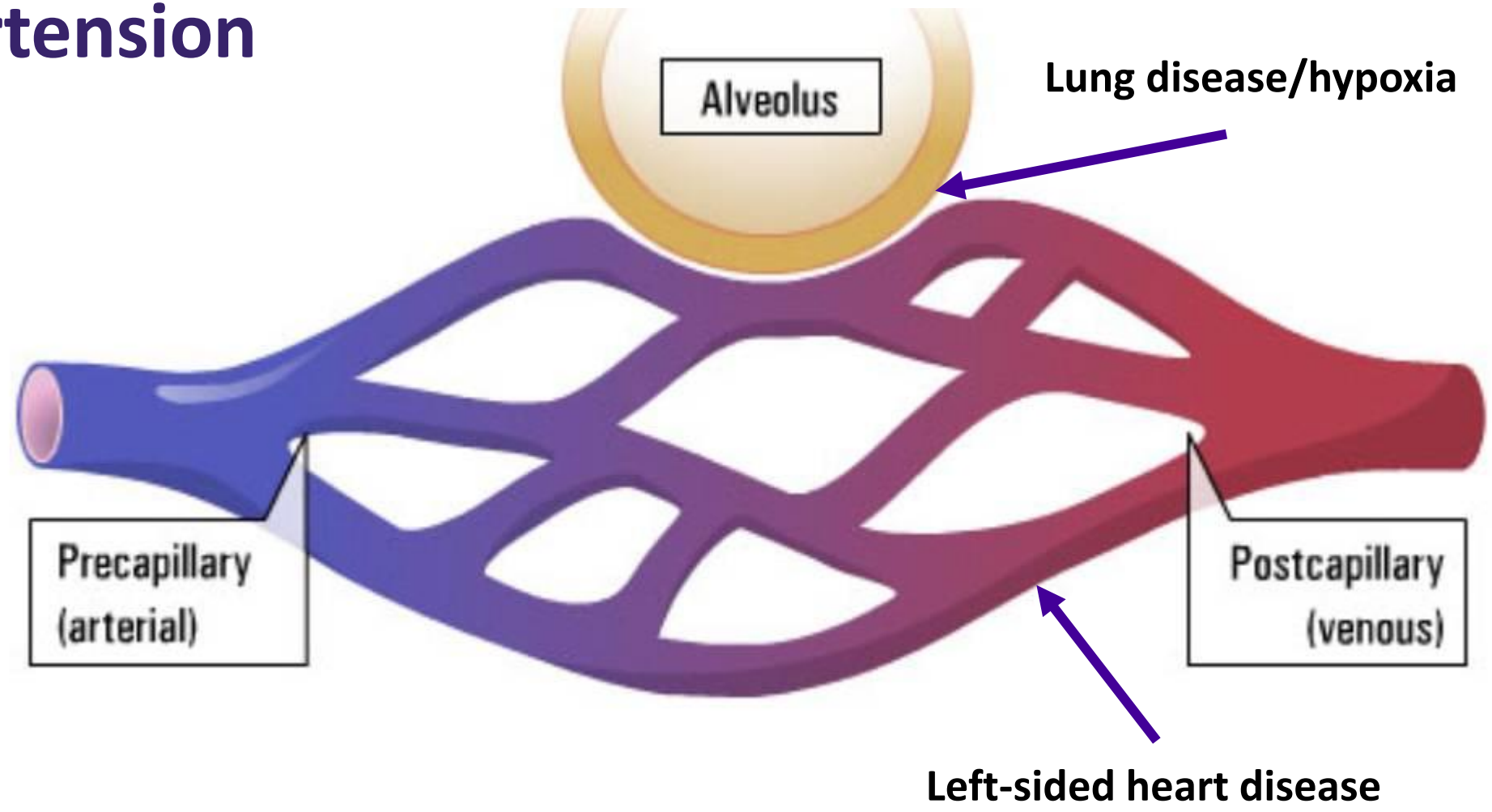

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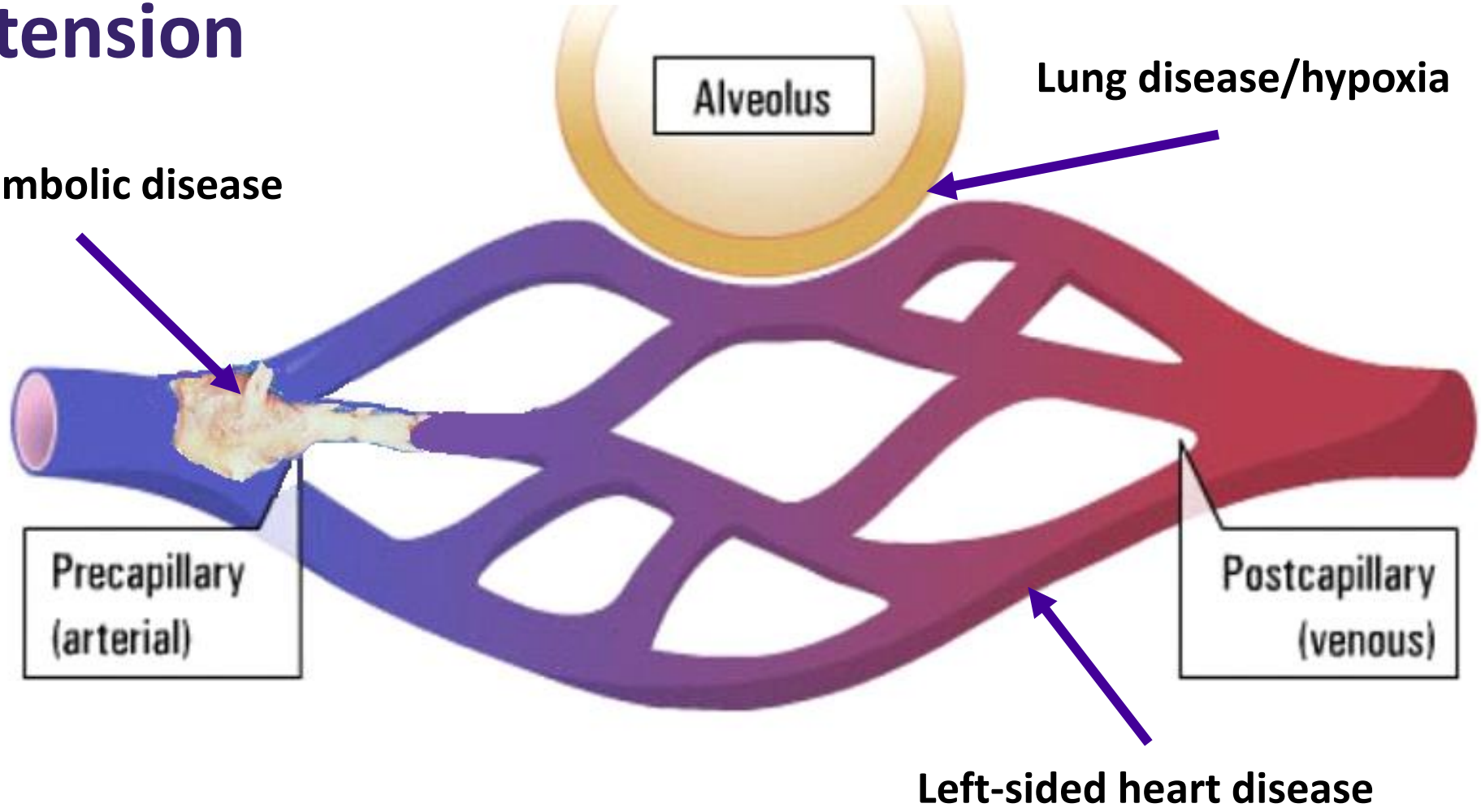

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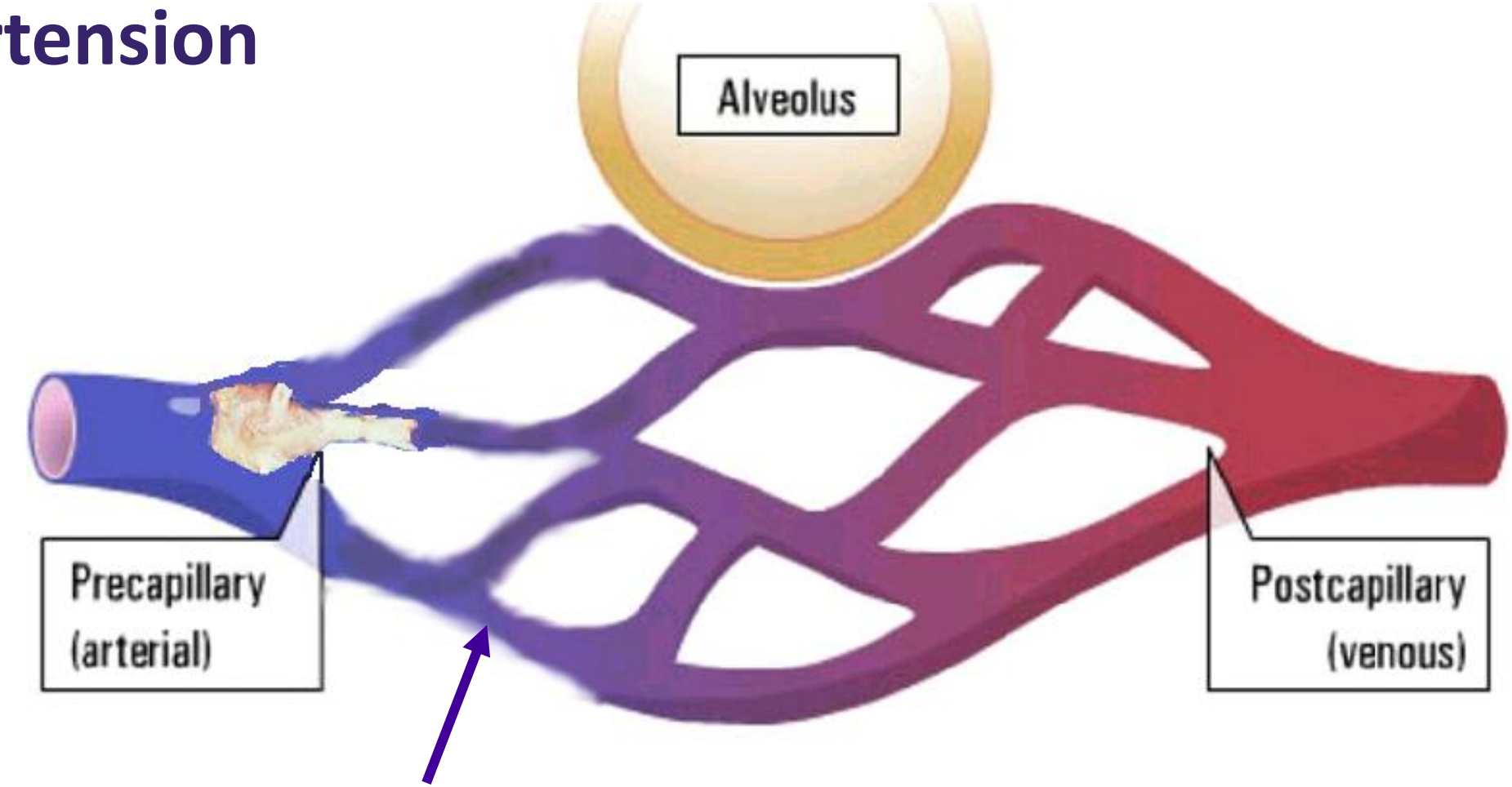

IPAH and APAH

Pulmonary Hypertension: Diagnostic classification

1. Pulmonary arterial hypertension (PAH)

1.1. Idiopathic PAH (IPAH)

1.2. Heritable

1.2.1. BMPR2

1.2.2. ALK1, ENG, SMAD9, CAV1, KCNK3

1.2.3. Unknown

1.3. Drug- and toxin-induced

1.4. Associated with

1.4.1. Connective tissue diseases

1.4.2. HIV infection

1.4.3. Portal hypertension

1.4.4. Congenital heart diseases

1.4.5. Schistosomiasis

1’ Pulmonary veno-occlusive disease and / or pulmonary capillary hemangiomatosis

1’ Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

2.1. Left ventricular systolic dysfunction

2.2. Left ventricular diastolic dysfunction

2.3. Valvular disease

2.4. Congenital/acquired left heart inflow/ outflow tract obstruction and congenital cardiomyopathies

3. PH due to Lung Diseases and/or Hypoxemia

3.1. Chronic obstructive pulmonary disease

3.2. Interstitial lung disease

3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4. Sleep-disordered breathing

3.5. Alveolar hypoventilation disorders

3.6. Chronic exposure to high altitude

3.7. Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms

5.1. Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy

5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis: lymphangioleiomyomatosis

5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

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no approved therapy

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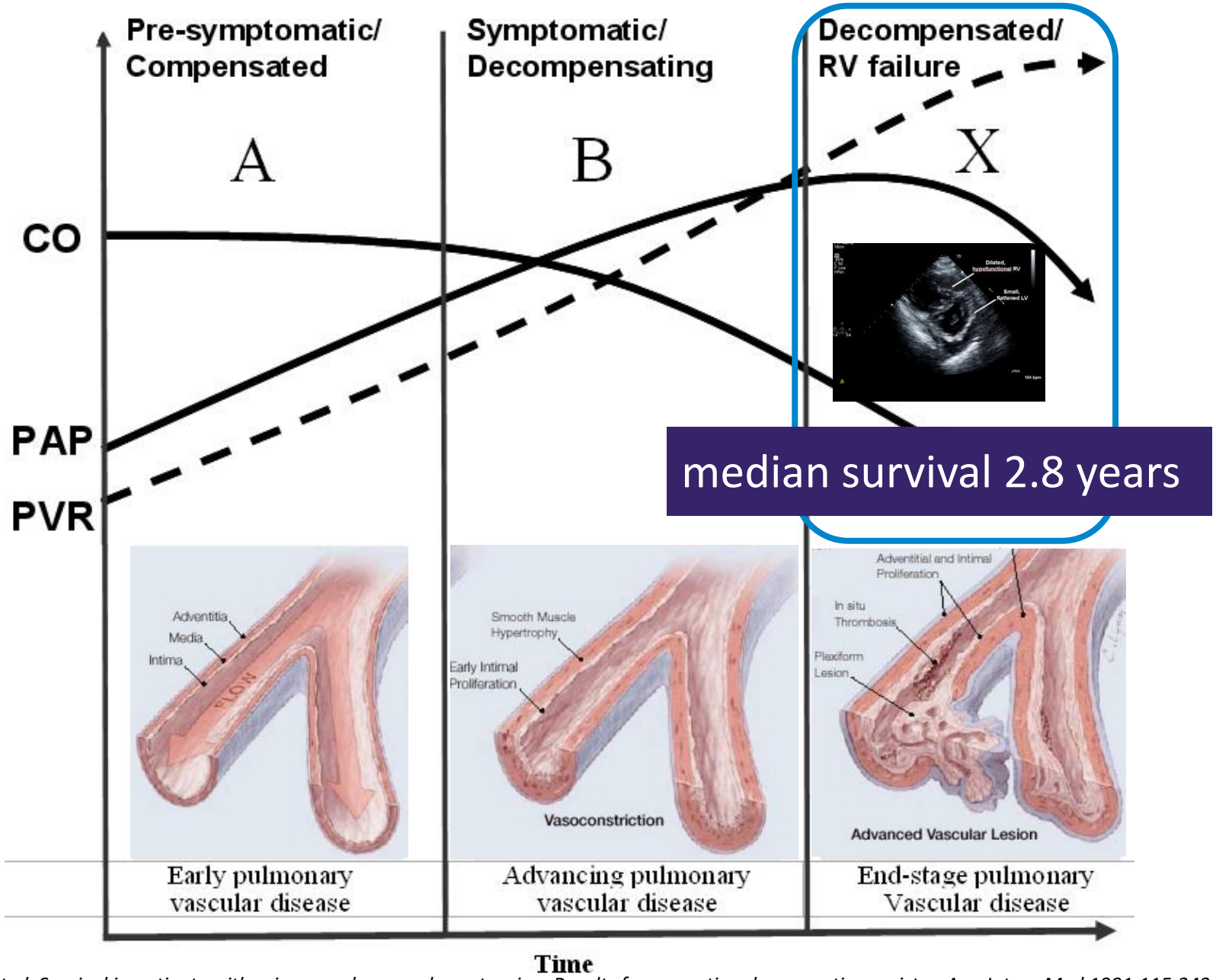
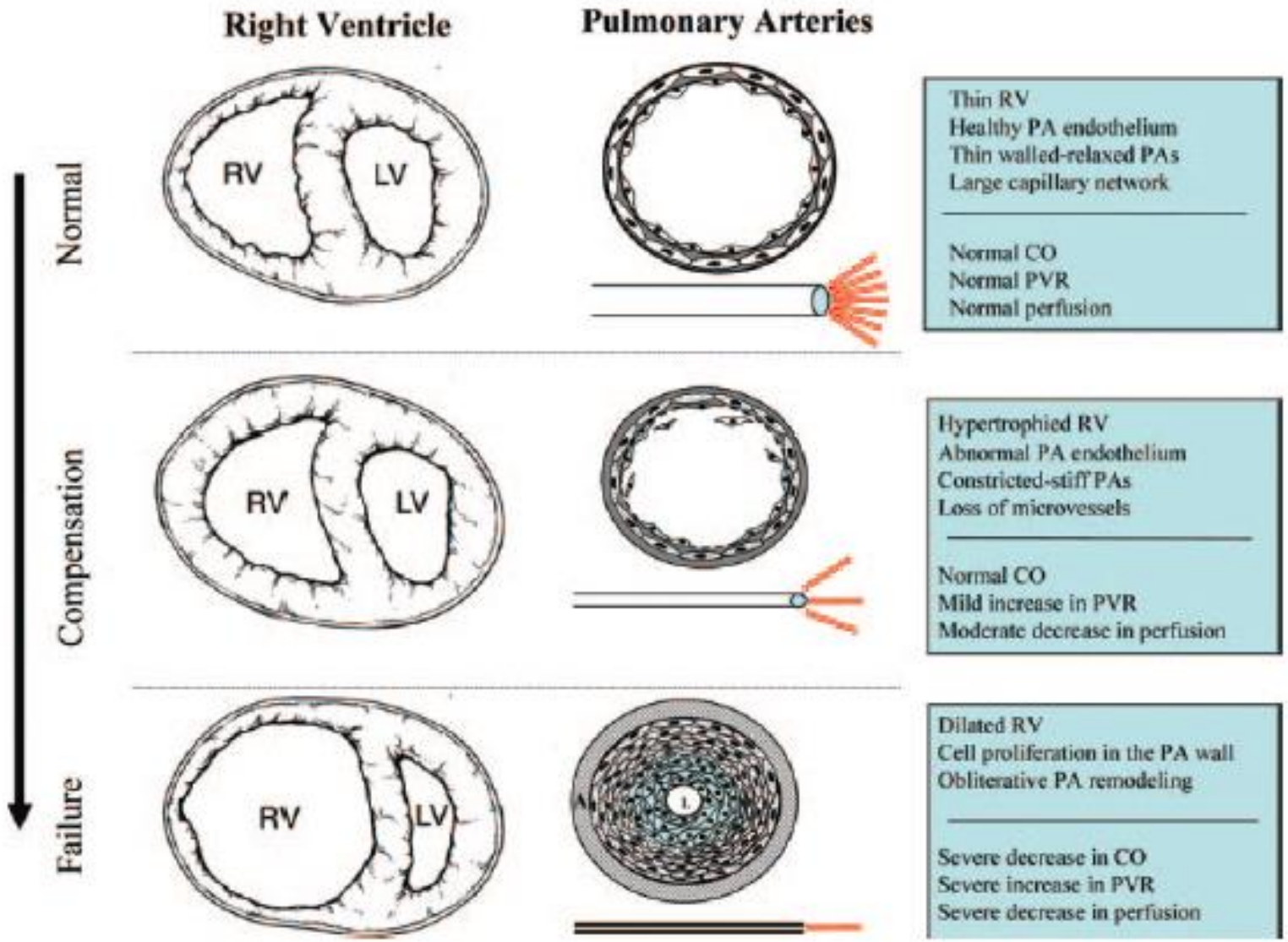


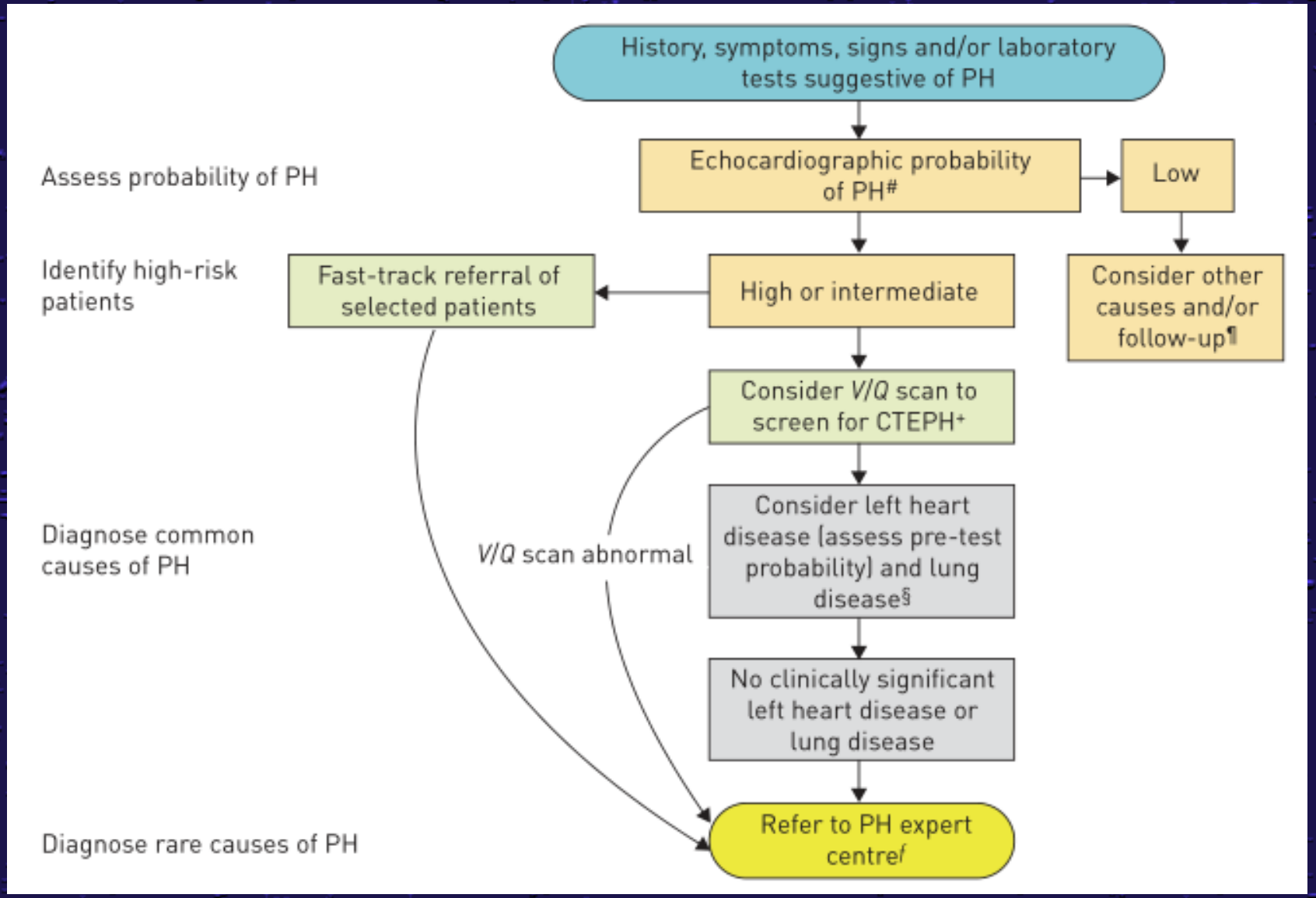
*D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343–349.

Progression of RV Dysfunction



Champion HC, Michelakis ED, Hassoun PM. Circulation 2009;120:992-1007

Algorithm for the diagnosis of PH and its causes



Frost, et al. Eur Resp J 2018

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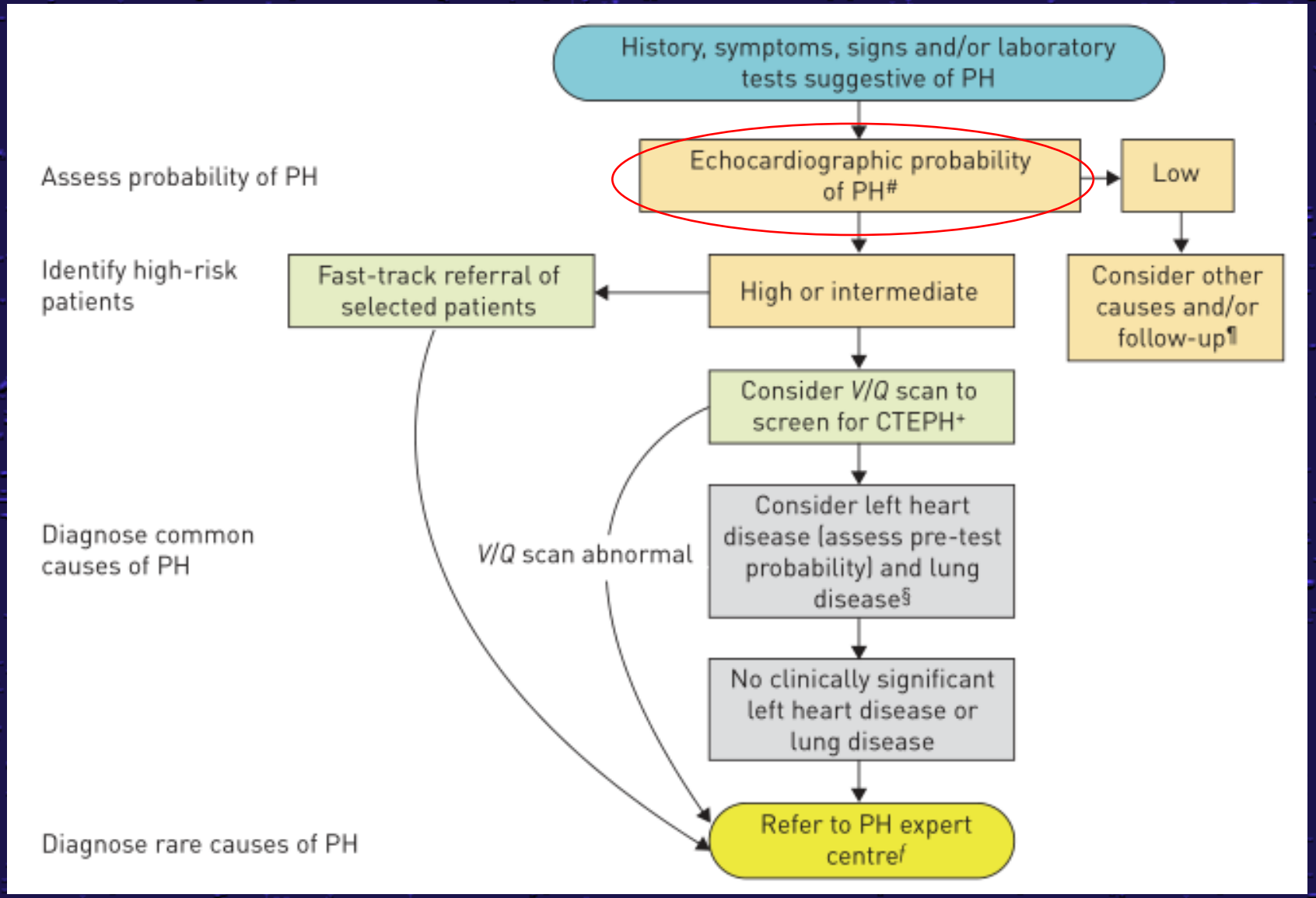

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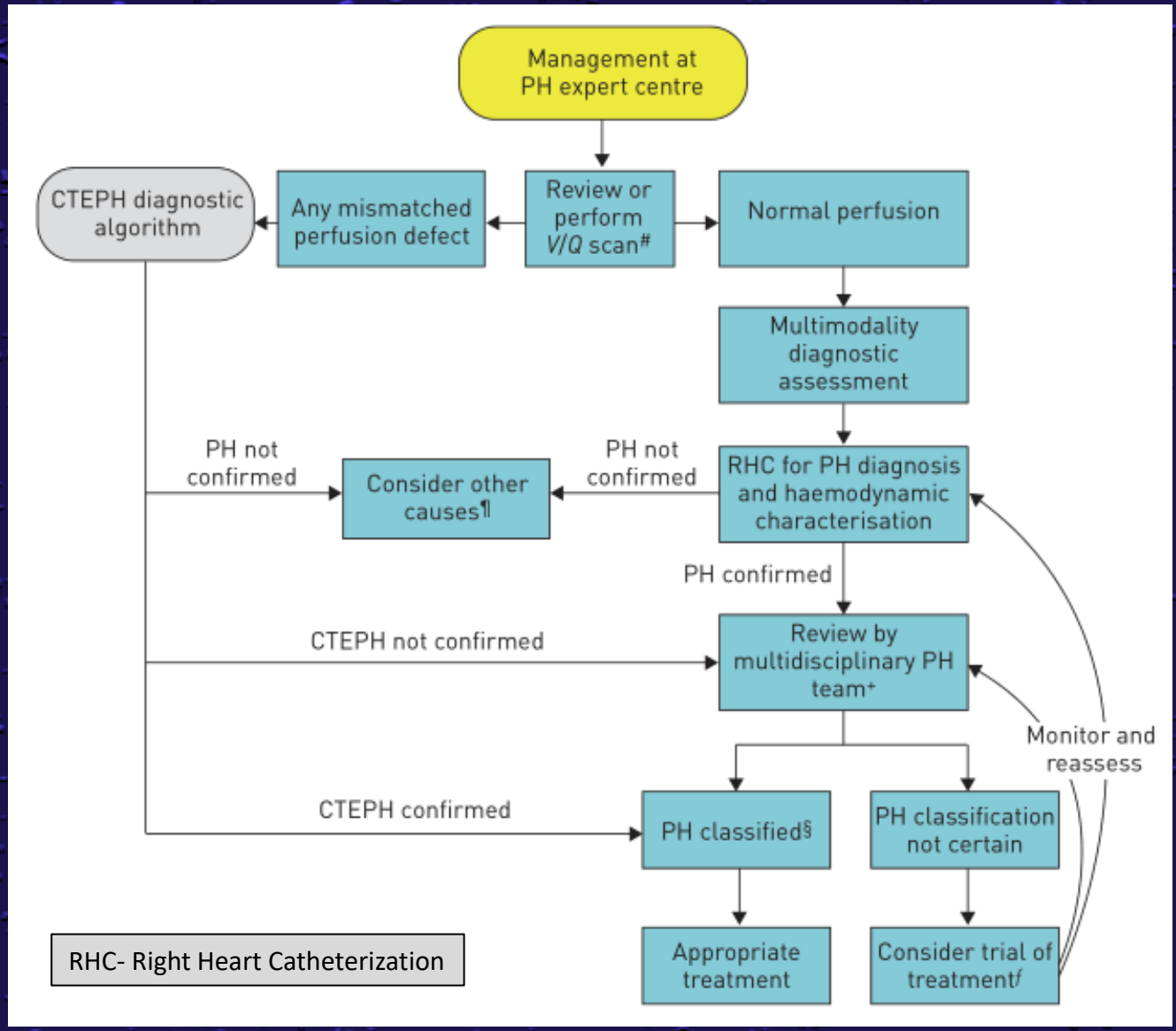

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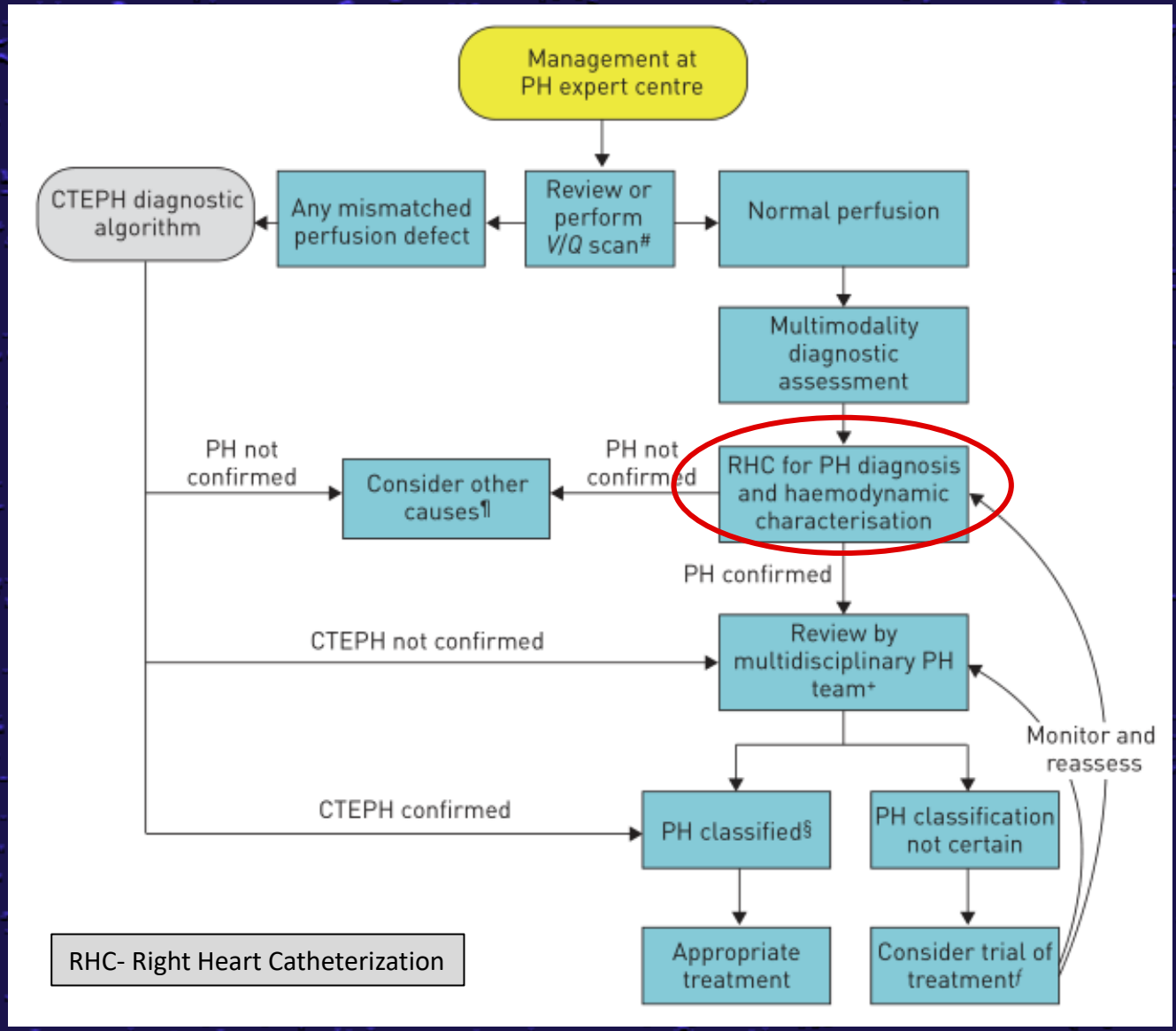
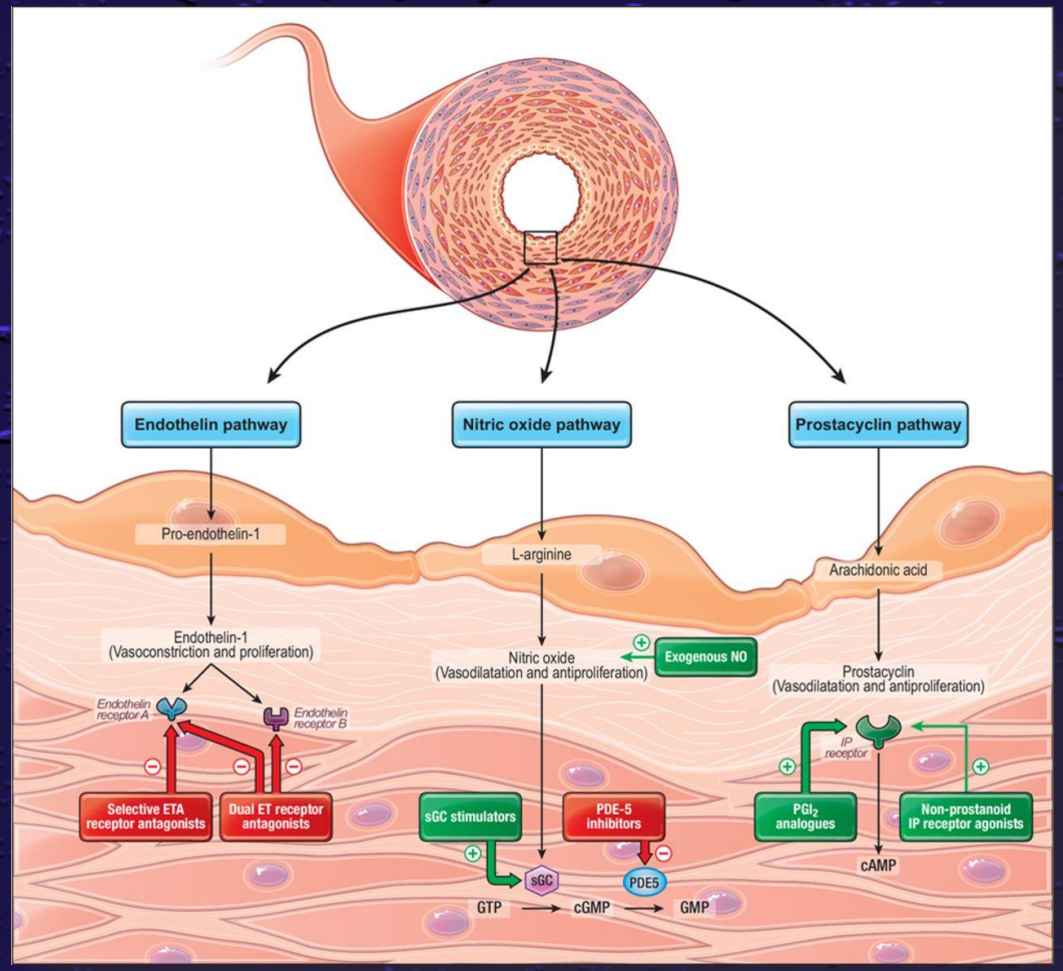
Algorithm for the diagnosis of PH and its causes (*cont*)



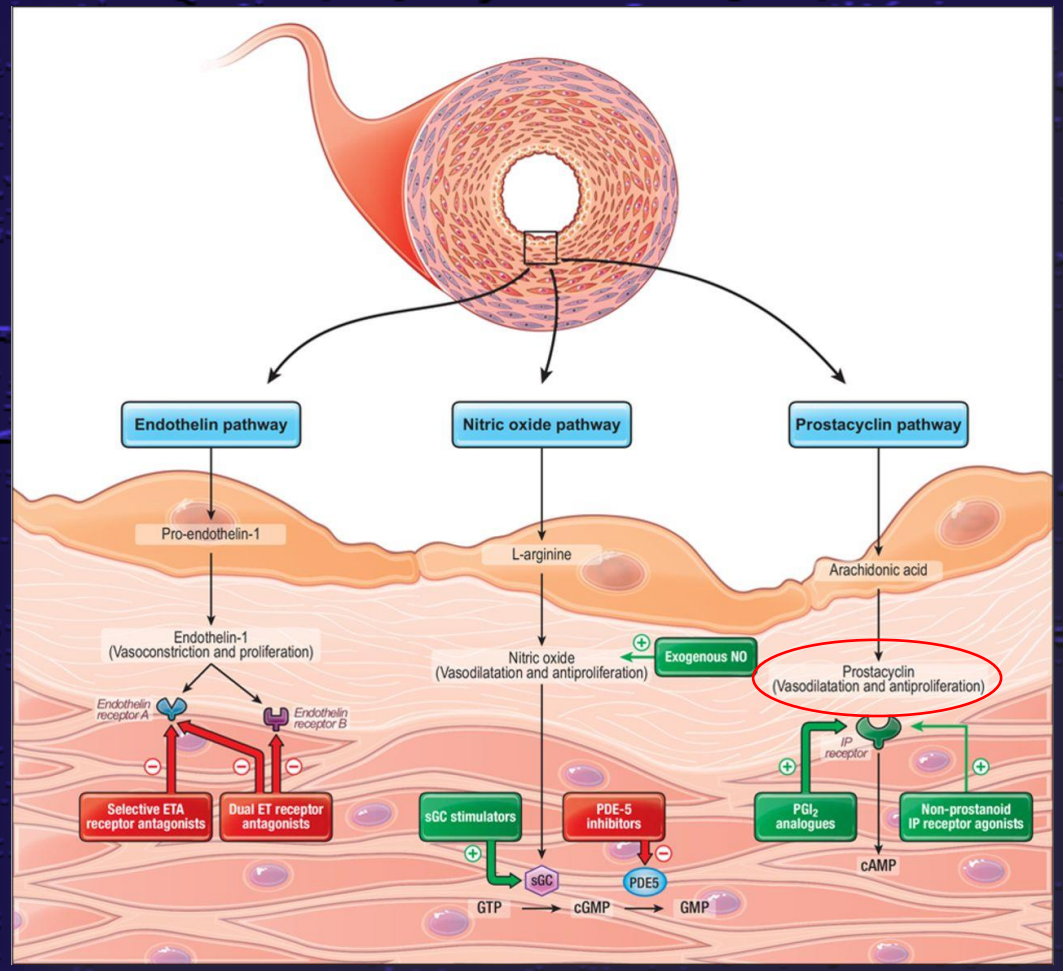
Frost, et al. Eur Resp J 2018

Pathways Affecting PAH Treatments



- Endothelin Pathway – targeted by ERAs
- Nitric Oxide Pathway – targeted by PDE5 inhibitors and sGCS
- Prostacylin Pathway – targeted by prostacyclin analogues and prostacyclin receptor agonists

Pathways Affecting PAH Treatments



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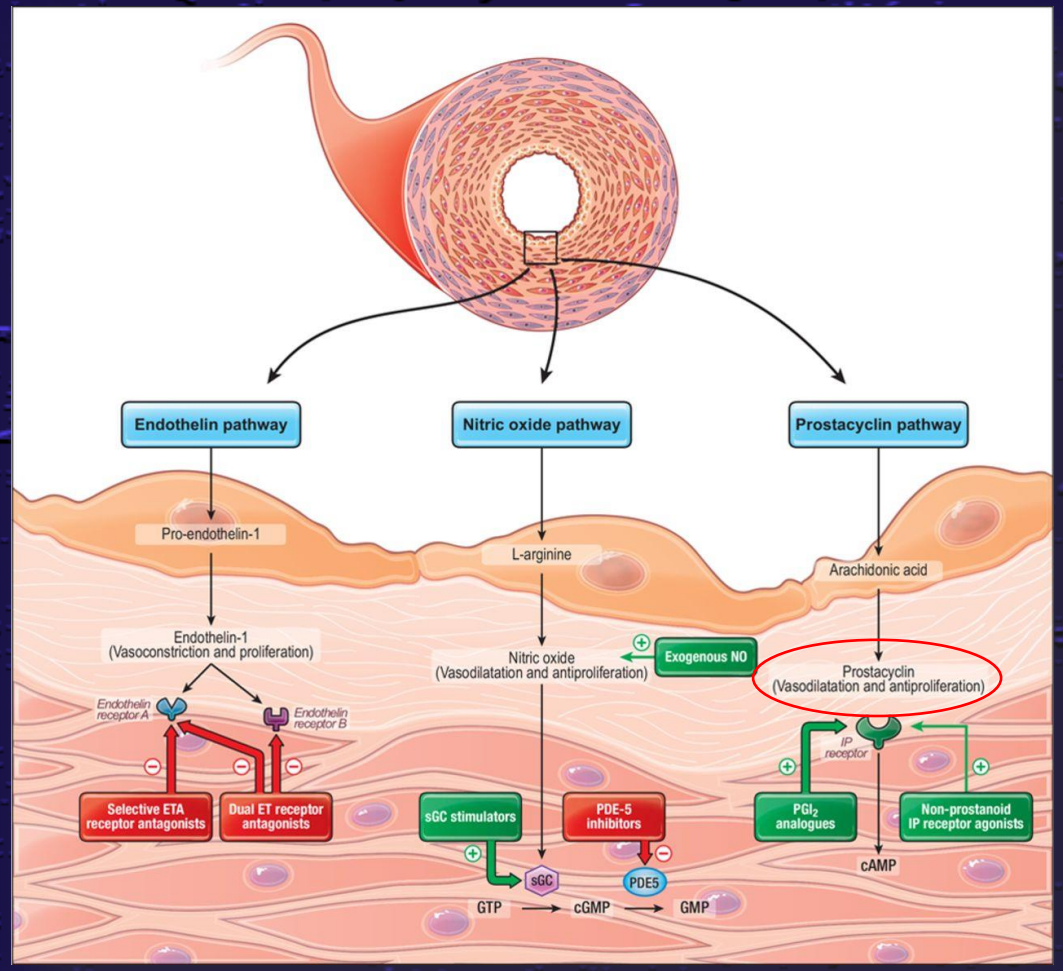

- Endothelin Pathway – targeted by ERAs
- Nitric Oxide Pathway – targeted by PDE5 inhibitors and sGCS
- Prostacylin Pathway – targeted by prostacyclin analogues and prostacyclin receptor agonists

Parenteral prostanoids are recommended as first-line therapy for FC IV patients and FC II and III patients with rapid progression. Inhaled prostanoids are recommended for indicated patients unwilling or unable to manage parenteral prostanoids, or as second-line alternatives for patients who are uncontrolled on ERAs or PDE5s (alone or in combination).

PAH Treatments – Approved Therapies

Specific PAH agents

Prostacyclin Analogues

- epoprostenol (IV)
- iloprost (inh)
- treprostinil (IV, SQ, inh, po)
- selexipag (po)

Endothelin antagonists

- bosentan (po)
- ambrisentan (po)
- macitentan (po)

PDE-5 inhibitors

- sildenafil (po)
- tadalafil (po)

Soluble gunalylate cyclase agonist

- riociguat (po)

Prostacyclin Advantages and Trade-Offs

Administration	Advantage	Limitations
Oral	Convenient	• GI side effects limit dosing
Parenteral	Effective	• Systemic toxicities limit dosing • Site pain, infection, inconvenience
Inhaled	Targeted	• Short treatment effect requires multiple administrations per day • Sawtooth PK/PD profile

Systemically administered prostanoids (oral or parenteral) are limited by the side effects:

- Hypotension
- Nausea/vomiting
- Diarrhea
- Headache
- Flushing
- Jaw pain

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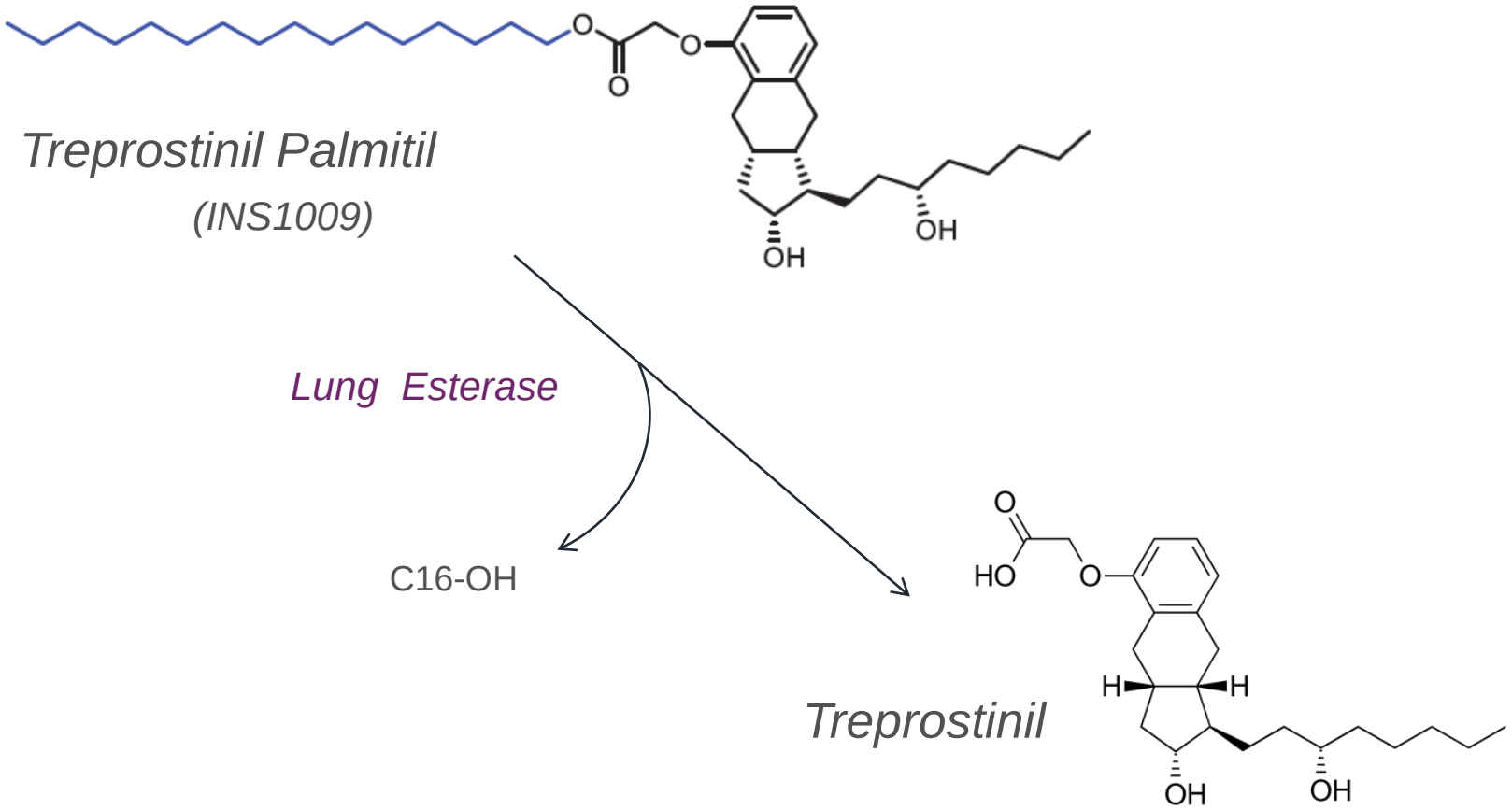
Goal for a new prostanoid therapy: convenient administration; sustained, high lung concentration; lower systemic exposures; potential for anti-proliferative, disease-modifying effects.

Treprostinil Palmitil

A Potentially Differentiated Prostanoid

Treprostinil Palmitil Inhalation Powder (TPIP)

- TPIP is a dry powder formulation of treprostinil prodrug, **treprostinil palmitil***
- The dry powder inhaler (DPI) device is the Plastiape RS01 capsule-based device
- Once delivered to the lung, treprostinil palmitil is hydrolyzed by endogenous esterases to active treprostinil



*Previously treprostinil palmitil was formulated as a nebulized suspension (TPIS).

Highlights of Preclinical Data

Highlights of Preclinical Data

Preclinical data demonstrate the following features of treprostinil palmitil:

Improved pharmacokinetics

- Prolonged lung residence time
- Lower systemic Cmax and prolonged T1/2 compared to treprostinil

Prolonged duration of pharmacodynamic activity compared to treprostinil

"Local" pharmacodynamic effect

- Achieves the same pharmacodynamic (vasodilatory) effect at significantly lower systemic concentrations, compared with IV treprostinil

Effect on hallmark histopathologic features in the sugen/hypoxia model

- Remodeling effect, superior to other prostanoids

Reduced incidence of cough (guinea pig model)

Highlights of Preclinical Data

Potential Implications of Preclinical Data

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Potential Implications of Preclinical Data

Preclinical data demonstrate the following features of treprostinil palmitil:

Once-or-twice-daily administration

Improved pharmacokinetics

- **Prolonged lung residence time**
- Lower systemic Cmax and **prolonged T1/2 compared to treprostinil**

Prolonged duration of pharmacodynamic activity compared to treprostinil

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Potential Implications of Preclinical Data

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Comparable effects at lower systemic exposures

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Potential Implications of Preclinical Data

Preclinical data demonstrate the following features of treprostinil palmitil:

Potential disease modifying activity

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Prolonged duration of pharmacodynamic activity compared to treprostinil

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Potential Implications of Preclinical Data

Preclinical data demonstrate the following features of treprostinil palmitil:

Potential Improved Tolerability

Improved pharmacokinetics

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Prolonged duration of pharmacodynamic activity compared to treprostinil

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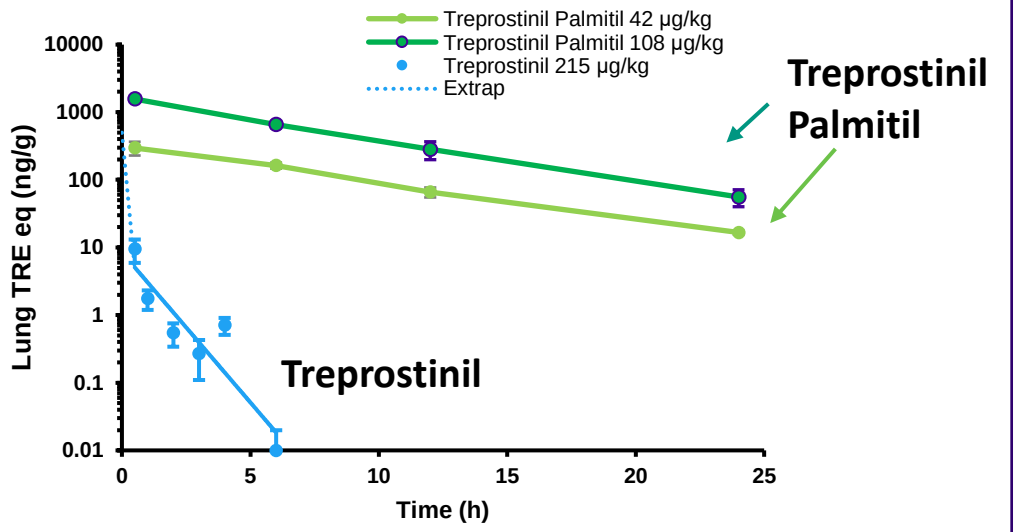
Effect on hallmark histopathologic features in the sugen/hypoxia model

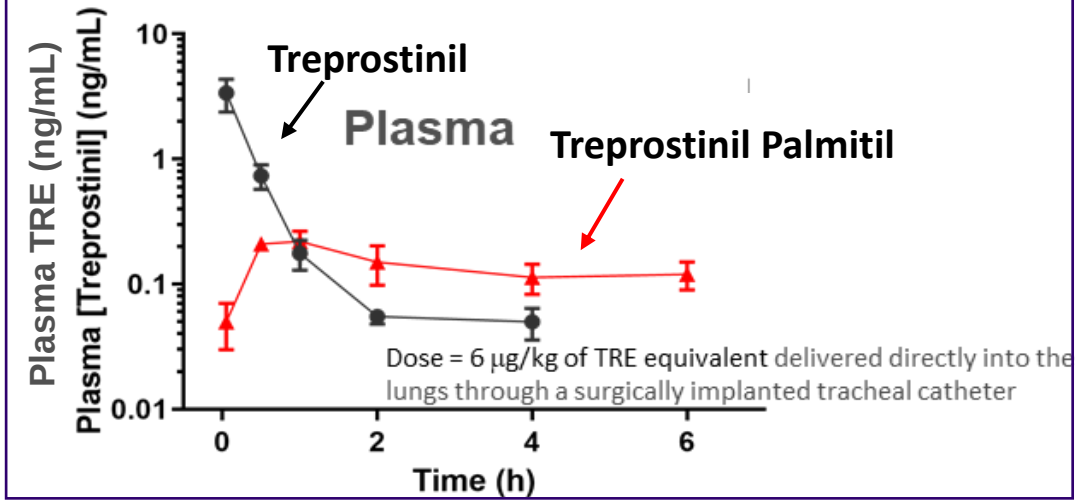
- Remodeling effect, superior to other prostanoids

Reduced incidence of cough (guinea pig model)

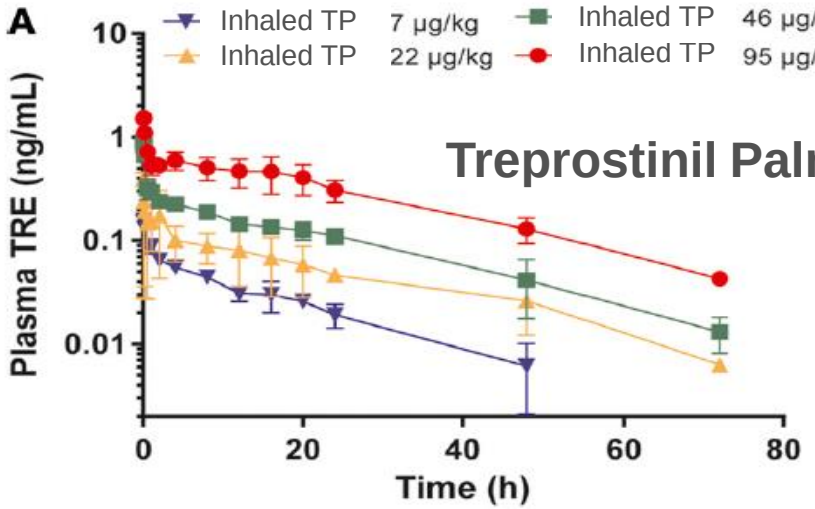
Improved Pharmacokinetics:
Prolonged Lung Residence, Lower Cmax, Prolonged Half Life (Rat and Dog)

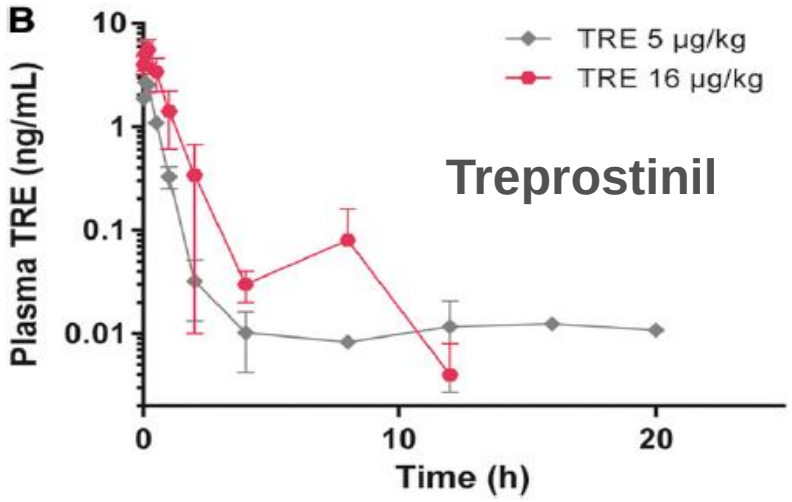
RAT Lung and Plasma Levels





DOG Plasma Levels





10X Cmax

F.G. Leifer et al. (2018) Drug Res 68: 1-10

M. R. Corboz, et al. (2017) J. Pharmacol. Exp. Ther. 363:348–357.

Highlights of Preclinical Data

Preclinical data demonstrate the following features of treprostinil palmitil:

Improved pharmacokinetics

- Prolonged lung residence time
- Lower systemic Cmax and prolonged T1/2 compared to treprostinil

Prolonged duration of pharmacodynamic activity compared to treprostinil

"Local" pharmacodynamic effect

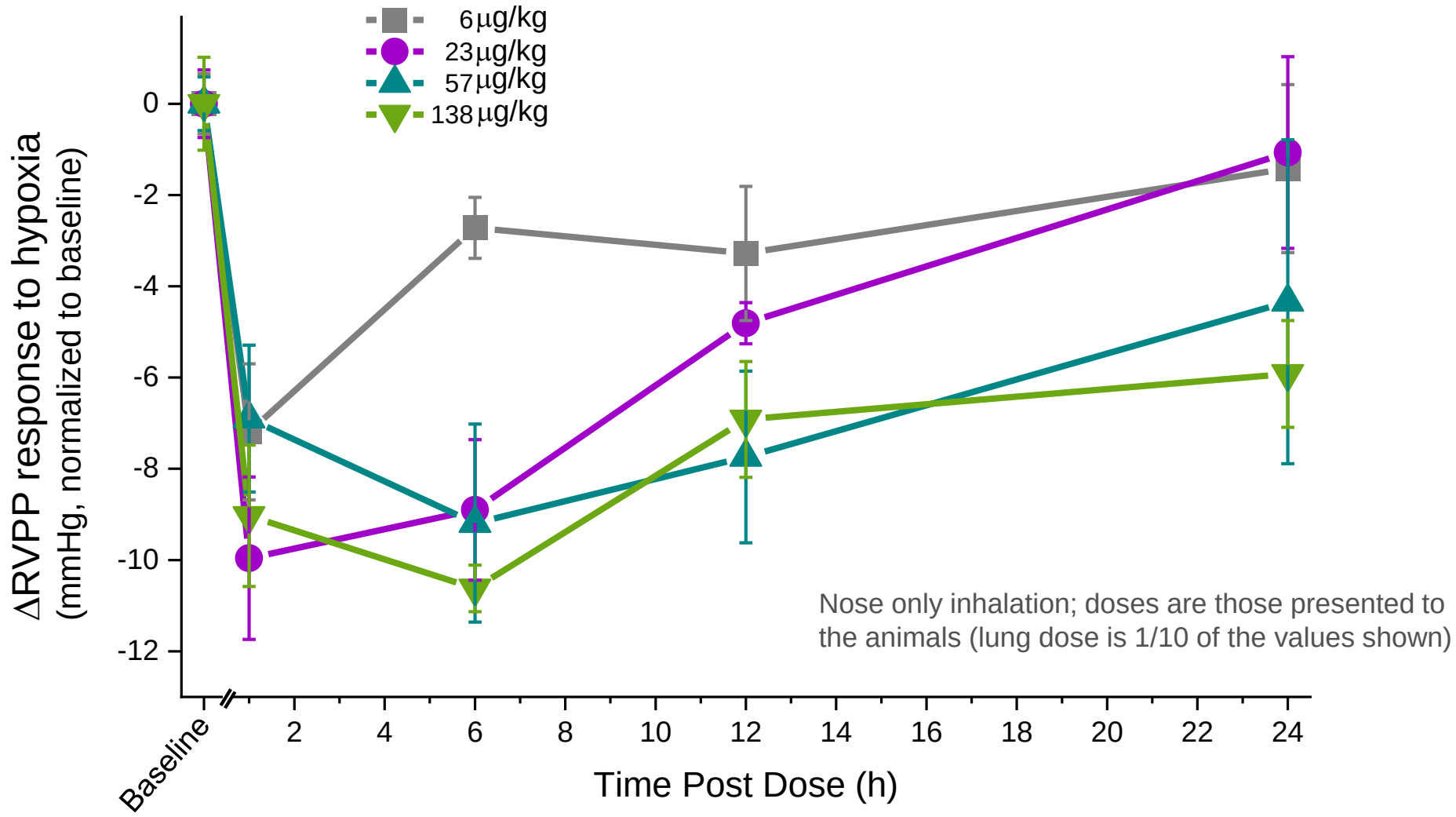
- Achieves the same pharmacodynamic (vasodilatory) effect at significantly lower systemic concentrations, compared with IV treprostinil

Effect on hallmark histopathologic features in the sugen/hypoxia model

- Remodeling effect, superior to other prostanoids

Reduced incidence of cough (guinea pig model)

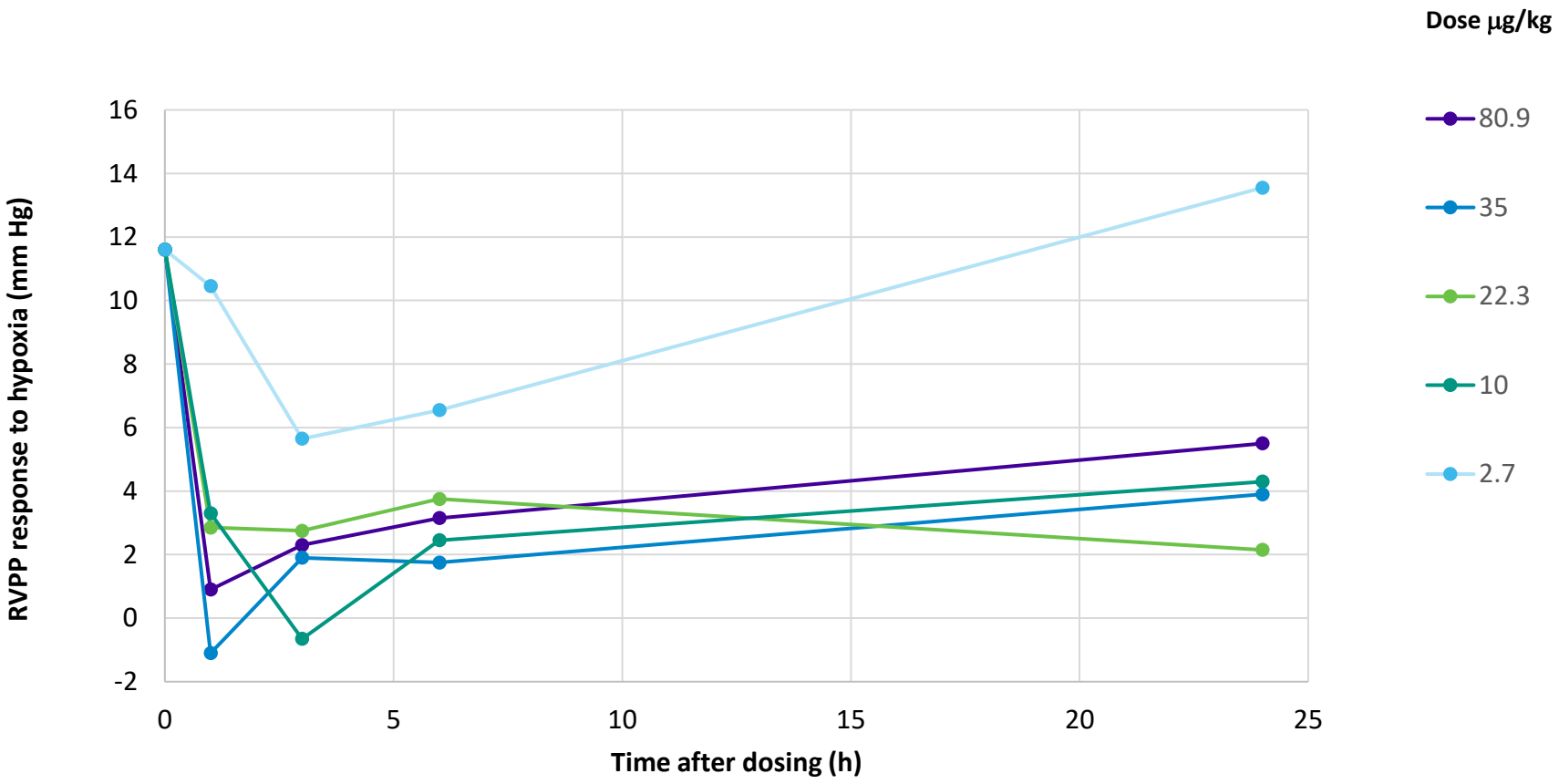
Prolonged Duration of Pharmacodynamic Activity
(Telemetered Rat, Hypoxic Challenge)



Data on file, Insmed Inc.

Prolonged Duration of Pharmacodynamic Activity

(Telemetered Dog, Hypoxic Challenge)



Average right ventricular pulse pressure (RVPP) response to hypoxia challenge in two dogs following inhalation of different doses of TP; the 'wash out' period between doses was ≥7days. Shown at t=0 is the no-treatment baseline average (values were taken before dosing).

Data on file, Insmed Inc.

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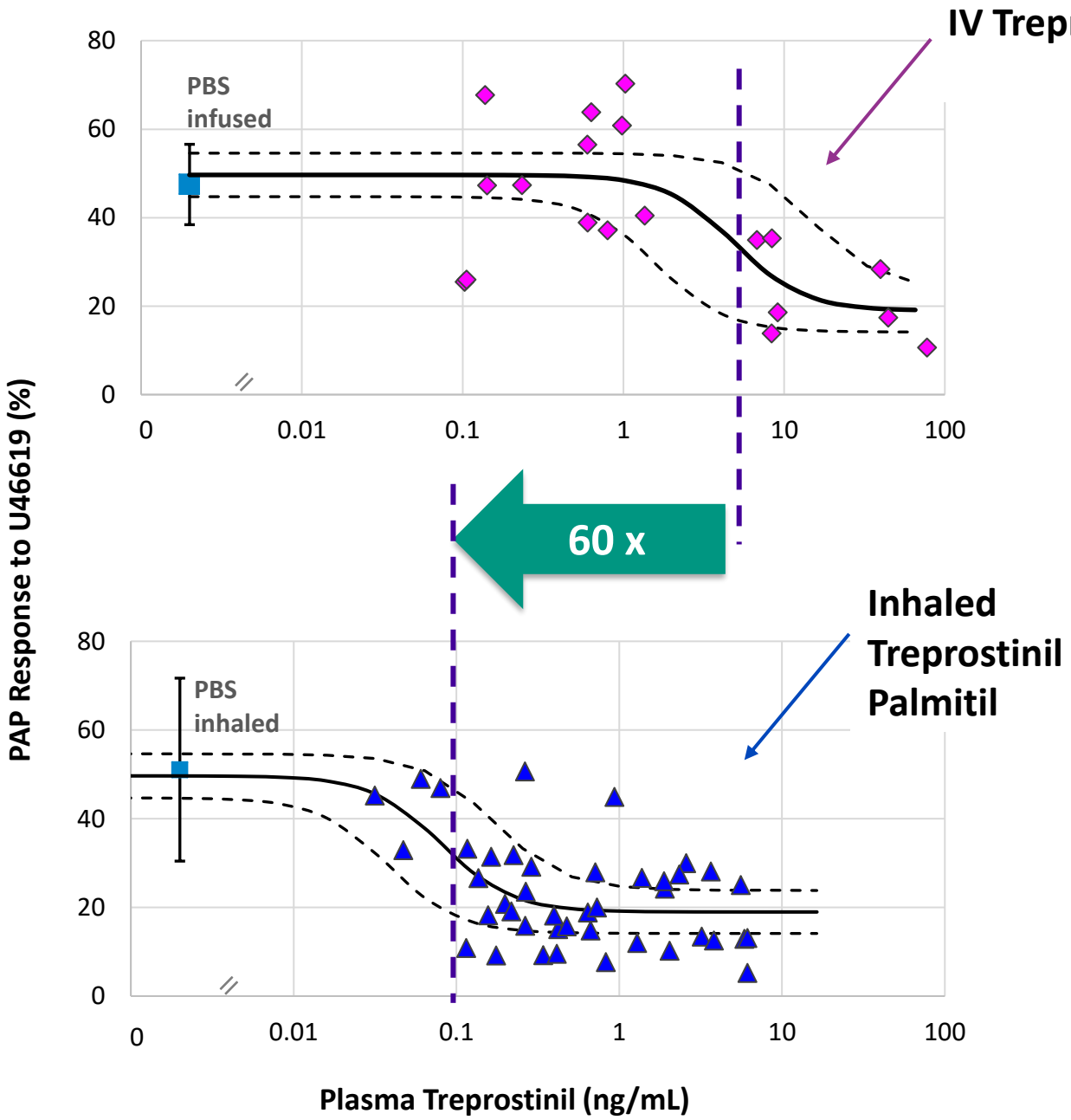
Local Pharmacodynamic Effect

Pulmonary Vasodilator Activity at Significantly Lower Plasma Treprostinil Concentrations (Rat)

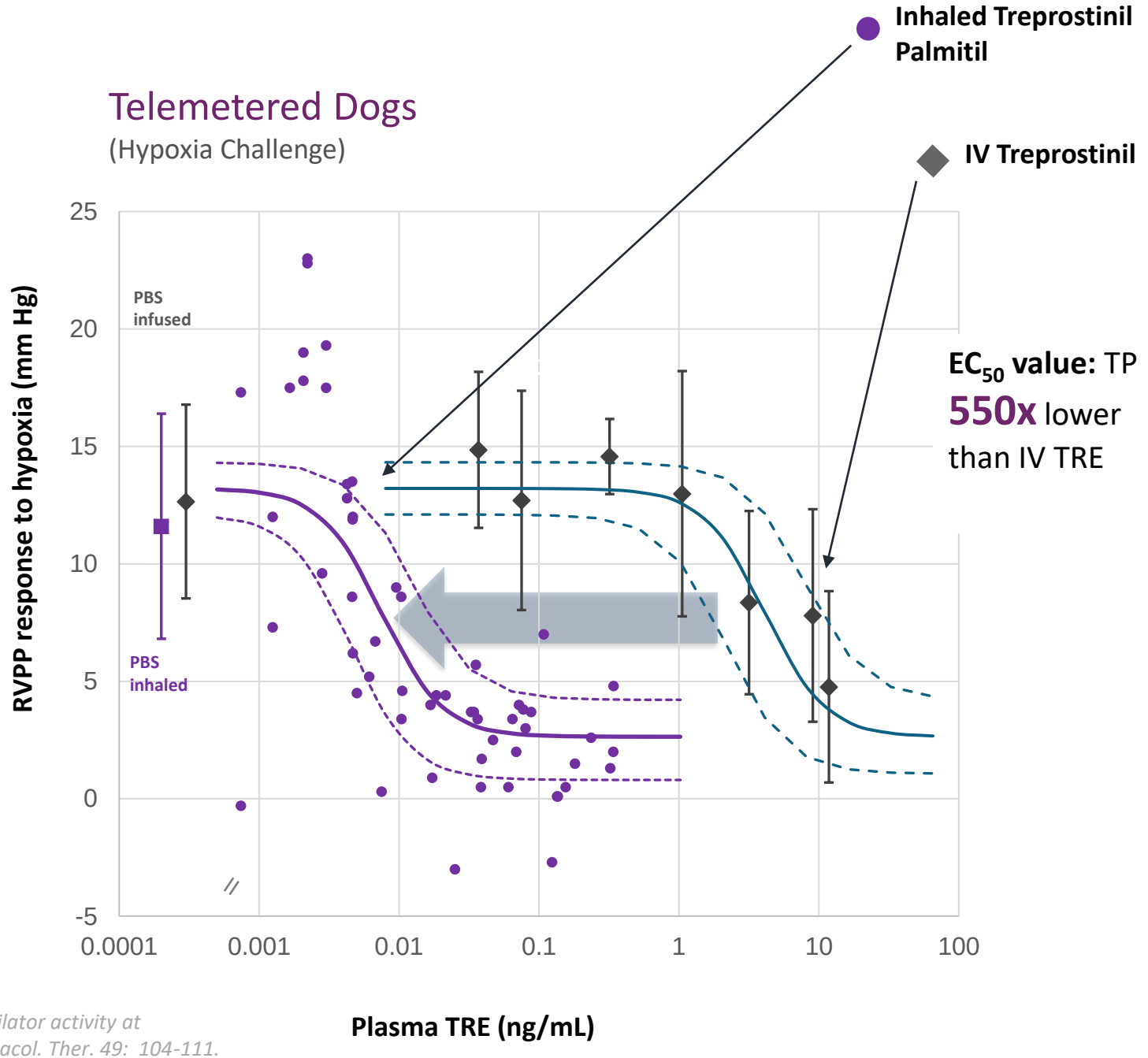
Rats challenged with the thromboxane mimetic U46619



Chapman et al. (2018). Inhaled hexadecyl-treprostinil provides pulmonary vasodilator activity at significantly lower plasma concentrations than infused treprostinil. Pulm. Pharmacol. Ther. 49: 104-111.

Local Pharmacodynamic Effect

Pulmonary Vasodilator Activity at Significantly Lower Plasma Treprostinil Concentrations (Dog)



Chapman et al. (2018). Inhaled hexadecyl-treprostinil provides pulmonary vasodilator activity at significantly lower plasma concentrations than infused treprostinil. Pulm. Pharmacol. Ther. 49: 104-111.

Local Pharmacodynamic Effect

Continuously Inhaled vs. Continuously Infused (IV) Treprostinil in Sheep

"…prostacyclin analogs are more potent pulmonary vasodilators when delivered by aerosol than when given intravenously. Systemic hemodynamic effects are also minimized by aerosol administration of the drug, making this approach especially appealing. Duration of action of prostacyclin is short, requiring an unrealistic frequency of administration for clinical use (6, 33), but development of analogs (e.g., treprostinil) or formulations that are long acting could make this approach feasible."

J Appl Physiol 99: 2363–2368, 2005.
First published September 1, 2005; doi:10.1152/japplphysiol.00083.2005.

Potent effects of aerosol compared with intravenous treprostinil on the pulmonary circulation

Brett L. Sandifer,[1,3] Kenneth L. Brigham,[1,2,3] E. Clinton Lawrence,[1,3] David Mottola,[4] Chris Cuppels,[1,2] and Richard E. Parker[1,2]

[1]Division of Pulmonary, Allergy, and Critical Care, [2]Center for Translational Research in the Lung, and [3]McKelvey Center for Lung Transplantation, Emory University School of Medicine, Atlanta, Georgia; and [4]United Therapeutics Corporation, Research Triangle Park, North Carolina

Submitted 24 January 2005; accepted in final form 20 July 2005

"We speculate that this may result from treprostinil stimulated production of vasodilatory mediators from pulmonary epithelium.

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- **Remodeling effect, superior to other prostanoids**

Reduced incidence of cough (guinea pig model)

Treprostinil Palmitil Inhalation Solution

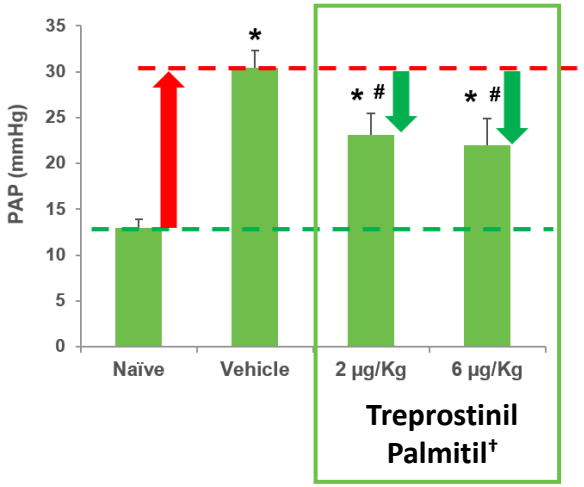
Improved Both Hemodynamics and Vascular Remodeling in the Rat Sugen-Hypoxia Model of PAH

* significantly different from the naïve group

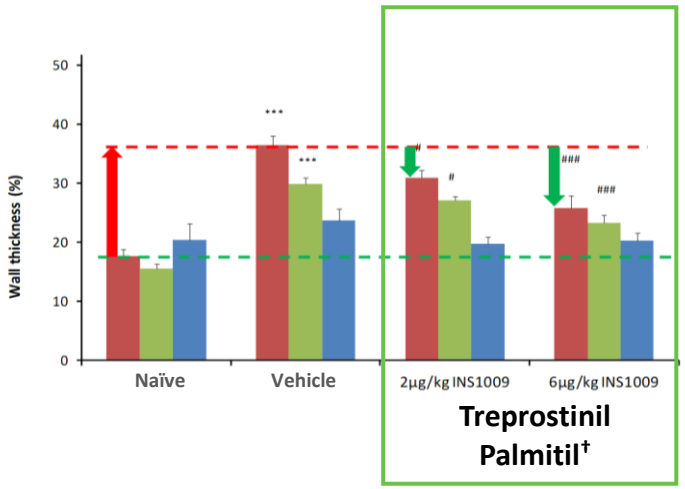
significantly different from the vehicle group

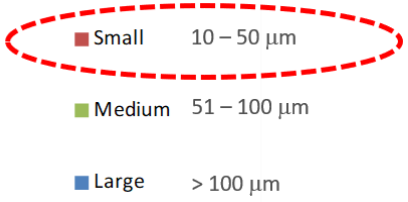
[1]Fulton Index is a commonly used quantitative measure of the degree of right ventricular hypertrophy
Am. J. Res. Crit. Care Med. 2020: 201, A2094. Poster was not presented due to COVID19.
Data on file, Insmed Inc.

Improves Pulmonary Arterial Pressure

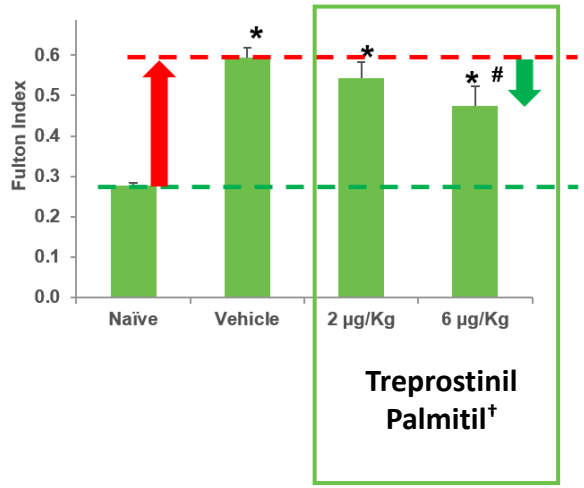


Reduces Wall Thickening

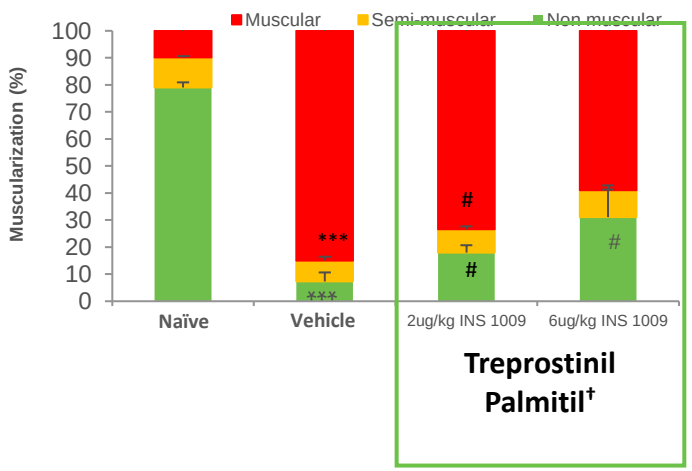




Improves Fulton Index[1]



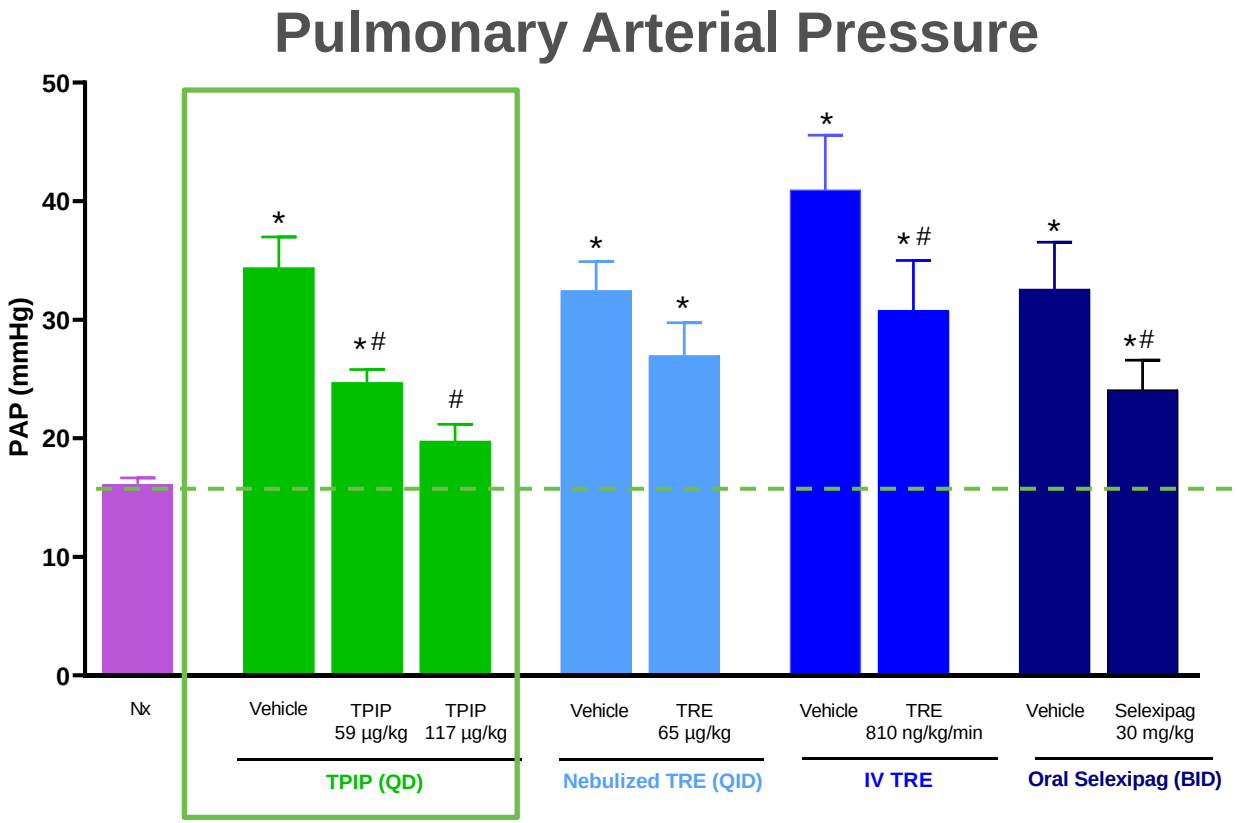
Reduces Muscularization

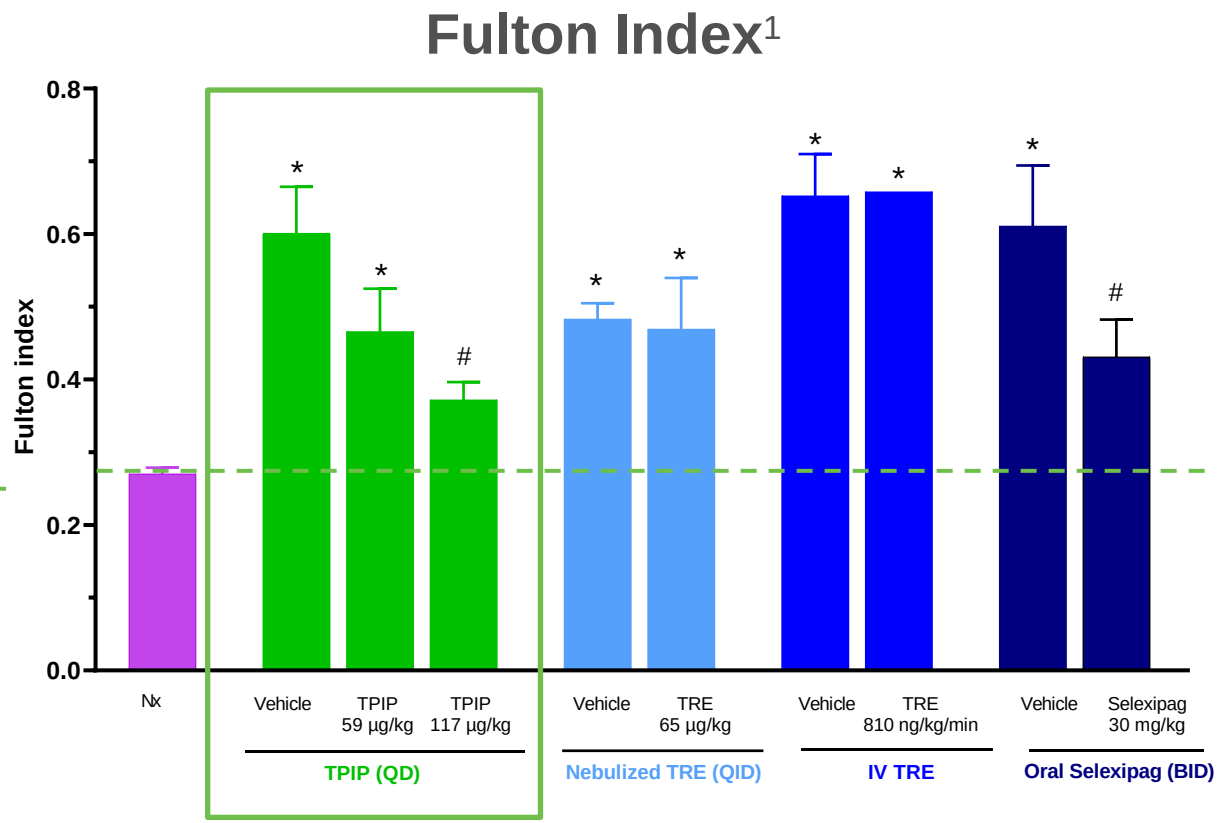


Data on file, Insmed Inc.
†Pulmonary doses

TPIP Demonstrated Superior Effect

on PA Pressure and RV Hypertrophy in the Rat Sugen-Hypoxia Model of PAH





* significantly different from Normoxic control (Nx)

\# significantly different from Vehicle Group

[1]*Fulton Index is a commonly used quantitative measure of the degree of right ventricular hypertrophy: it is the weight ratio of right ventricle/(left ventricle + septum)*

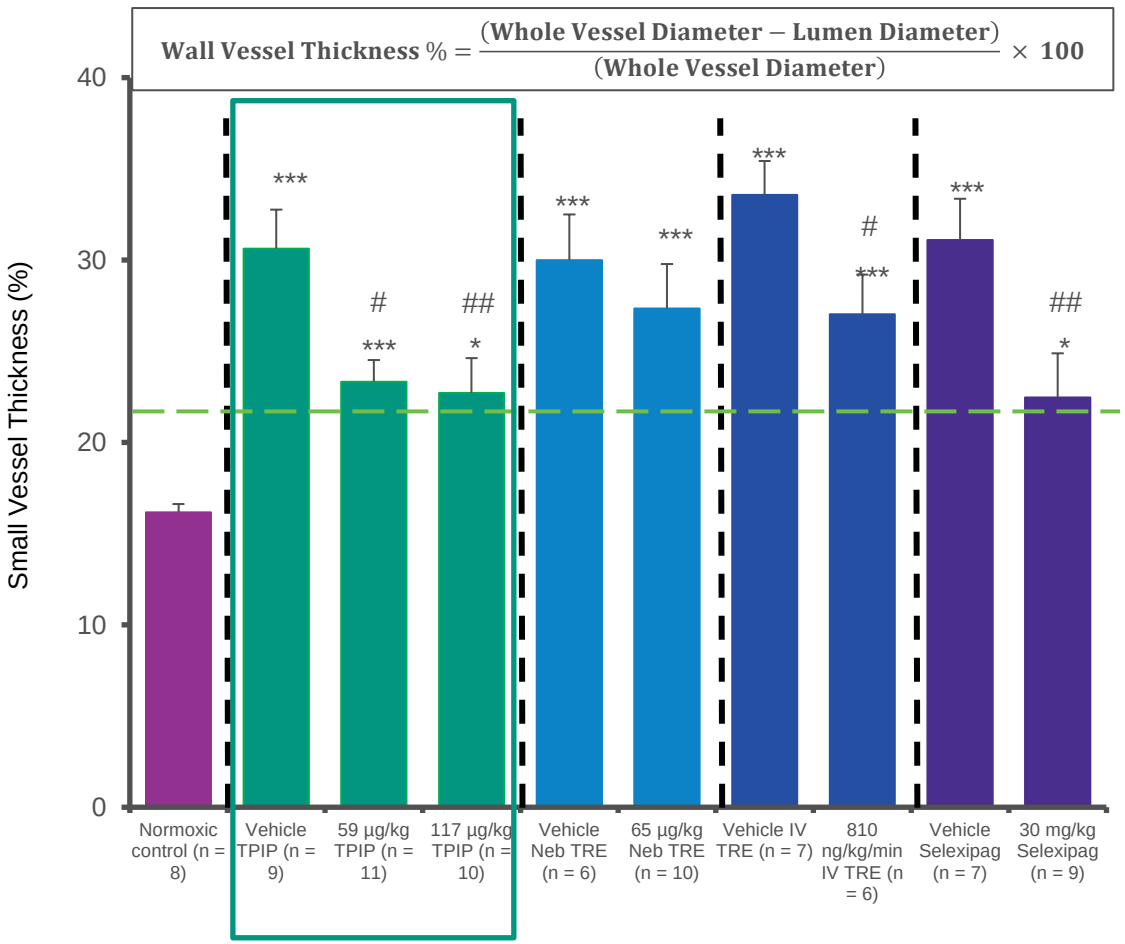
Data on file, Insmed Inc.

TPIP Demonstrated Superior Effect

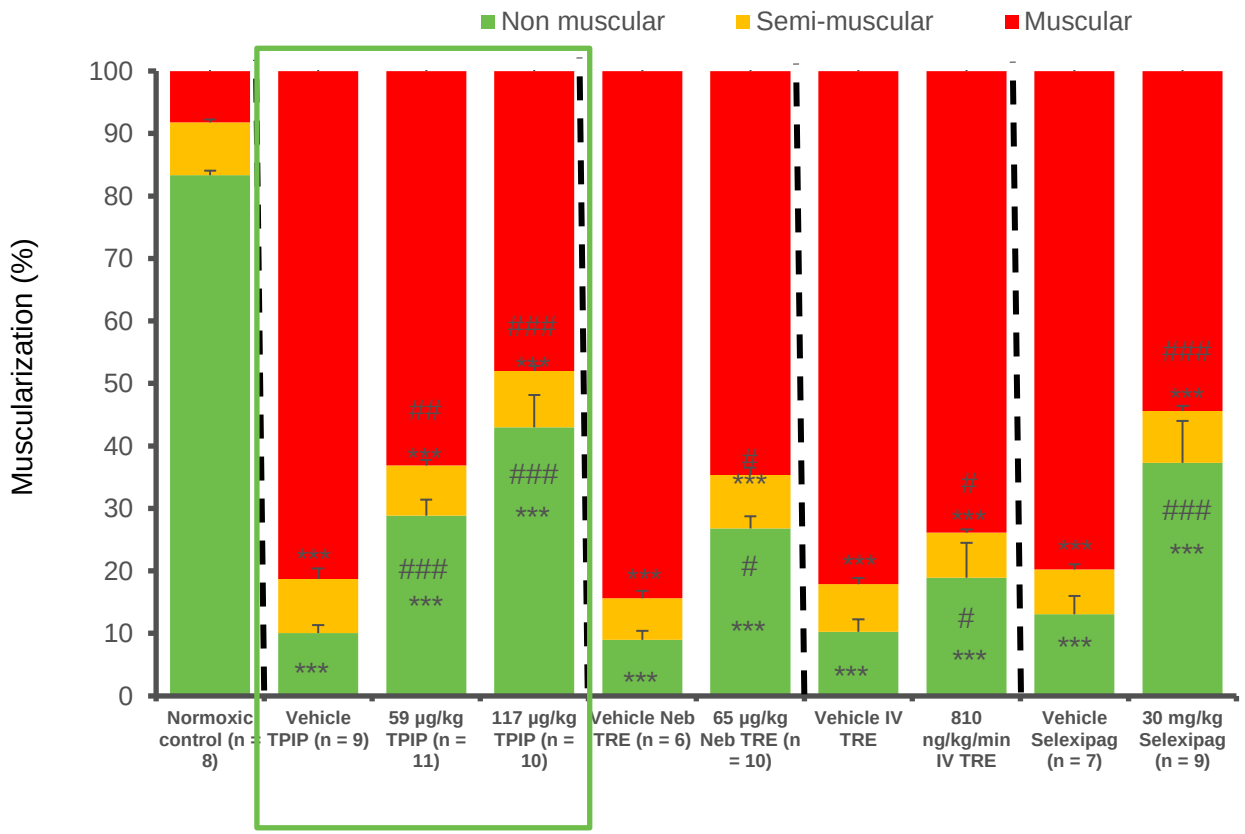
on Vascular Remodeling in the Sugen-Hypoxia Rat Model of PAH

Wall Thickness

$$\text{Wall Vessel Thickness \%} = \frac{(\text{Whole Vessel Diameter} - \text{Lumen Diameter})}{(\text{Whole Vessel Diameter})} \times 100$$



Muscularization



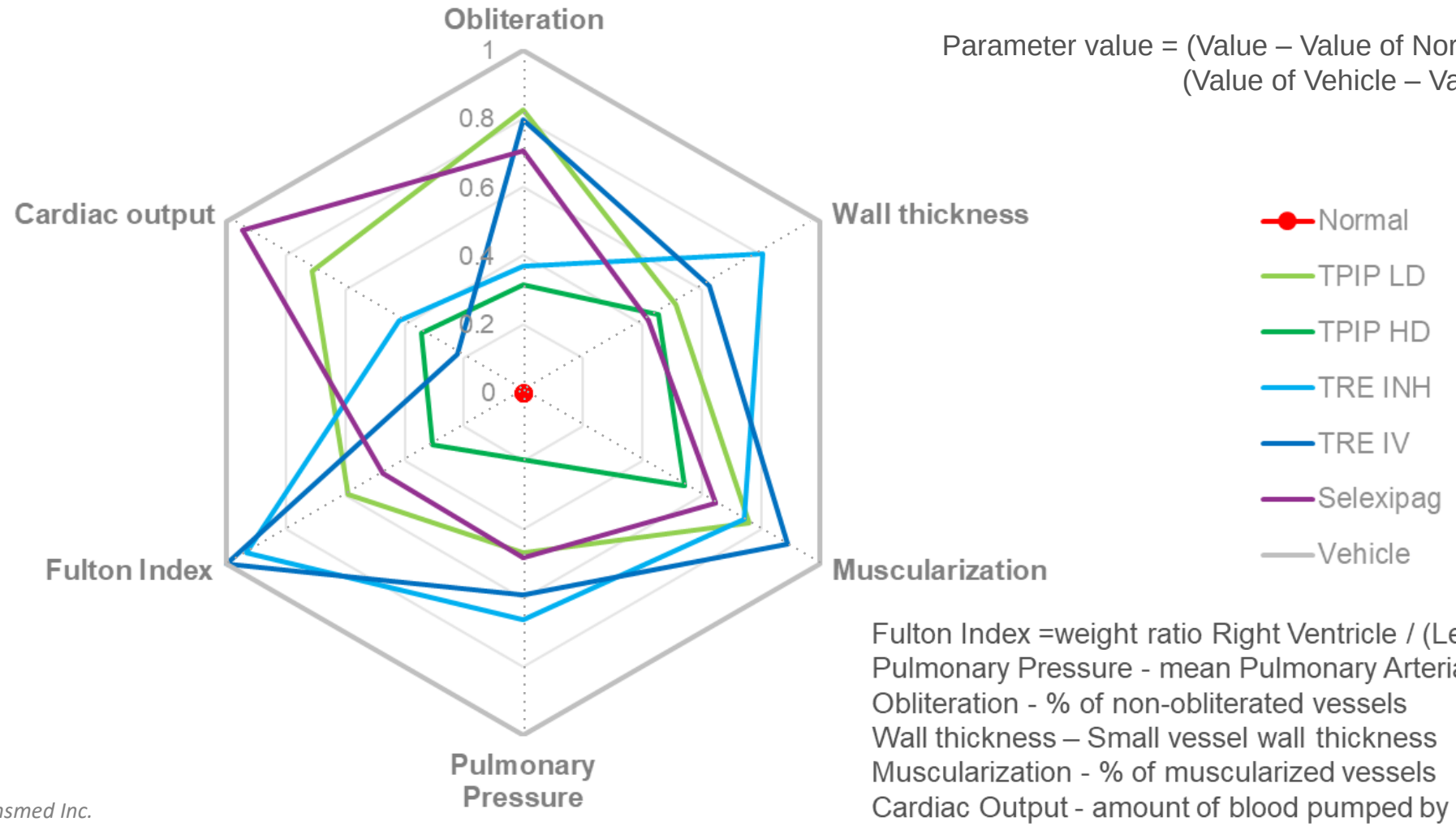
Data on file, Insmed Inc.

* significantly different from Normoxic control group
\# significantly different from Vehicle group

* and # p <0.05
** and ## p < 0.01
*** and ### p < 0.001

TPIP at High Dose

Shows Superior Effect Overall in the Sugen-Hypoxia Rat Model for PAH



Parameter value = (Value – Value of Normal) / (Value of Vehicle – Value of Normal)

Fulton Index =weight ratio Right Ventricle / (Left Ventricle + Septum)
Pulmonary Pressure - mean Pulmonary Arterial Pressure
Obliteration - % of non-obliterated vessels
Wall thickness – Small vessel wall thickness
Muscularization - % of muscularized vessels
Cardiac Output - amount of blood pumped by the heart per minute

Data on file, Insmed Inc.

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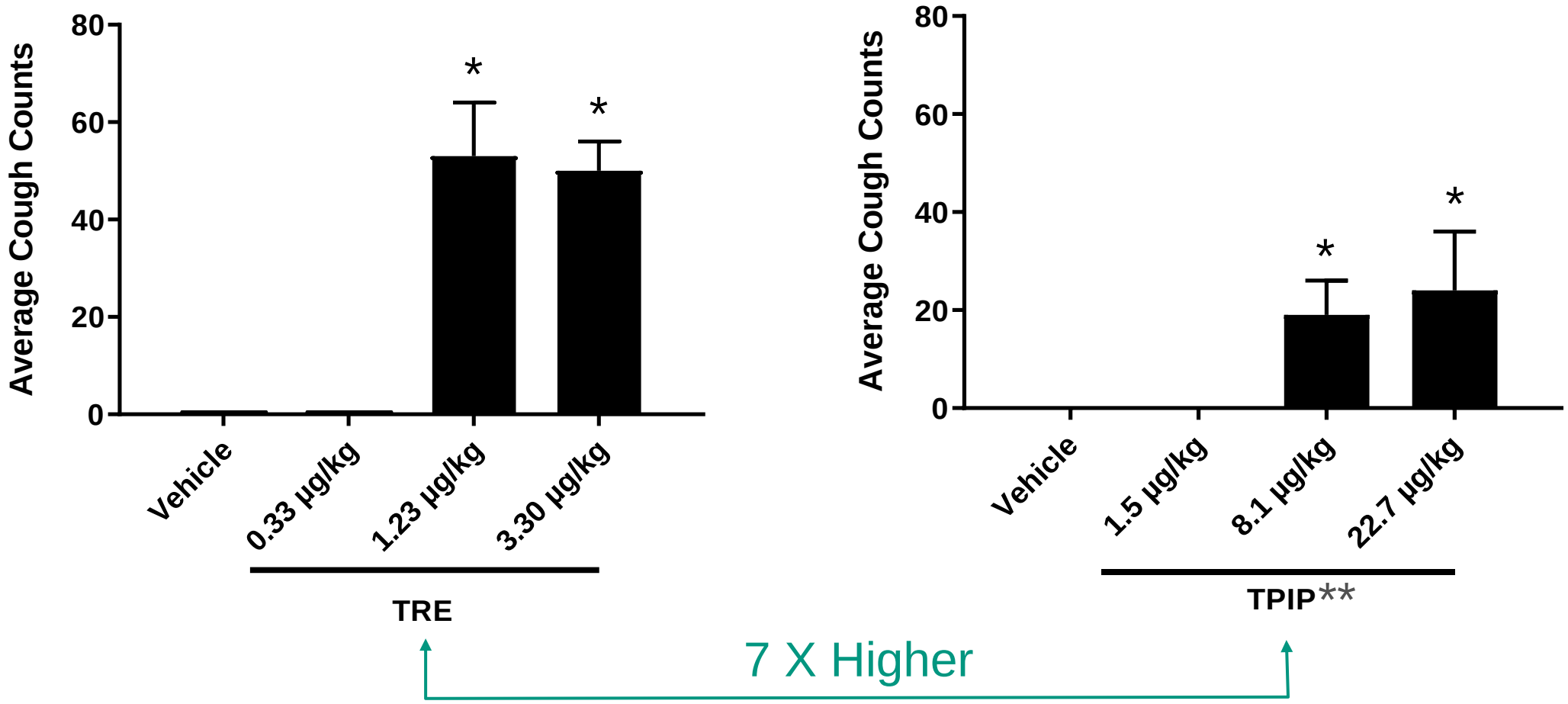
Reduced incidence of cough (guinea pig model)

Reduced Incidence of Cough

Threshold to Induce Cough Increased 7-Fold (guinea pig model)



*Significantly different from vehicle.

**Treprostinil molar equivalent doses; TP doses are 2.3, 12.8 and 35.8 µg/kg.

Data on file, Insmed Inc.

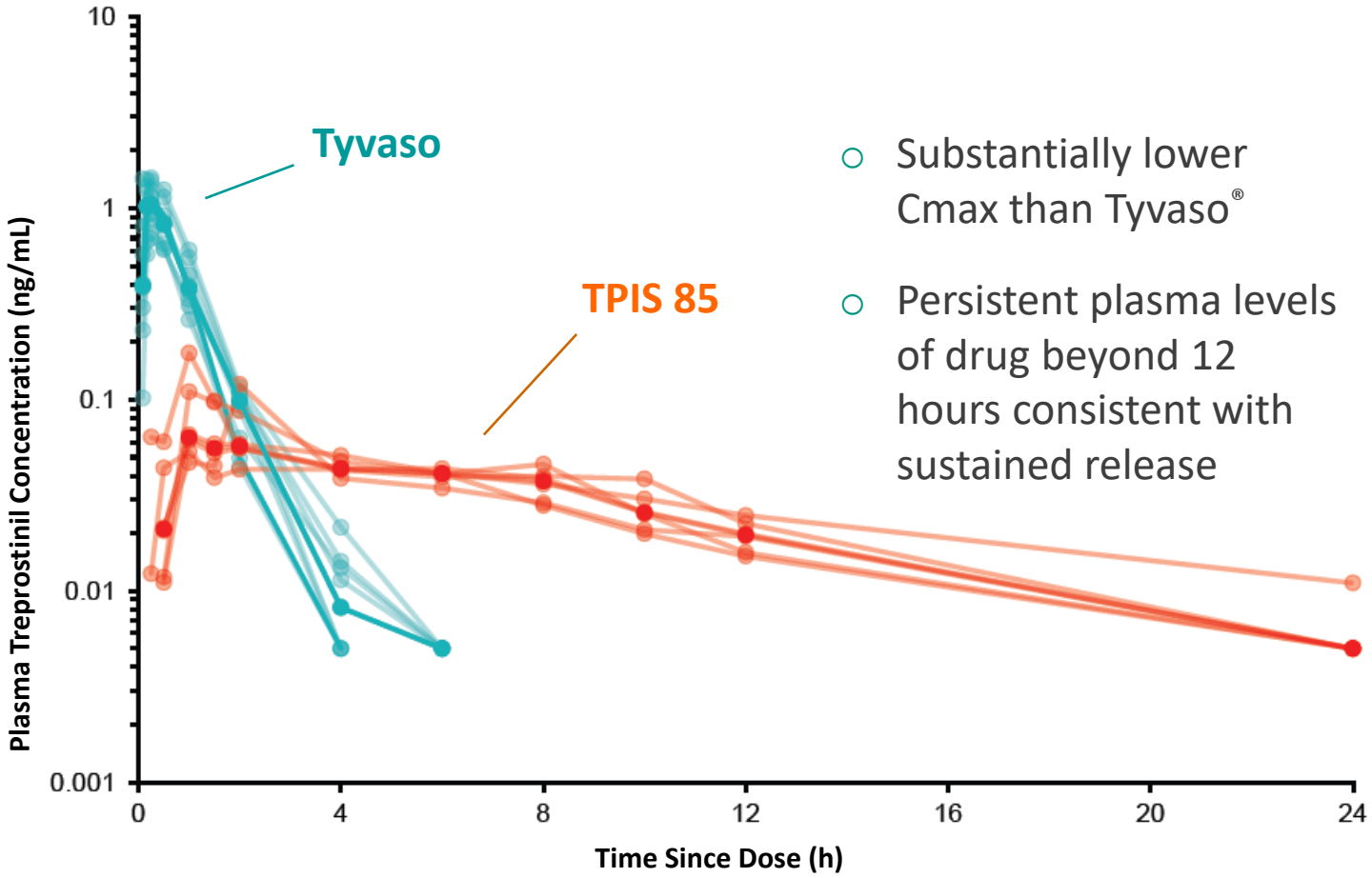
Product Differentiation

Treprostinil Palmitil Inhalation Solution Phase 1 Study

Plasma PK in Healthy Volunteers

Treprostinil Plasma PK Summary

Cohort 1 (n = 6)	TPIS 85 µg	Tyvaso 54 µg
C_{max} (ng/mL)	0.089	0.958
AUC_{0-24} (ng*h/mL)	0.614	0.872
T_{max} (h)	1.02	0.258
$T_{1/2}$ (h)	5.69	0.485



- Substantially lower Cmax than Tyvaso®
- Persistent plasma levels of drug beyond 12 hours consistent with sustained release

Han et al. (2016) Single-Dose Pharmacokinetics of C16TR for Inhalation (INS1009) vs Treprostinil Inhalation Solution. ERS International Congress, September 3-7, London, United Kingdom, abs 3505 (poster PA2303).

Treprostinil Palmitil Inhalation Powder (TPIP)

a Potentially Differentiated Prostanoid

If the characteristics suggested by the preclinical studies are borne out in the clinical development program, TPIP could represent a differentiated product

Convenience: portable, dry powder inhaler

QD or BID dosing (prolonged lung residence time, prolonged half life, prolonged duration of pharmacodynamic activity)

Improved safety/tolerability

- Systemic tolerability (lower Cmax)
- Local tolerability (reduced cough)

Greater vasodilatory pharmacodynamic effect at lower systemic exposures (sustained lung residence time takes advantage of the local effect seen in multiple animal models)

Potential disease modifier – may be able to benefit the histopathologic process, whereas Tyvaso, due to transient local exposure, cannot

Path Forward

Next Steps for TPIP Development

Phase 1 Underway

SAD/MAD Study

Objective
Establish PK and tolerability profile

Top line results expected in Q1 2021

Initiate Phase 2a in Early 2021

Exploratory, single dose study

Objective
Demonstrate proof of mechanism, understand PK/PD relationship, confirm tolerability

Results expected in 2021

Initiate Phase 2b in H2 2021

Objective
Demonstrate hemodynamic effect size, inform design for pivotal program

Kevin C. Mange, M.D., MSCE
SVP, Clinical Development

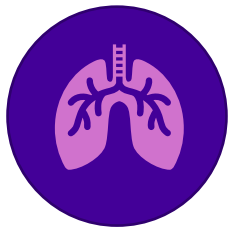
Colleen Silk
General Manager, Brensocatib

Brensocatib

Reversible, Oral DPP1 Inhibitor

Brensocatib

NCFBE to Serve as ‘Launch Pad’ for Neutrophil-mediated Portfolio



NCFBE Program WILLOW + ASPEN

Serious Unmet Need Conditions

- Cystic Fibrosis
- Granulomatosis with Polyangiitis
- Apha-1 Antitrypsin Deficiency

Larger Markets

- Inflammatory Bowel Disease*
- Rheumatoid Arthritis*
- Lupus Nephritis*
- COPD/Asthma†
- Oncology

Research Pipeline

- External collaborations
- Insmed expertise

NCFBE, non-CF bronchiectasis
** Preclinical data generated*
†AstraZeneca has exercised its option to develop brensocatib in COPD & asthma through Phase 2b. Further development subject to agreement on commercial terms with Insmed.

Brensocatib

Clinical Development

Bronchiectasis: Pathogenesis

Bronchiectasis Vicious Cycle*

INFLAMMATION

Persistent inflammatory response, causing lung damage

BACTERIAL COLONIZATION

Increased susceptibility to chronic bacterial infection and colonization

AIRWAY DESTRUCTION

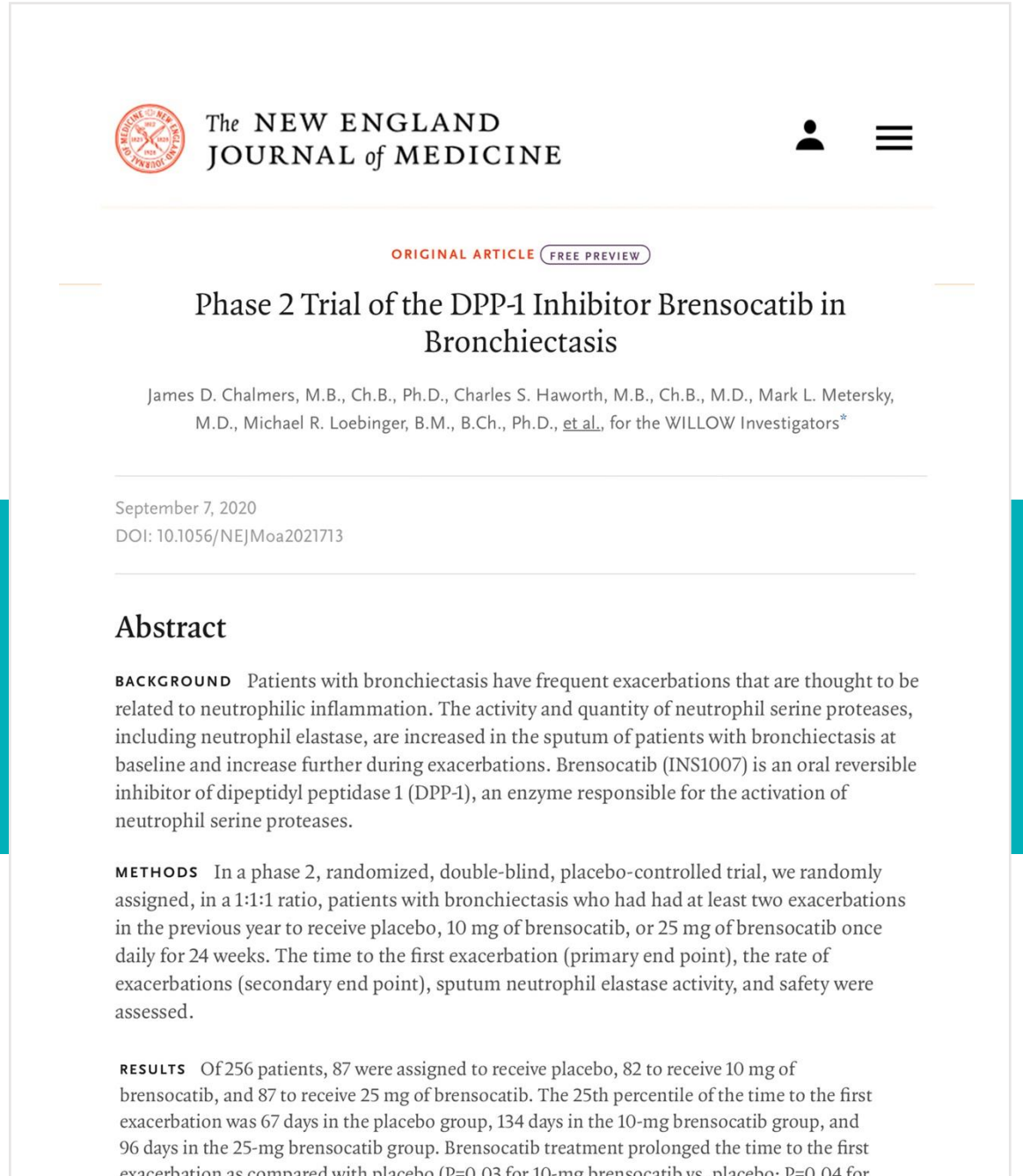
An environmental insult or disease process leads to bronchial wall destruction and dilation

ABNORMAL MUCOCILIARY CLEARANCE

Structural damage impairs protective mucociliary clearance

** All references to bronchiectasis related to our WILLOW and ASPEN clinical studies, potential launch of brensocatib and global prevalence refer to non-cystic fibrosis bronchiectasis.*

WILLOW Study Results Underscore Potential of Brensocatib



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE FREE PREVIEW

Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

James D. Chalmers, M.B., Ch.B., Ph.D., Charles S. Haworth, M.B., Ch.B., M.D., Mark L. Metersky, M.D., Michael R. Loebinger, B.M., B.Ch., Ph.D., et al., for the WILLOW Investigators*

September 7, 2020
DOI: 10.1056/NEJMoa2021713

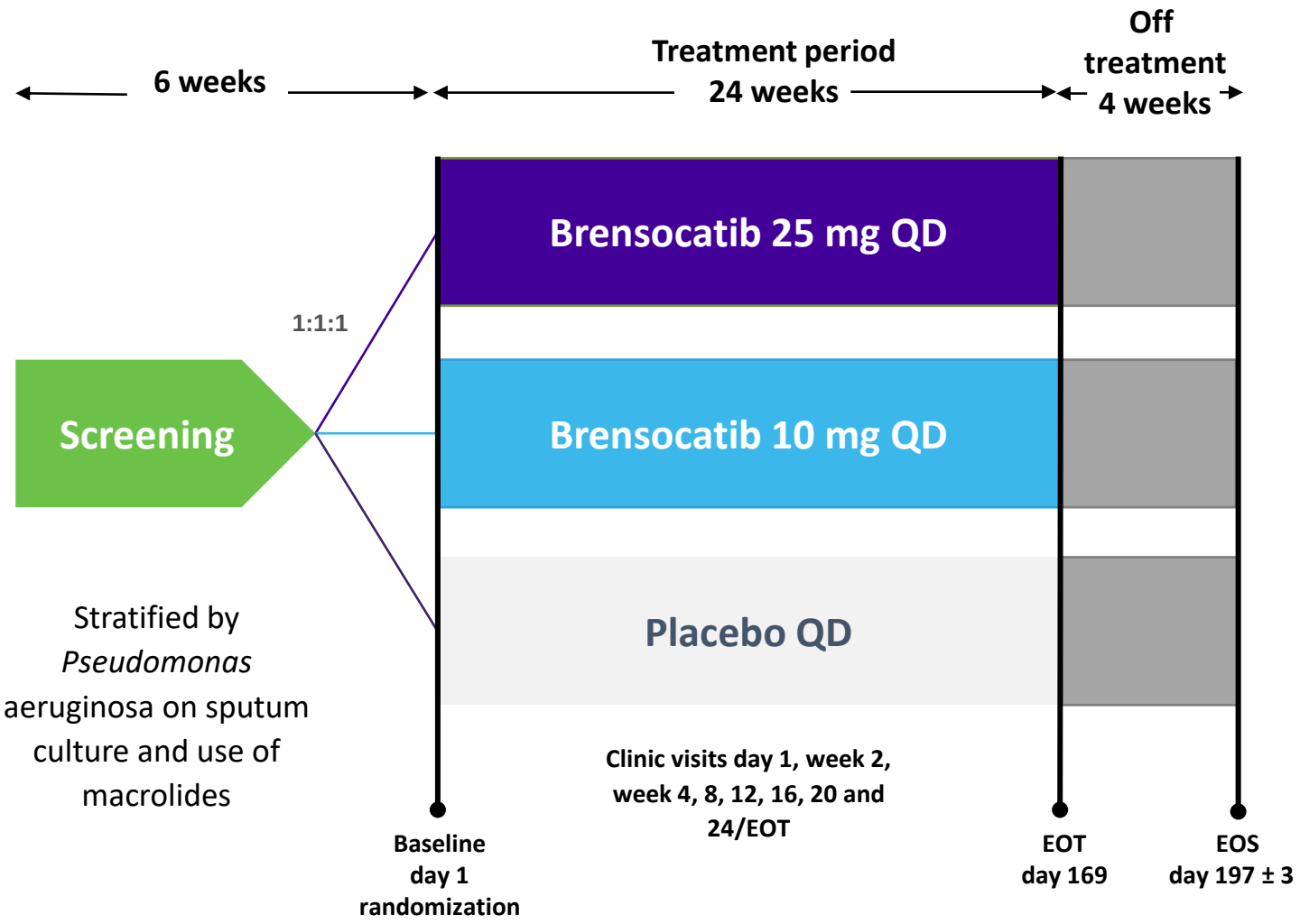
Abstract

BACKGROUND Patients with bronchiectasis have frequent exacerbations that are thought to be related to neutrophilic inflammation. The activity and quantity of neutrophil serine proteases, including neutrophil elastase, are increased in the sputum of patients with bronchiectasis at baseline and increase further during exacerbations. Brensocatib (INS1007) is an oral reversible inhibitor of dipeptidyl peptidase 1 (DPP-1), an enzyme responsible for the activation of neutrophil serine proteases.

METHODS In a phase 2, randomized, double-blind, placebo-controlled trial, we randomly assigned, in a 1:1:1 ratio, patients with bronchiectasis who had had at least two exacerbations in the previous year to receive placebo, 10 mg of brensocatib, or 25 mg of brensocatib once daily for 24 weeks. The time to the first exacerbation (primary end point), the rate of exacerbations (secondary end point), sputum neutrophil elastase activity, and safety were assessed.

RESULTS Of 256 patients, 87 were assigned to receive placebo, 82 to receive 10 mg of brensocatib, and 87 to receive 25 mg of brensocatib. The 25th percentile of the time to the first exacerbation was 67 days in the placebo group, 134 days in the 10-mg brensocatib group, and 96 days in the 25-mg brensocatib group. Brensocatib treatment prolonged the time to the first exacerbation as compared with placebo (P=0.03 for 10-mg brensocatib vs. placebo; P=0.04 for

Brensocatib Phase 2 WILLOW Study Design



- **Primary objective:**
  - **Time to first exacerbation over 24 weeks in patients with non-cystic fibrosis bronchiectasis (NCFBE)**
- **Secondary objectives:**
  - **Pulmonary exacerbation rate over 24 weeks**
  - **Change in QOL-Bronchiectasis questionnaire respiratory symptoms domain over 24 weeks**
  - **Change in post-bronchodilator $ppFEV_1$ over 24 weeks**
  - **Change in sputum NE activity from pretreatment to on-treatment**

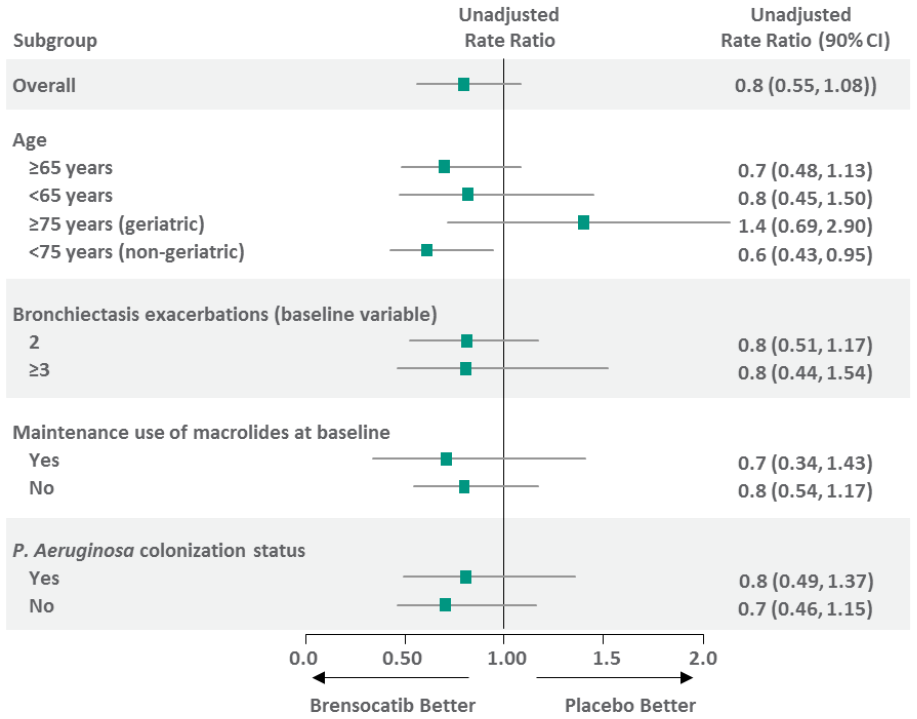
EOS, end of study; EOT, end of treatment; NE, neutrophil elastase; ppFEV1, percent predicted forced expiratory volume in 1 second; QD, once daily.
Phase 2 WILLOW Study: NCT03218917

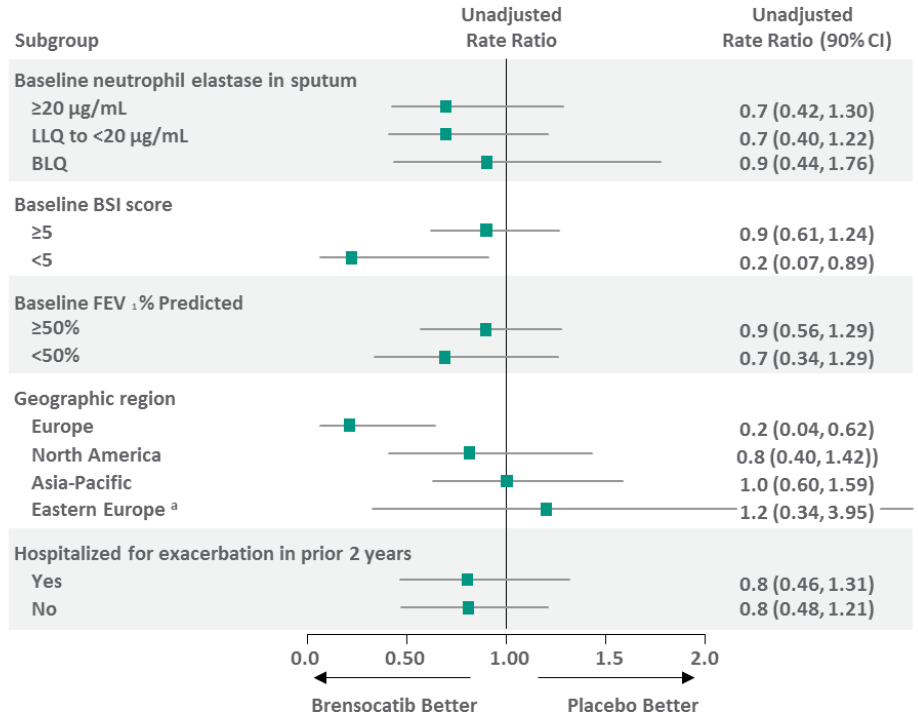
25 mg brensocatib vs. placebo

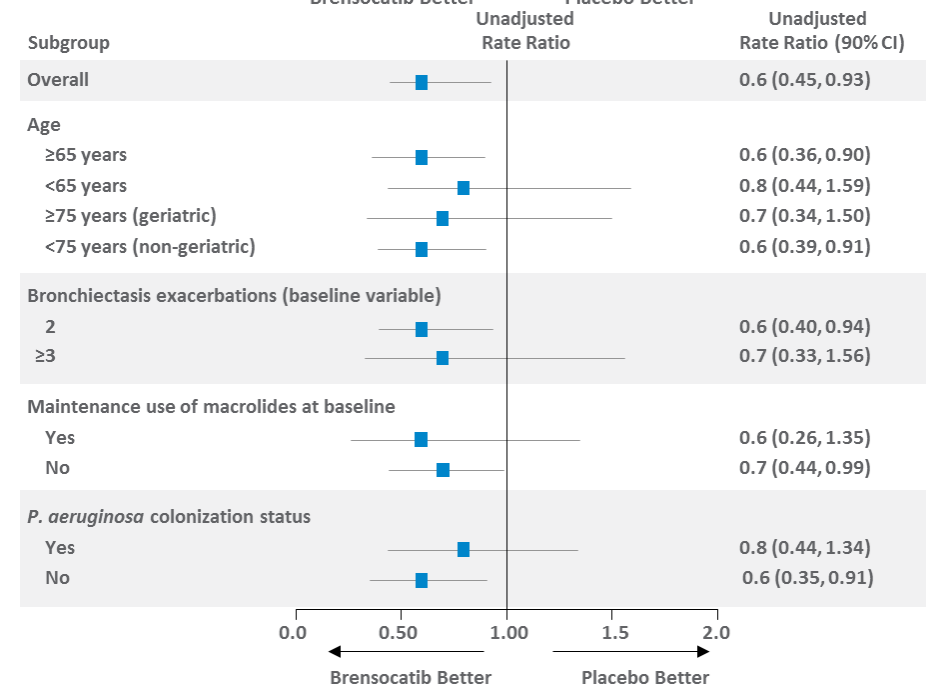
Rate of Exacerbations

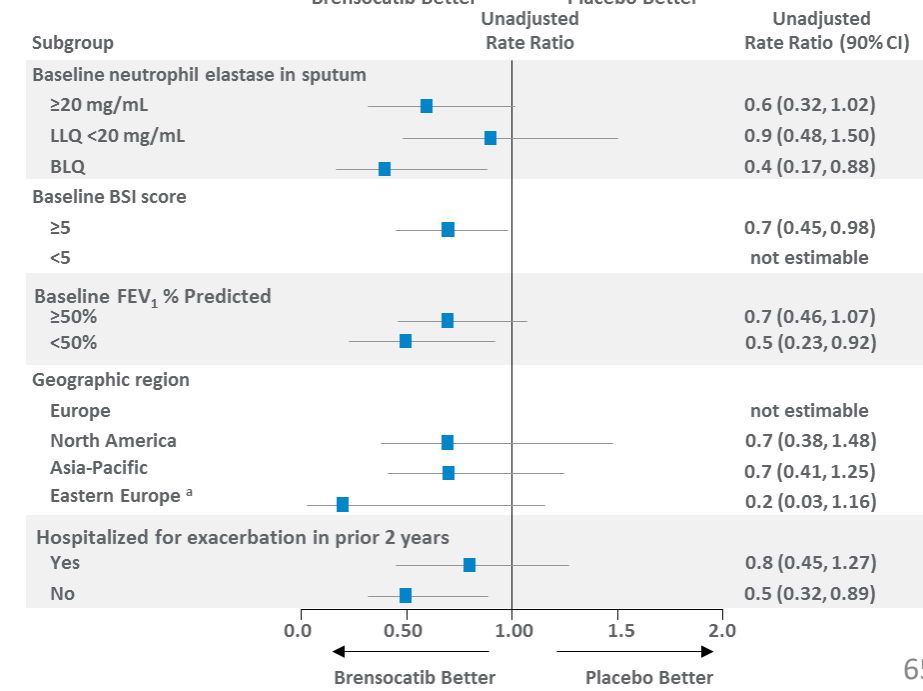
by Patient Subgroups

10 mg brensocatib vs. placebo







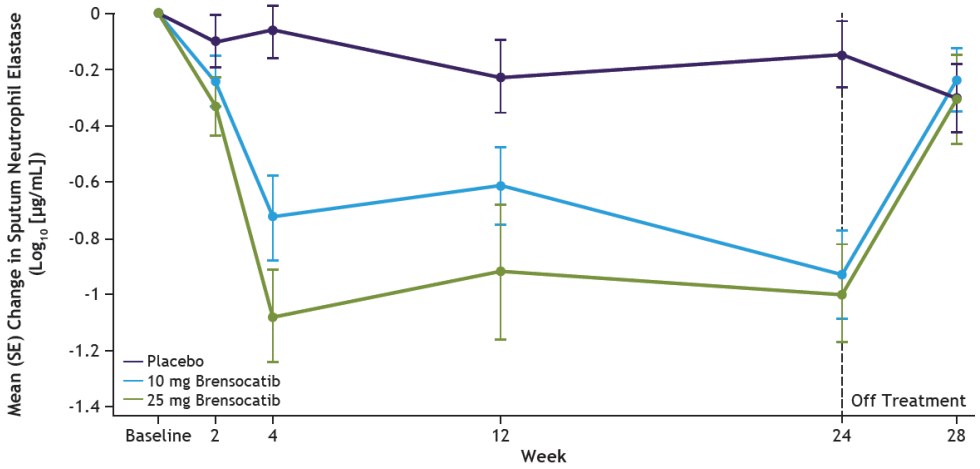


Chalmers et al, ERS International Congress 2020, 7-9 September. RCT4135
BSI, bronchiectasis severity index; FEV1, forced expiratory volume in 1 second
[a]Bulgaria/Poland

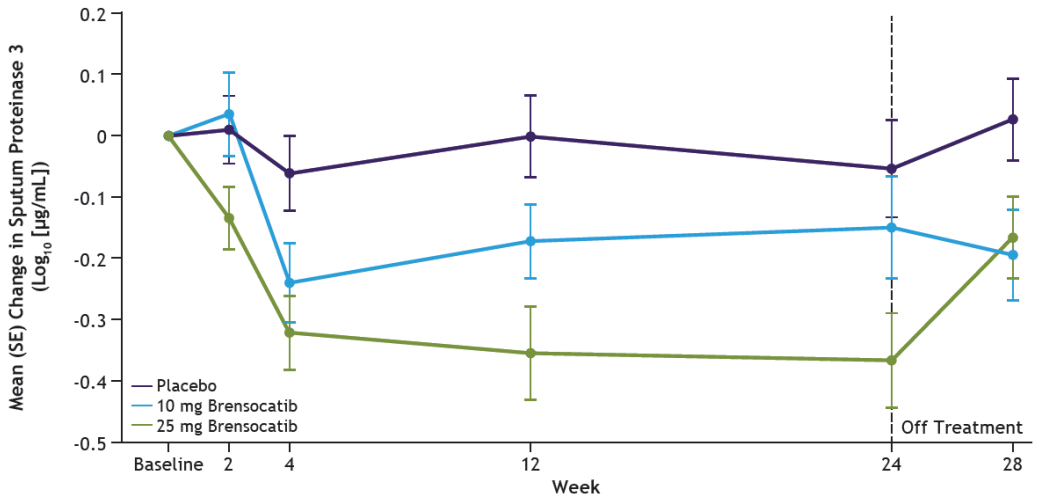
Dose Response Effect Seen Consistently Across Sputum Neutrophil Serine Proteases (NSPs)

Mean (SE) Change from Baseline to Week 24 (log10 [mg/mL])

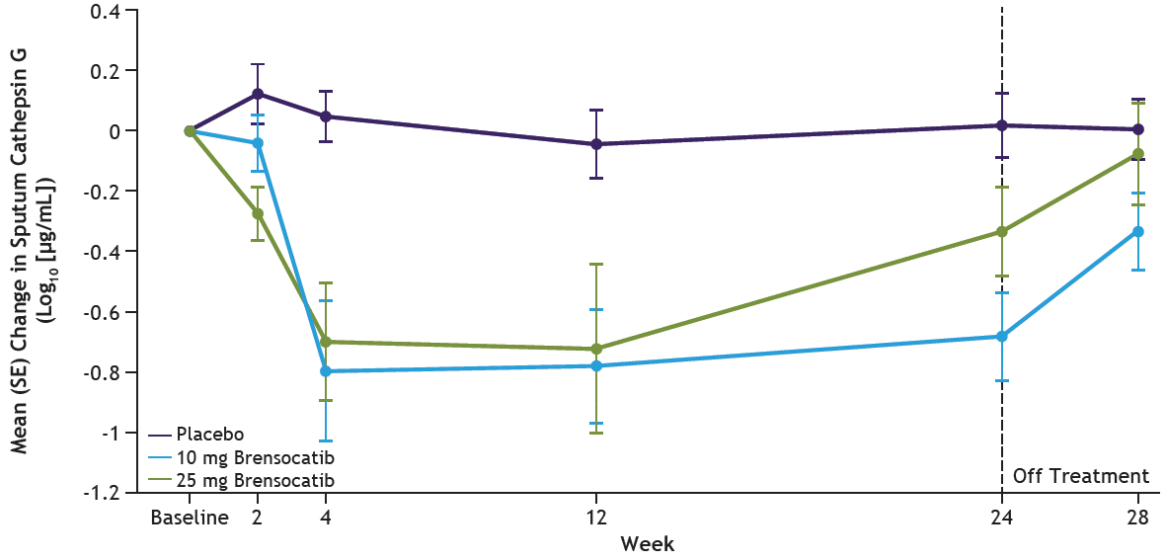
Neutrophil Elastase



Proteinase 3



Cathepsin G



Chalmers et al, ERS International Congress 2020, 7-9 September. RCT4135

WILLOW Safety Data

no. (%)	Placebo (n=85)	Brensocatib 10 mg (n=81)	Brensocatib 25 mg (n=89)
TEAE resulting in study discontinuation	3 (3.5)	3 (3.7)	4 (5.5)
TEAE resulting in treatment discontinuation	9 (10.6)	6 (7.4)	6 (6.7)
Serious TEAE	19 (22.4)	11 13.6)	10 (11.2)
Serious TEAEs in ≥ 3% of patients in any group			
Infective exacerbation of bronchiectasis	9 (10.6)	5 (6.2)	4 (4.5)
Pneumonia	3 (3.5)	0	4 (4.5)
Any TEAE	67 (78.8)	75 (92.6)	74 (83.1)
TEAEs in ≥ 10% of patients in any group			
Cough	10 (11.8)	15 (18.5)	12 (13.5)
Headache	3 (3.5)	8 (9.9)	12 (13.5)
Sputum increased	6 (7.1)	9 (11.1)	9 (10.1)
Dyspnea	2 (2.4)	3 (3.7)	9 (10.1)
Infective exacerbation of bronchiectasis	9 (10.6)	5 (6.2)	4 (4.5)
Diarrhea	9 (10.6)	5 (6.2)	3 (3.4)

Brensocatib

Phase 3 Development Program

ASPEN Study: Single Trial Designed to Support Global Filing

Breakthrough Therapy Designation for brensocatib in non-cystic fibrosis bronchiectasis (NCFBE)

Robust efficacy endpoints, supported by WILLOW results

Integrates feedback from Health Authorities

ASPEN Phase 3 Study Design

Primary Endpoint:

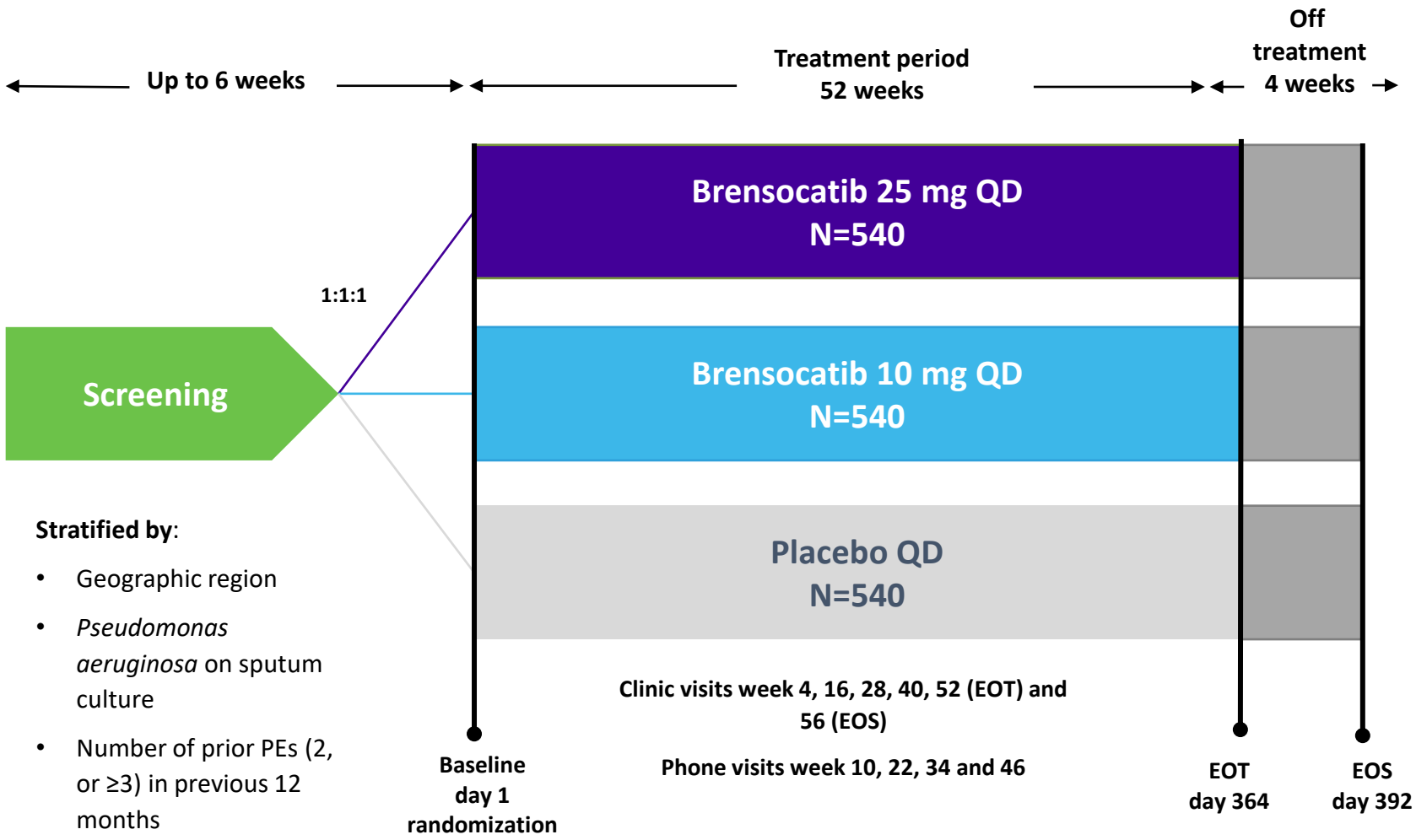
- Rate of pulmonary exacerbations over the 52-week treatment period

Key Secondary Endpoints:

- Time to first pulmonary exacerbation over the 52-week treatment period
- Proportion of subjects who remain exacerbation-free over the 52-week treatment period
- Change in FEV1

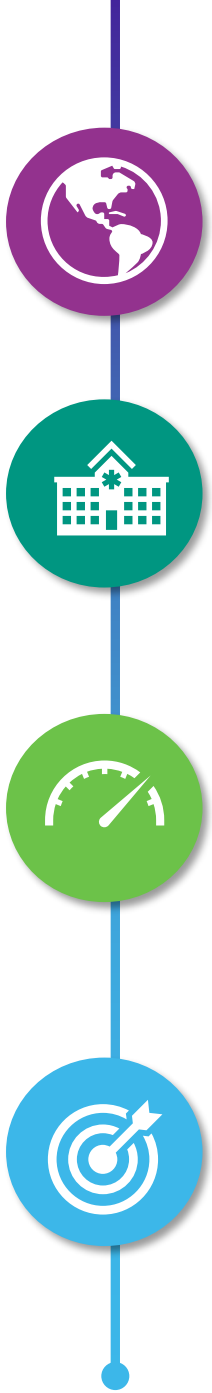
Powered at 90% to detect 30% reduction in exacerbation rate

- Type I error: 0.01 (two-sided)
- P-value = less than 0.01



EOS, end of study; EOT, end of treatment; FEV1, forced expiratory volume in 1 second; QD, once daily; PE, pulmonary exacerbation

ASPEN Timeline Considerations



36 Countries

~480 sites

6 Fast Track Countries

Targeting WILLOW study sites

Brensocatib

Commercial Outlook

Brensocatib Strategy Builds on Successful First Launch in NCFBE

- ASPEN Phase 3 trial for non-cystic fibrosis bronchiectasis (NCFBE)
- Prepare for successful global launch in NCFBE
- Advance clinical programs for cystic fibrosis
- Evaluate other neutrophil-modulated diseases for future research & label expansion

An Approved NCFBE Treatment to Reduce Exacerbations

Could Address Unmet Needs Across Stakeholders

Patients

- Symptoms of cough, dyspnea, fatigue interfere with daily life
- Fear of exacerbations negatively impacts emotional and social well-being
- Frustrated with time-consuming therapies that are not specific to BE

Healthcare Providers

- Lack of efficacious anti-inflammatory option
- Treatments that improve patient QOL and prevent exacerbations seen as largest unmet need
- Recognize current treatments lack BE-specific clinical trial data

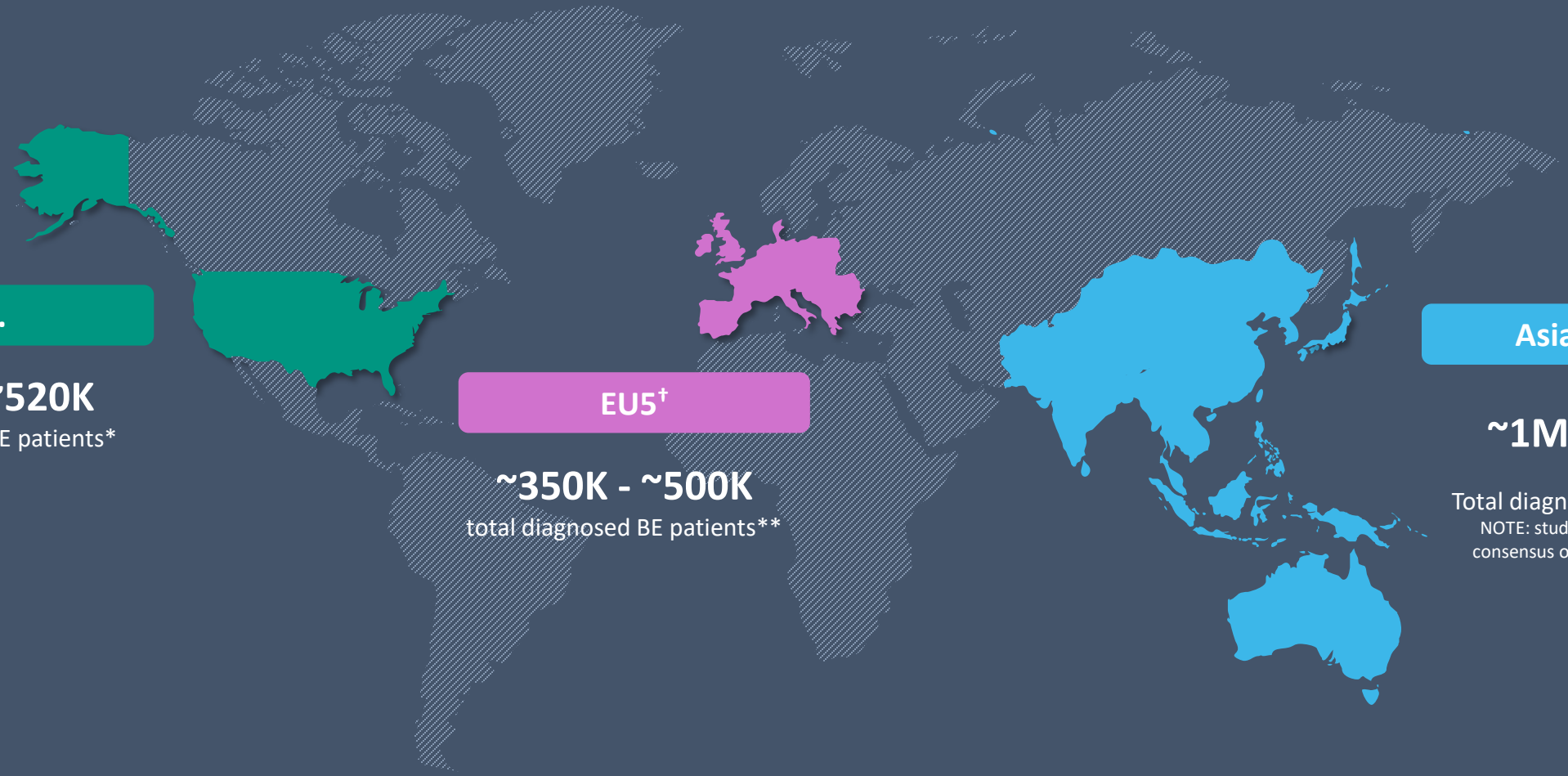
Payers

- Treatment option with BE indication, greater efficacy, and reduction in exacerbations seen as unmet needs

> **“It’s like waiting for a hurricane – there’s a constant level of fear and anxiety of the unknown. When will an exacerbation hit?”**
>
> **- BRONCHIECTASIS PATIENT**

Bronchiectasis is a Globally Prevalent Disease

Preliminary Data Suggest Significant Global Need



U.S.

~340K - ~520K

total diagnosed BE patients*

EU5†

~350K - ~500K

total diagnosed BE patients**

Asia-Pacific

~1M to ~5M

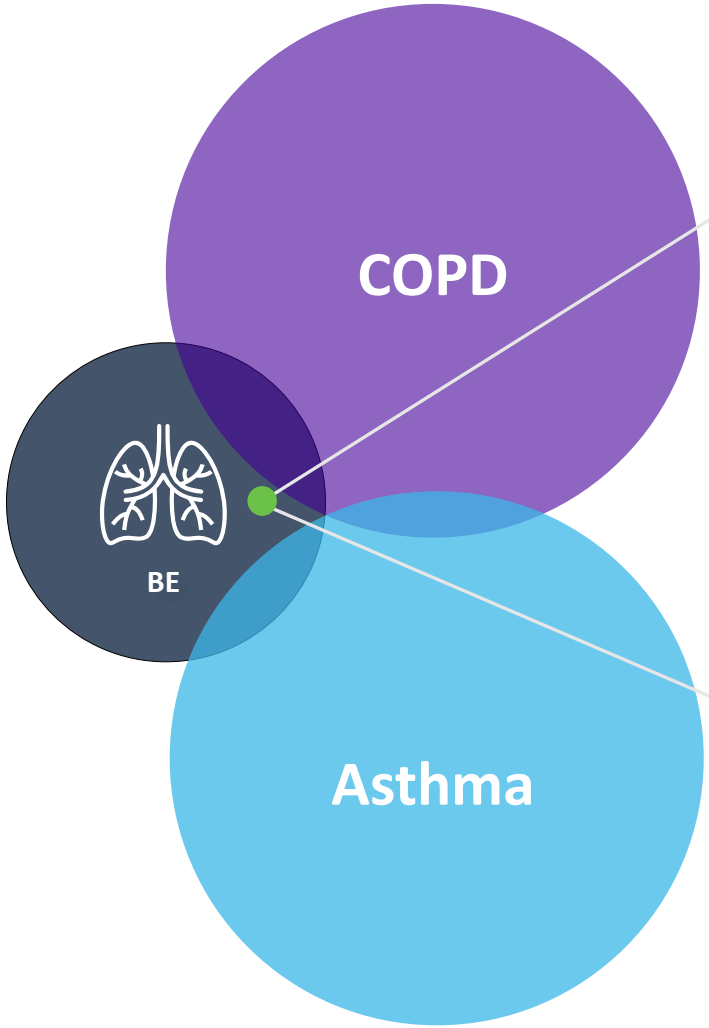
Total diagnosed BE patients

NOTE: studies indicate lack of consensus on prevalence rates◊

**Weycker, et al. Prevalence and incidence of NCFBE among US adults in 2013. Chronic Respiratory Disease. 2017; **Estimates suggest broadly similar per capita prevalence in EU5 as in US; ◊Asia-Pacific rates 3X to ~10X higher than those in the US; Zhou, YM et al. The prevalence and risk factors of bronchiectasis in residents aged 40 years old and above in seven cities in China. 2013 † EU5 comprised of France, Germany, Italy, Spain and the United Kingdom*

Current Prevalence Estimates May Underestimate Global Patient Population,

Given Underdiagnosis of NCFBE



Between 650K – 9M COPD patients in the US (4%[1]-54%[2]) may also have NCFBE

Between **450K – 675K asthma patients in the US** (2%-3%[3]) may also have NCFBE

1. Agusti, A., Calverley, P.M., Celli, B. et al. Characterisation of COPD heterogenecity in the ECLIPSE cohort. Respir Res. 2010; 11: 122
2. Ni, Y., Shi, G., Yu, Y. et al. Clinical characteristics of patients with chronic obstructive pulmonary disease with co-morbid bronchiectasis: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2015; 10: 1465–1475
3. Kang HR, Choi GS, Park SJ, et al. The effects of bronchiectasis on asthma exacerbation. Tuberc Respir Dis (Seoul). 2014;77(5):209-214.

Well Positioned to Support a Successful Global Launch in NCFBE

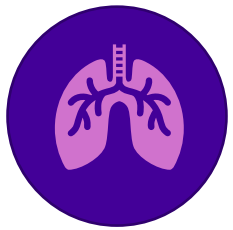
Uniquely positioned to commercialize brensocatib, if approved, given the synergies that exist between NCFBE and NTM lung disease

- Well-developed US launch capabilities with ARIKAYCE
- Experience with patient finding and activation
- Geographic and target HCP overlap with current US Sales structure
- EU/Japan teams mobilized for launch success
- Advocacy and patient support

Brensocatib

Additional Opportunities

Strategy to Build a Neutrophil-mediated Portfolio



NCFBE Program

Serious Unmet Need Conditions

- Cystic Fibrosis
- Granulomatosis with Polyangiitis
- Apha-1 Antitrypsin Deficiency

Larger Markets

- Inflammatory Bowel Disease*
- Rheumatoid Arthritis*
- Lupus Nephritis*
- COPD/Asthma†
- Oncology

Research Pipeline

- External collaborations
- Insmed expertise

** Preclinical data generated*

†AstraZeneca has exercised its option to develop brensocatib in COPD & asthma through Phase 2b. Further development subject to agreement on commercial terms with Insmed.

Cystic Fibrosis and GPA Identified for Further Clinical Development

	Cystic Fibrosis	GPA
MOA Applicability	Clear role for neutrophils and NE in CF; Chronic bacterial infections of CF are neutrophil-mediated, and very elevated neutrophil counts in sputum are seen in CF patients	Two distinct MOAs could be applicable: (1) Inhibits activity of NSPs, (2) Reduces expression of membrane-bound PR3
Value Proposition	Potential to fill a need for CF-specific anti-inflammatory therapy, a category not currently met by marketed products An important additive therapy (on top of CFTR modulators) for CF patients who experience any pulmonary exacerbations	Potential for additional treatment option for GPA patients during induction for a more efficacious response, or as an alternative option for sustained remission
Providing a Roadmap for Development from CF to GPA	Previously approved products (CFTR modulators) and support from the CF Foundation Therapeutics Development Network	Previously approved product (Rituxan) and phase 3 development of avacopan

Ongoing Investigator-Sponsored Clinical Study for Treatment of Severe COVID-19 Infections

Could brensocatib be used to treat COVID-19?

Currently under investigation in multi-site UK investigator-initiated research (IIR) study

Double-blind, prospective, placebo-controlled, randomized trial

Up to 300 patients; 10 sites

Led by University of Dundee's Professor James Chalmers, MBChB, Ph.D.

Prioritized by UK's National Institute for Health Research

Potential Data read-out: **H1 2021**

Kevin C. Mange, M.D., MSCE
SVP, Clinical Development

Neil Hughes
General Manager, Head of EMEA

Roger Adsett
Chief Operating Officer

ARIKAYCE

Not for promotional use

Kevin C. Mange, M.D., MSCE
SVP, Clinical Development

ARIKAYCE

Front Line Program

Not for promotional use

ARIKAYCE® (amikacin liposomal inhalation suspension) Indication and Use

- LIMITED POPULATION: ARIKAYCE® is indicated in adults, who have limited or no alternative treatment options, for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for ARIKAYCE are currently available, reserve ARIKAYCE for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients.

- This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as 3 consecutive negative monthly sputum cultures) by Month 6. Clinical benefit has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

- **Limitation of Use:** ARIKAYCE has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. The use of ARIKAYCE is not recommended for patients with non-refractory MAC lung disease.

WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS
ARIKAYCE has been associated with an increased risk of respiratory adverse reactions, including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases.

First-in-Disease Therapy for MAC Lung Disease

MAC lung disease is a rare, progressive, and chronic condition that can cause severe, permanent damage to the lungs

Symptoms often worsen over time, including chronic cough, dyspnea, fatigue, fever, weight loss, and chest pain

Caused by bacteria in the environment and is more likely to affect those with a history of lung conditions, like bronchiectasis or COPD

ARIKAYCE

Novel, inhaled, once-daily formulation of liposomal amikacin taken with a nebulizer

Pulmovance™ liposomal technology delivers drug directly to the lungs

Prolongs release of amikacin in the lungs while limiting systemic exposure

Complementary portfolio
Meaningful overlap in patient populations, with over 60% of bronchiectasis patients also having an NTM infection

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ARIKAYCE Front Line Indication – Trial Summary

ARISE (INS-415)

Psychometric validation study

Subjects: 100

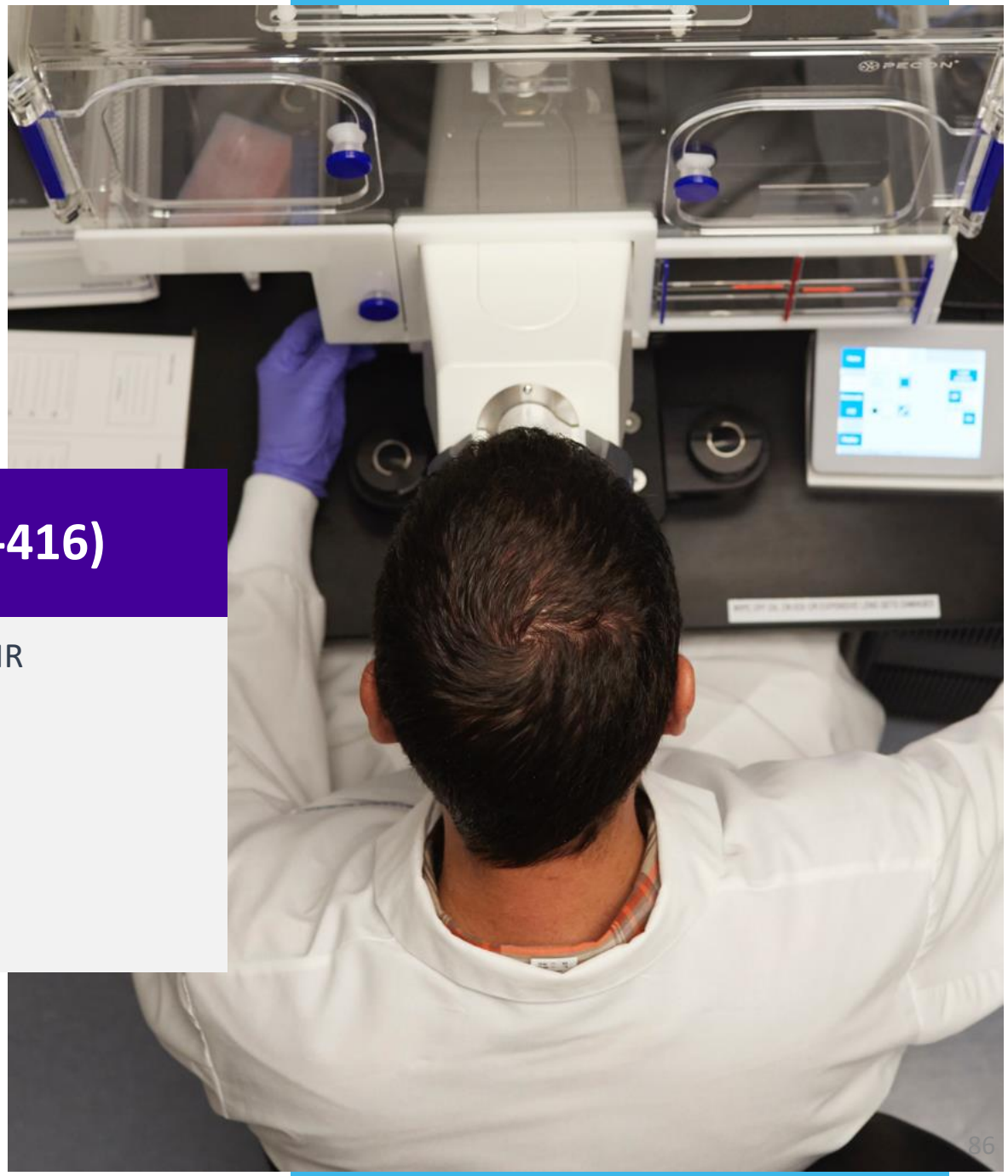
Start: Q4 2020

ENCORE (INS-416)

Double-blind PMR trial

Subjects: 250

Start: Q4 2020



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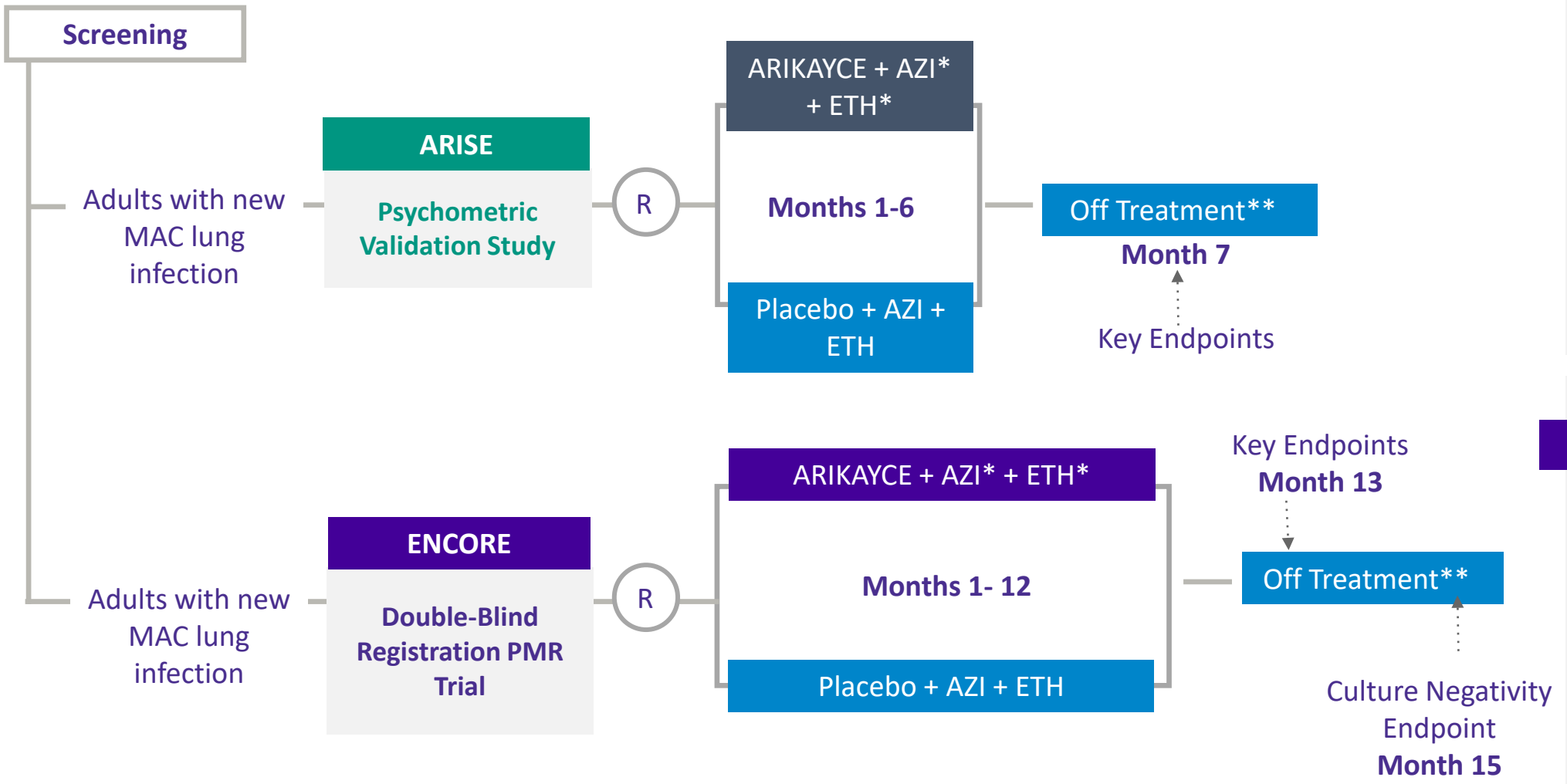
Front Line Indication

Registration Program



ARISE

Primary Objective
Demonstrate reliability, validity and responsiveness of the PRO/symptom scores

Secondary Objective
Demonstrate effect of ARIKAYCE on culture conversion, time to culture conversion

ENCORE

Primary Endpoint
Change from Baseline to Month 13 (one month off treatment) in respiratory symptom score

Key Secondary Endpoint
Proportion of subjects achieving durable culture conversion at Month 15 (3 months off treatment)

**Azithromycin (AZI), Ethambutol (ETH)*
***Patients will be enrolled into separate open label extension study*

https://clinicaltrials.gov/ct2/show/NCT03672630

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Developing a Symptom Score for Front Line Indication

Leveraging Existing Instruments to Expedite Work

Respiratory Symptom Score

Quality of Life- Bronchiectasis (QoL-B) Patient Reported Outcome (PRO) Questionnaire

Fatigue Symptom Score

PROMIS-Fatigue Short Form 7a Questionnaire

In general, FDA requires description (validation) of questionnaires (PROs) to be used to support efficacy in the context of use (population of interest)

Completed Concept Elicitation work with 25 patients with newly diagnosed MAC disease

Supports specific questions in respiratory domain in QoL-B, and in PROMIS-Fatigue are meaningful / understandable to these patients and are likely the basis of computing symptom scores pending completion of Cognitive Interview work later this year.

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Developing a Symptom Score for Front Line Indication

Lessons Learned from Prior Drug Development Programs

Describing longitudinal properties of questionnaires / PROs is required by FDA, in general

Global Blood Therapeutics incorporated describing longitudinal properties into Phase 3 study (HOPE study) for their new PRO in sickle cell disease

ARISE & ENCORE will evaluate symptom scores and other endpoints after completion of three-drug treatment regimen vs two-drug treatment regimen

ARISE will evaluate longitudinal properties as a separate study that will complete while ENCORE is enrolling

- Provides for ability to adjust what/how items are used to compute final version of symptom scores in ENCORE while preserving integrity of ENCORE

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Neil Hughes

General Manager, Head of EMEA

ARIKAYCE

EU Launch Update

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ARIKAYCE a Blueprint for Future Success

2019 **$136M** net sales

Q2 2020 **$42.5M**

Engaged HCP & patient population

Positive reimbursement trends

- **Engaged healthcare providers**
- **Educated patient population**
- **Focus on payers to ensure reimbursement**

ARIKAYCE was one of the Top 10 most successful non-oncology rare disease launches

We plan to repeat history with our growing pipeline

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ARIKAYCE Added to International Treatment Guidelines for Treatment of MAC Lung Disease

Guidelines are a globally recognized standard for the prevention, diagnosis and treatment of NTM lung disease

Addition of ARIKAYCE to new standard treatment regimen for adult patients with limited or no treatment options who failed to convert to a negative sputum culture after at least six months of treatment

Treatment should be continued for 12 months after culture conversion

ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

IDSA Infectious Diseases Society of America

AMERICAN THORACIC SOCIETY 1905 ATS®
We help the world breathe®
PULMONARY • CRITICAL CARE • SLEEP

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

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Solid EU Infrastructure in Place to Support Launch*

*If approved

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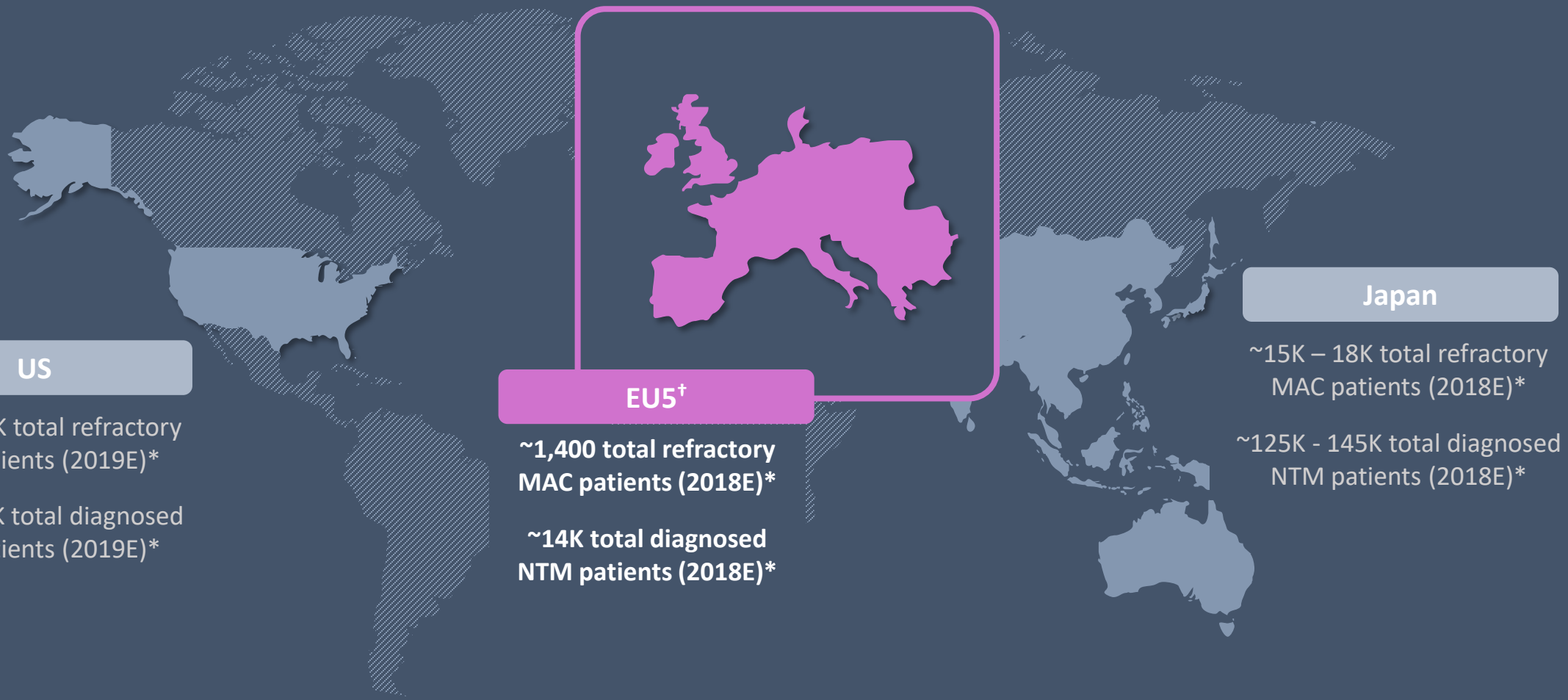
Commercial Approach

Meaningful Opportunity in Europe



US

~12K – 17K total refractory MAC patients (2019E)*

~80K – 90K total diagnosed NTM patients (2019E)*

EU5†

~1,400 total refractory MAC patients (2018E)*

~14K total diagnosed NTM patients (2018E)*

Japan

~15K – 18K total refractory MAC patients (2018E)*

~125K - 145K total diagnosed NTM patients (2018E)*

**Source: Internal analysis of published NTM epidemiology, primary market research with treating HCPs, and anonymized patient level claims data in US*

† EU5 comprised of France, Germany, Italy, Spain and the United Kingdom

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ARIKAYCE Received Positive CHMP Opinion

July 24, 2020

Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has adopted a positive opinion recommending ARIKAYCE for the treatment of NTM lung infections caused by MAC in non-CF Patients with limited treatment options

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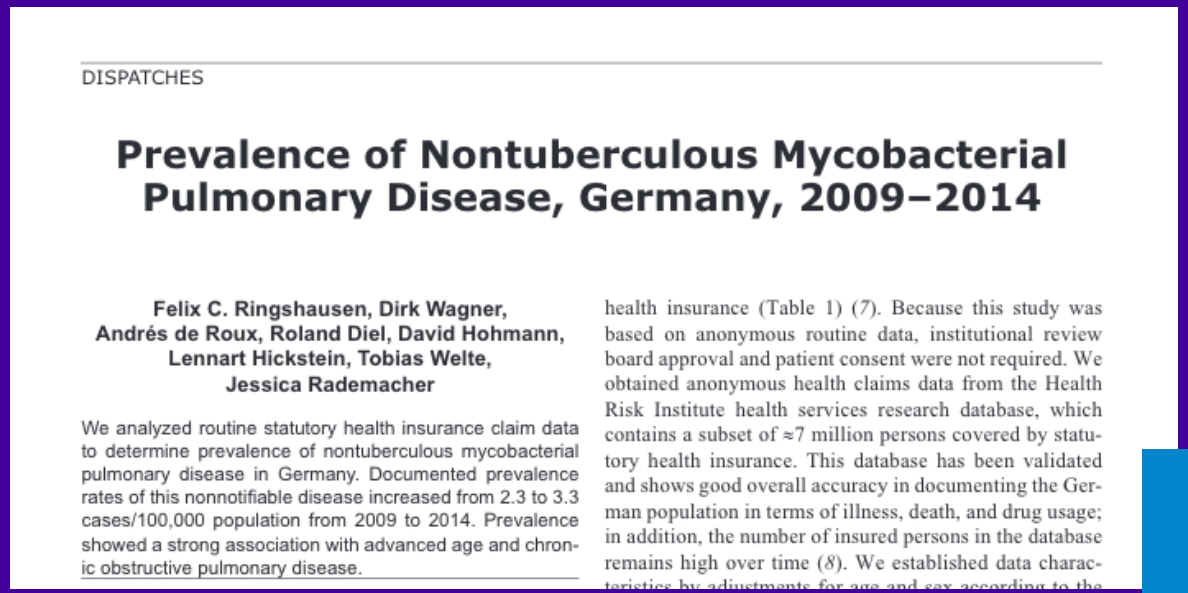
Prevalence of NTM in EU May be Greater Than Previously Reported



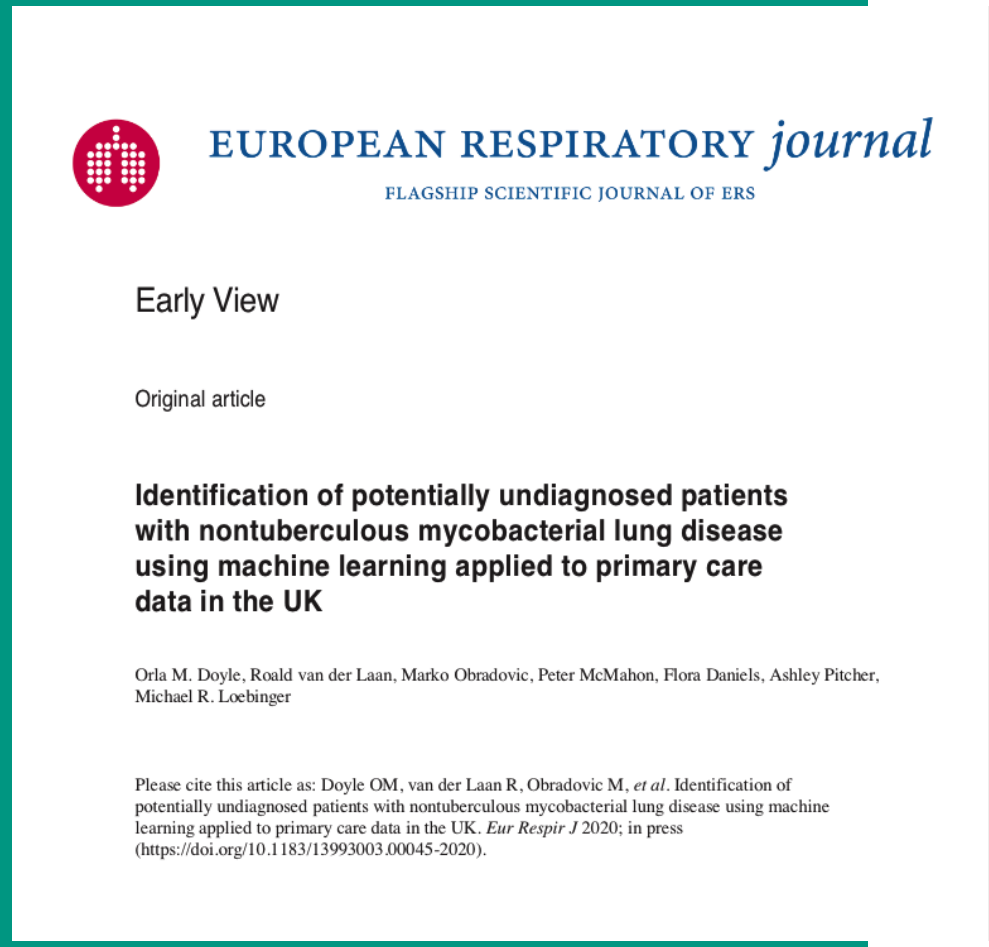
DISPATCHES

Prevalence of Nontuberculous Mycobacterial Pulmonary Disease, Germany, 2009–2014

Felix C. Ringshausen, Dirk Wagner, Andrés de Roux, Roland Diel, David Hohmann, Lennart Hickstein, Tobias Welte, Jessica Rademacher

We analyzed routine statutory health insurance claim data to determine prevalence of nontuberculous mycobacterial pulmonary disease in Germany. Documented prevalence rates of this nonnotifiable disease increased from 2.3 to 3.3 cases/100,000 population from 2009 to 2014. Prevalence showed a strong association with advanced age and chronic obstructive pulmonary disease.

health insurance (Table 1) (*7*). Because this study was based on anonymous routine data, institutional review board approval and patient consent were not required. We obtained anonymous health claims data from the Health Risk Institute health services research database, which contains a subset of ≈7 million persons covered by statutory health insurance. This database has been validated and shows good overall accuracy in documenting the German population in terms of illness, death, and drug usage; in addition, the number of insured persons in the database remains high over time (*8*). We established data characteristics by adjustments for age and sex according to the



EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Identification of potentially undiagnosed patients with nontuberculous mycobacterial lung disease using machine learning applied to primary care data in the UK

Orla M. Doyle, Roald van der Laan, Marko Obradovic, Peter McMahon, Flora Daniels, Ashley Pitcher, Michael R. Loebinger

Please cite this article as: Doyle OM, van der Laan R, Obradovic M, *et al*. Identification of potentially undiagnosed patients with nontuberculous mycobacterial lung disease using machine learning applied to primary care data in the UK. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.00045-2020).

…while anticipated EU indication slightly wider than only refractory MAC

Not for promotional use

EU Launch Strategy

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Insmed Projected EMEA Country Footprint

Specific Field Force Structures Reflect Country-Specific Patient Pathways and NTM Management Protocols

Country Key

- Regional HQ – No Local Commercial Org
- Insmed Commercial Organization
- Under Review - Insmed vs Distributor

Customer facing FTEs grow as country reimbursement comes online*

FTEs	2020	2021	2022
Field Based Medical	14	18	21
Field Based Commercial	10	21	29

*Projections

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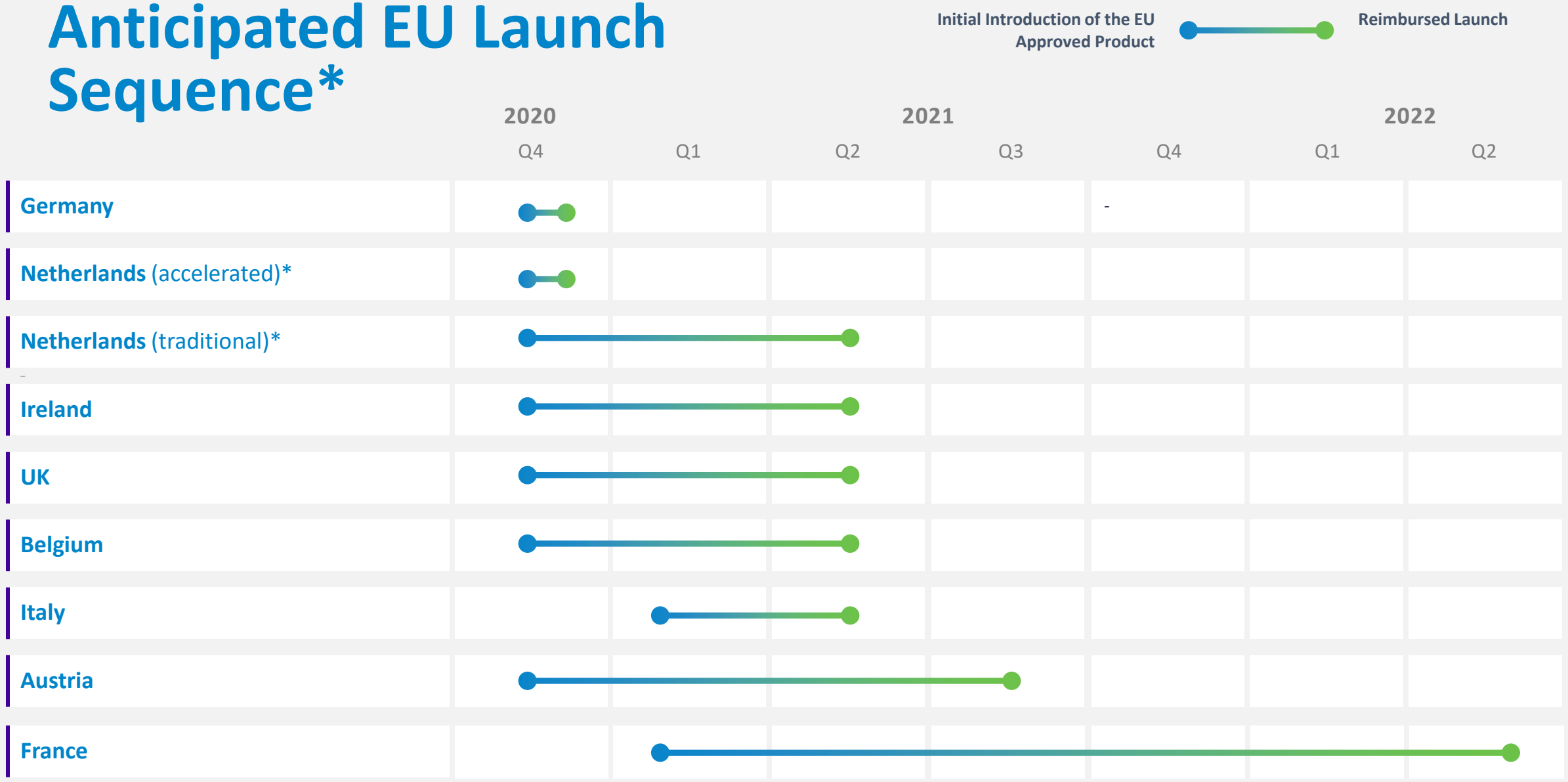
Anticipated EU Launch Sequence*



*If approved

Anticipated timelines shown

Insmed has been accepted to participate in an accelerated reimbursement process being piloted by the Dutch Health Care Institute (ZIN). While ARIKAYCE is currently well advanced in the accelerated review process, there is no guarantee ARIKAYCE will ultimately qualify for accelerated reimbursement. In the event that ARIKAYCE does complete this process, we anticipate to launch in the Netherlands according to the traditional timeline shown above.

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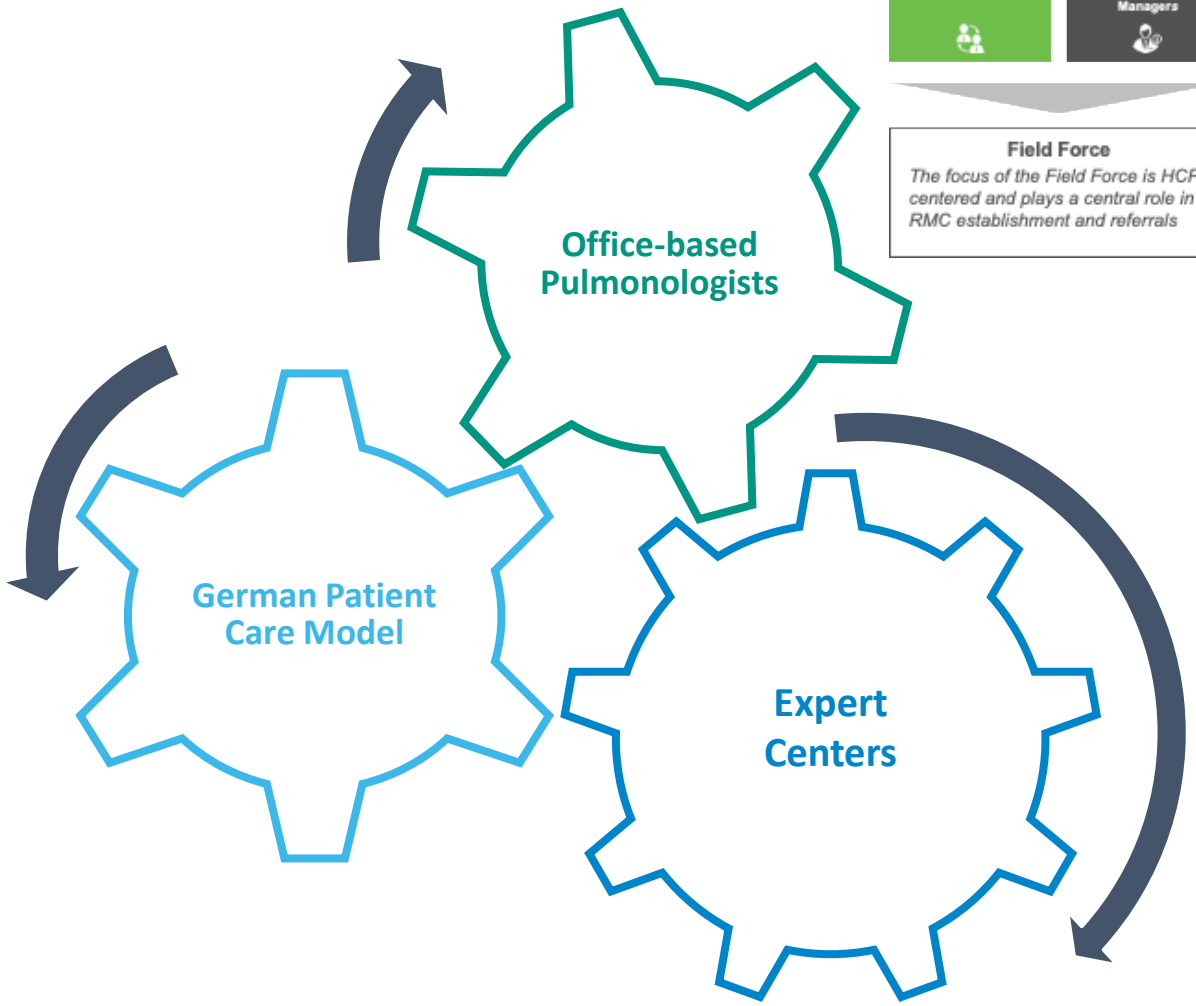
Germany

First Anticipated Launch & Largest European Market



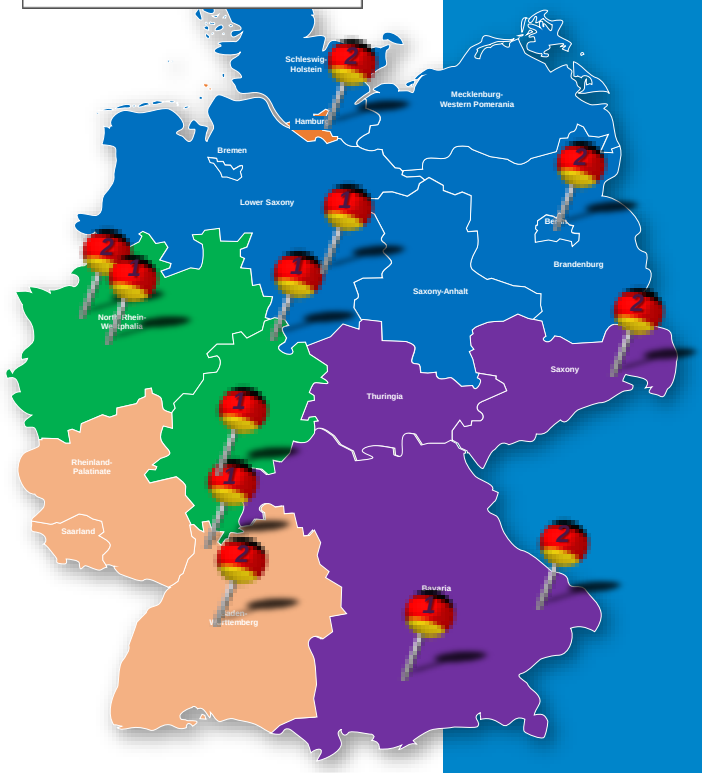
HCP-centered		Patient Support Program	
MSLs	Regional Development Managers	Patient Service Nurses	Case manager / Pharmacist

Field Force

The focus of the Field Force is HCP-centered and plays a central role in RMC establishment and referrals

Arikares Model

The patient service team is primary focused on patient solutions and is described within the Arikares Model



Four “3-up” territories

MSL, RDM & PSP nurse cover identical geography to allow for smooth collaboration between the different parts of the Field Force

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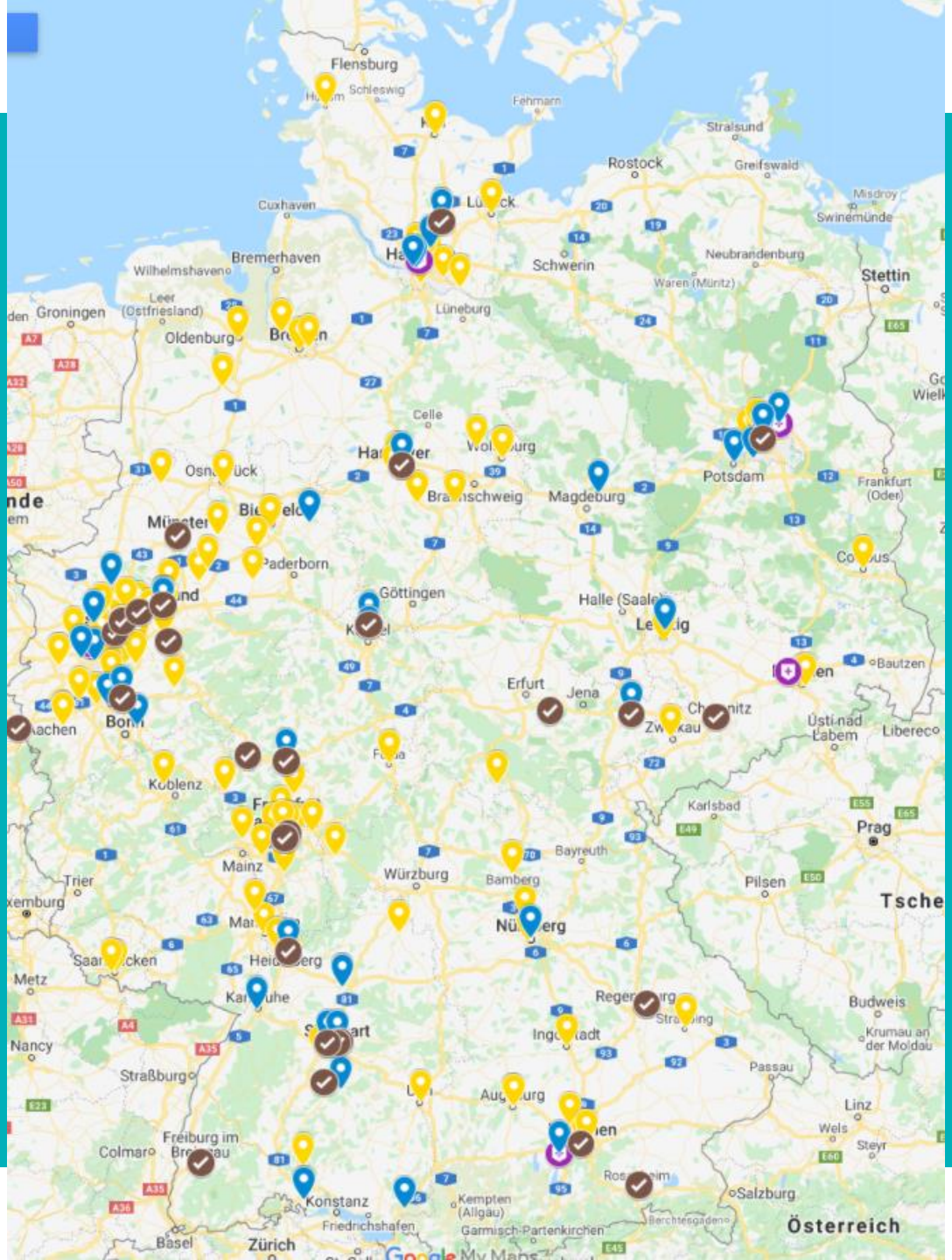
Analytics Enable Focused Commercialization Model in Germany

Geographic analysis based on:

- Centers of Excellence
- Areas of high NTM prevalence
- Existing clinical experience with ARIKAYCE

Split into priority focus areas and “white space”



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Roger Adsett

Chief Operating Officer

ARIKAYCE

Japan Launch Update

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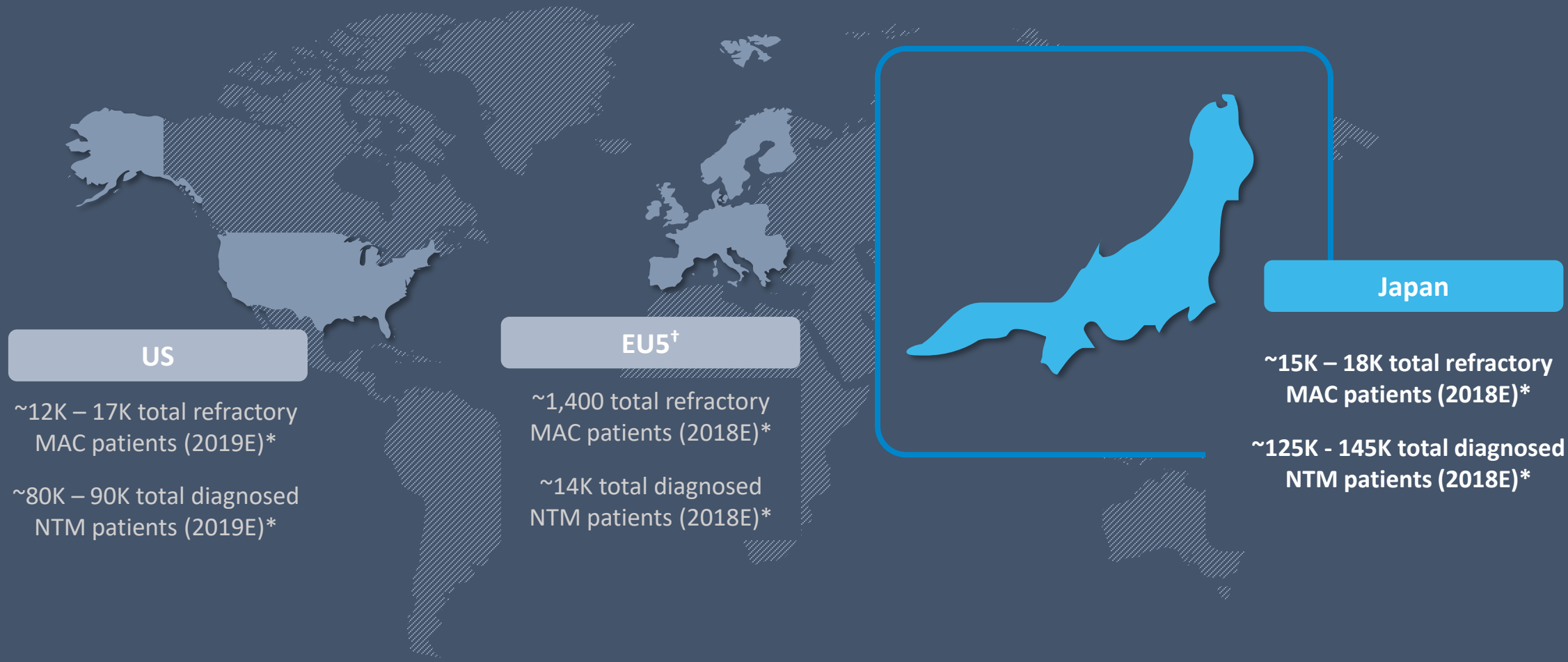
Commercial Approach: Expansion to Japan



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**Source: Internal analysis of published NTM epidemiology, primary market research with treating HCPs, and anonymized patient level claims data in US*

† EU5 comprised of France, Germany, Italy, Spain and the United Kingdom

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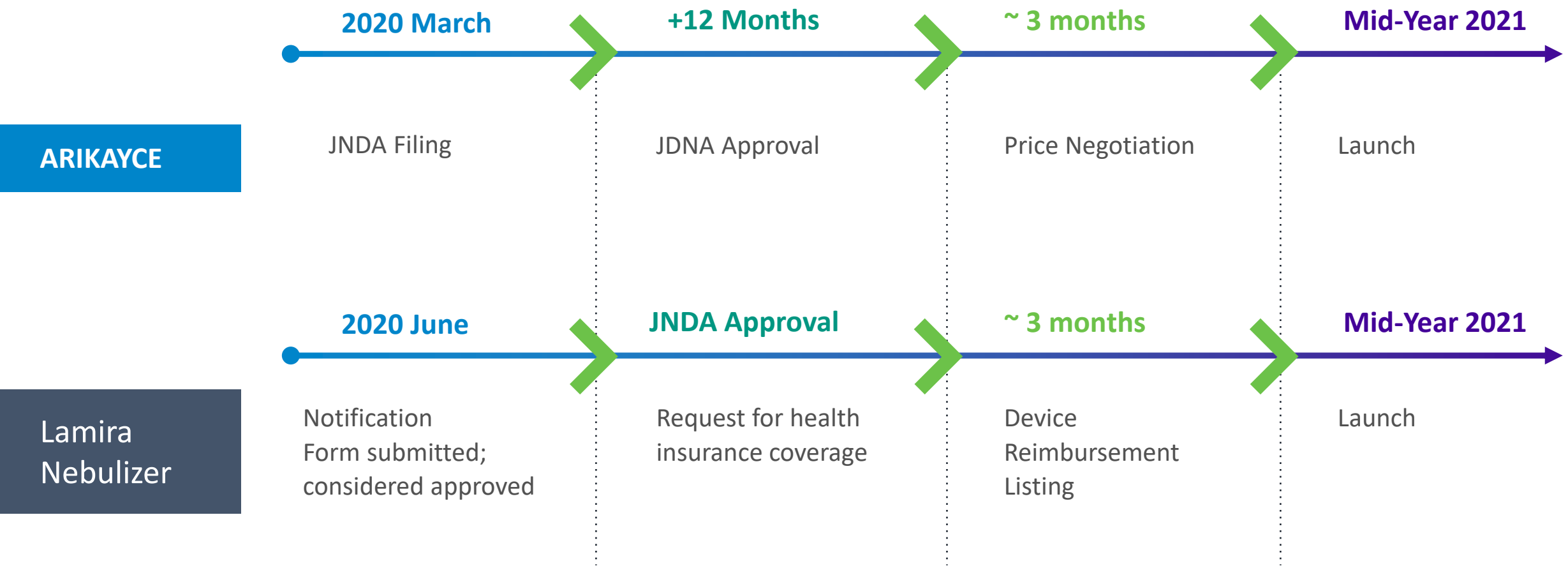
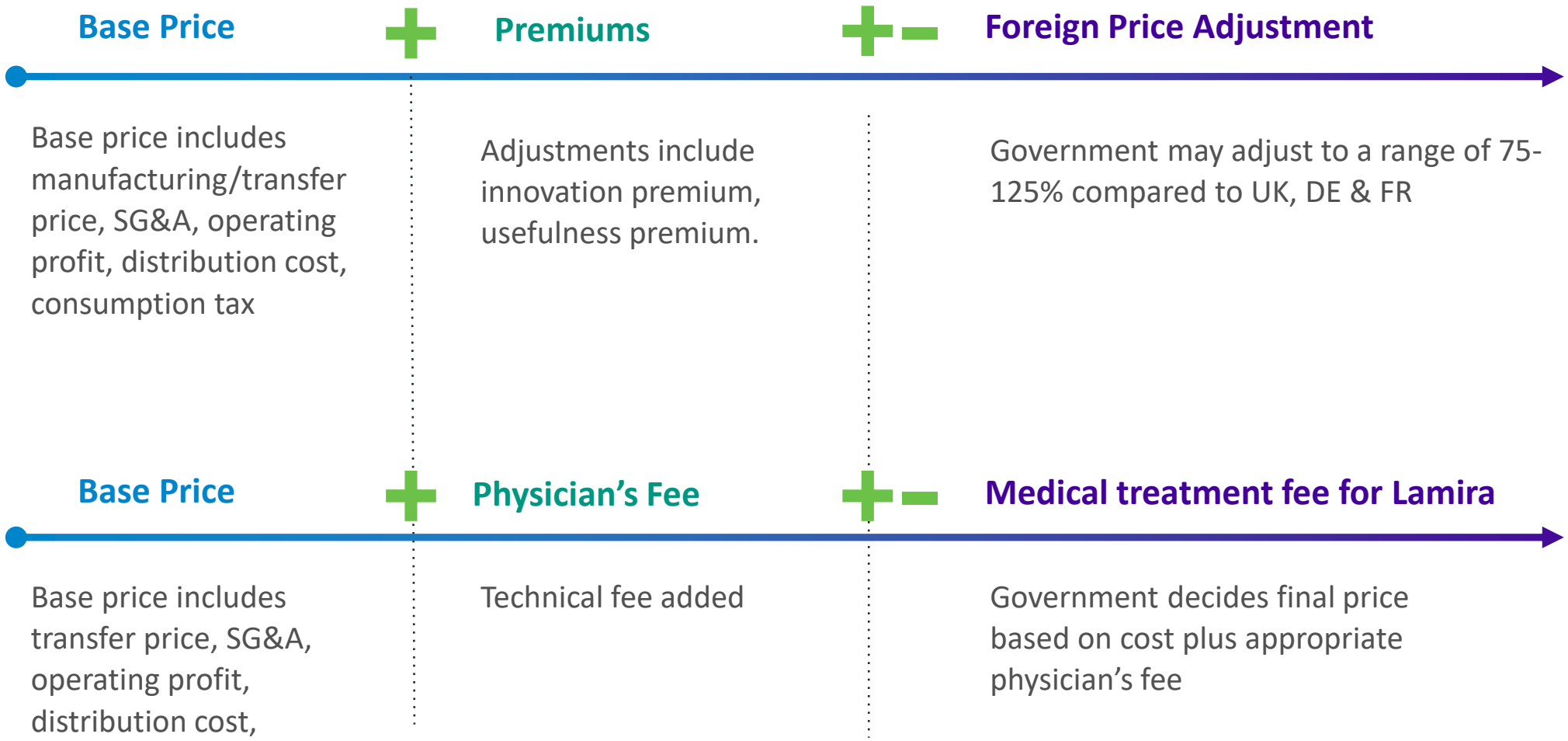
On Track for Anticipated Approval, Mid-Year 2021 Japan Launch



Anticipated timelines shown

Not for promotional use

“Cost Plus” Approach for Japanese Pricing



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Nuances of Japanese Market

Prescriptions are limited to **two-week supply** for the first year drug is on the market

Co-pay market: approved drugs reimbursed at fixed rates

Physician offices would exclusively train patients on use of ARIKAYCE with Lamira device

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Building a Strong Presence in Japan

28 People with Japanese Affiliate

Not for promotional use

Engaging Major Medical Associations

The Research Institute of Tuberculosis, Japan Anti-tuberculosis Association

The Japanese Association for Infectious Diseases

The Japanese Respiratory Society 1961

一般社団法人
日本結核・非結核性抗酸菌症学会
THE JAPANESE SOCIETY FOR TUBERCULOSIS AND NONTUBERCULOUS MYCOBACTERIOSIS

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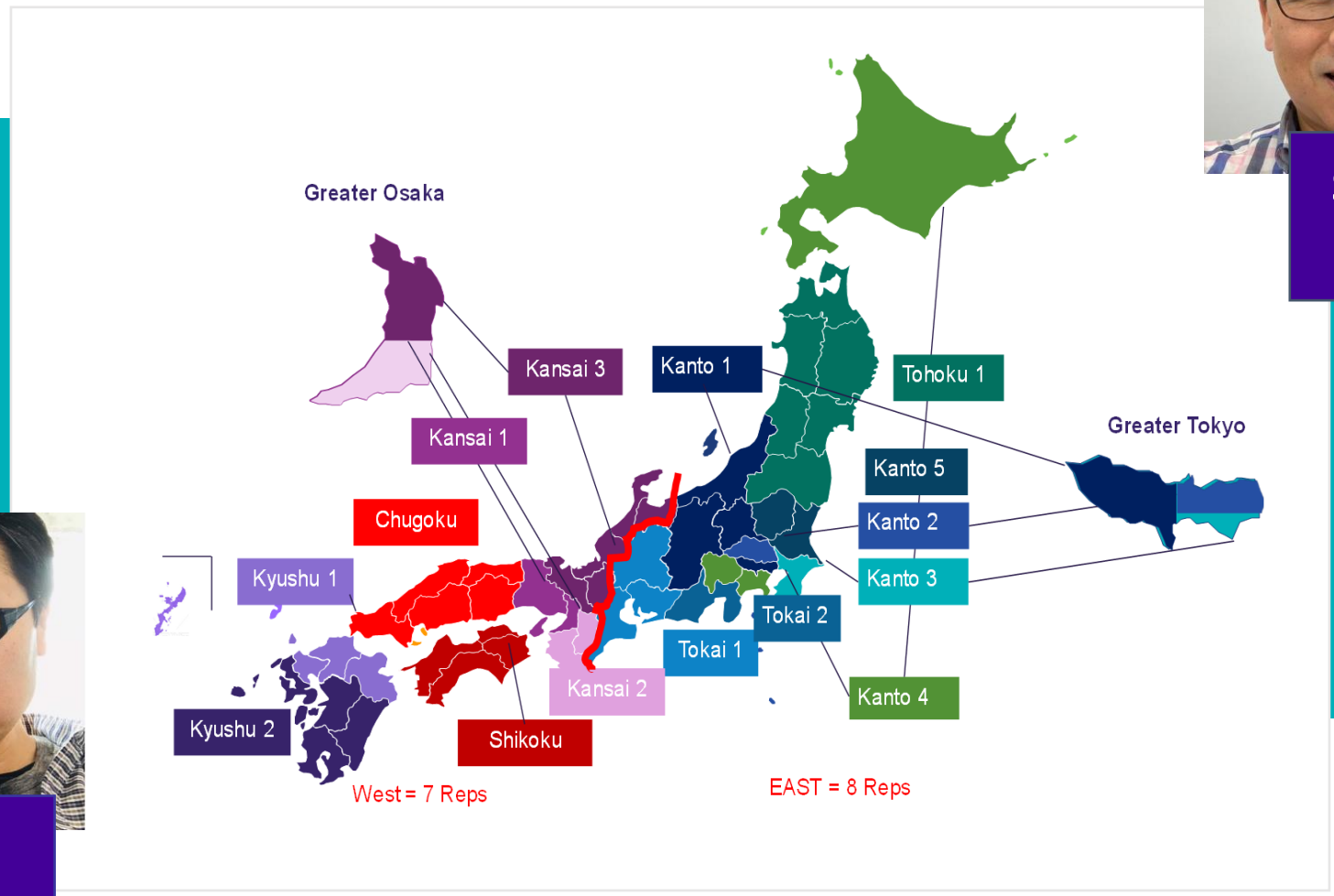
Sales Territories in Japan*

Sales Director
East Japan



Sales Director
West Japan

**If approved*

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Sara Bonstein
Chief Financial Officer

Financial Update & Closing Remarks

Pipeline

** As a condition of accelerated approval, Insmed plans to conduct an additional clinical study to support full approval.*

Financial Strength to Achieve Our Objectives

$641.9M
as of 6/30/20

Cash and Cash Equivalents

>3 Years
as of 9/30/20

Estimated Cash Runway

101M*
as of 6/30/20

Common Shares Outstanding

**Excludes stock options, unvested RSUs and shares underlying outstanding convertible notes*

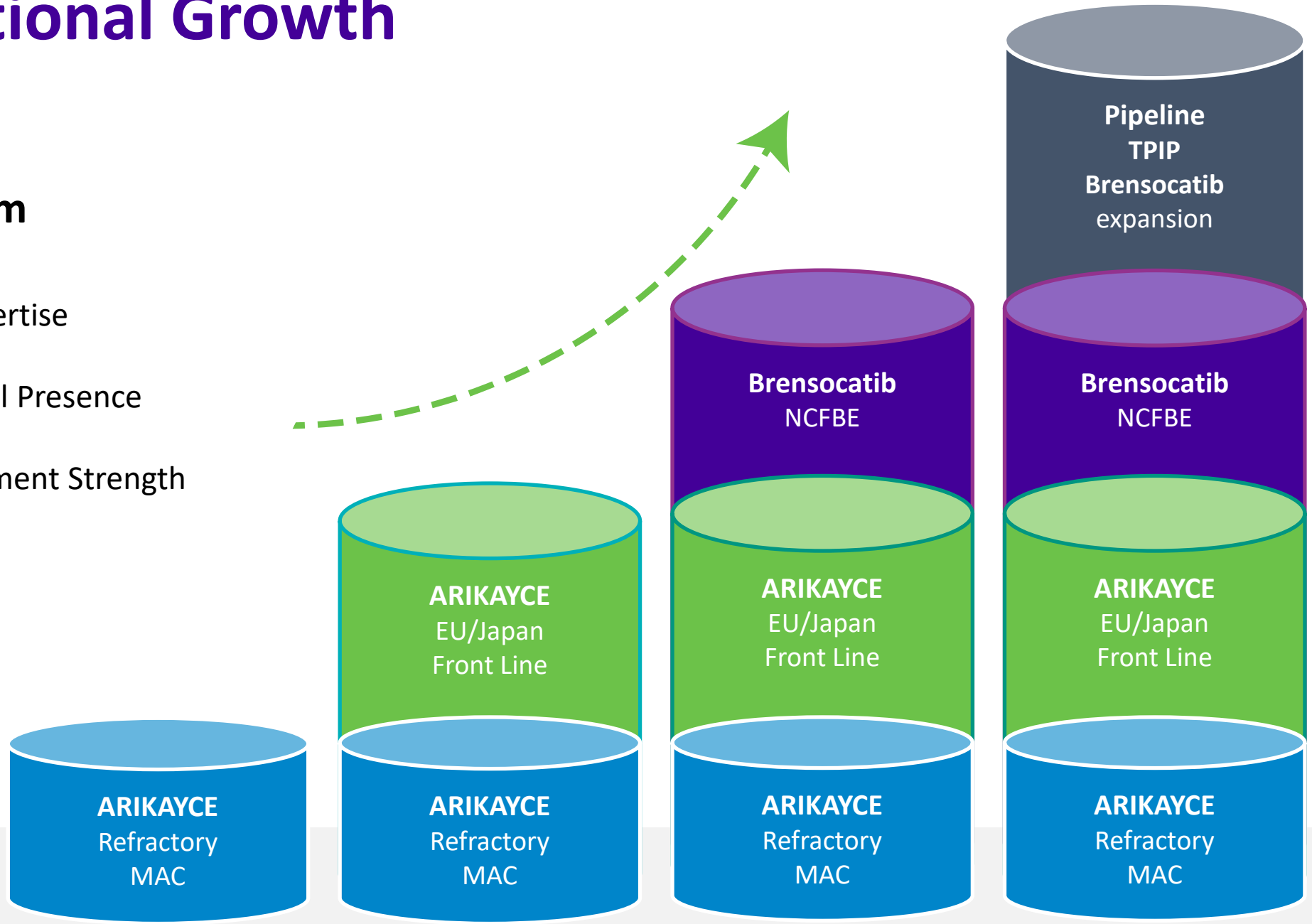
Transformational Growth Strategy

World Class Team

Research &
Development Expertise

Global Commercial Presence

Business Development Strength



Questions & Answers

We are committed to bringing forth technologies and medicines in therapeutic areas with the greatest potential to make a difference in patients' lives

Thank You

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