Insmed®
Promising Therapies Inspired by
Urgent Unmet Patient Needs

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 to be effective or safe for patients in ongoing and future clinical studies, including the ASPEN and STOP-COVID19 studies; 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 in the United States or European Union (amikacin liposome inhalation suspension and Liposomal 590 mg Nebuliser Dispersion, respectively), or to maintain U.S. or EU 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 the confirmatory post-marketing clinical trial required for full approval of ARIKAYCE; inability of the Company, PARI Pharma GmbH (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 the Company's product candidates; 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 are 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, trepostinil palmitil inhalation powder (TPIP) and the Company's other product candidates, due to the Company's limited experience in conducting preclinical development activities and clinical trials necessary for regulatory approval and the Company's potential inability to enroll or retain sufficient patients to conduct and complete the trials or generate data necessary for regulatory approval, among other things; 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 European Union 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 the Company's agreements or 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 third-party manufacturing facility approved by the FDA 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, June 30, 2020 and September 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.

What a Difference a Year Makes…

One Year Ago …	Today….
One Pillar	**Three** Pillars

ARIKAYCE

One Year Ago …	Today….
✓ Successful U.S. Launch in Refractory MAC Lung Disease	✓ International expansion: **EU Approval & Launch** + Japan Filing
	✓ **Strong recommendation for use** in international treatment guidelines*
	✓ **Frontline program** underway

Brensocatib

One Year Ago …	Today….
? A “lottery ticket”	✓ WILLOW data achieves statistical significance, resulting in **NEJM publication**
	✓ **Breakthrough Therapy Designation** from FDA and **PRIME** designation** by EMA
	✓ **Phase 3 ASPEN** study in Bronchiectasis **underway**
	✓ STOP-COVID19 **interim analysis complete** – awaiting final data

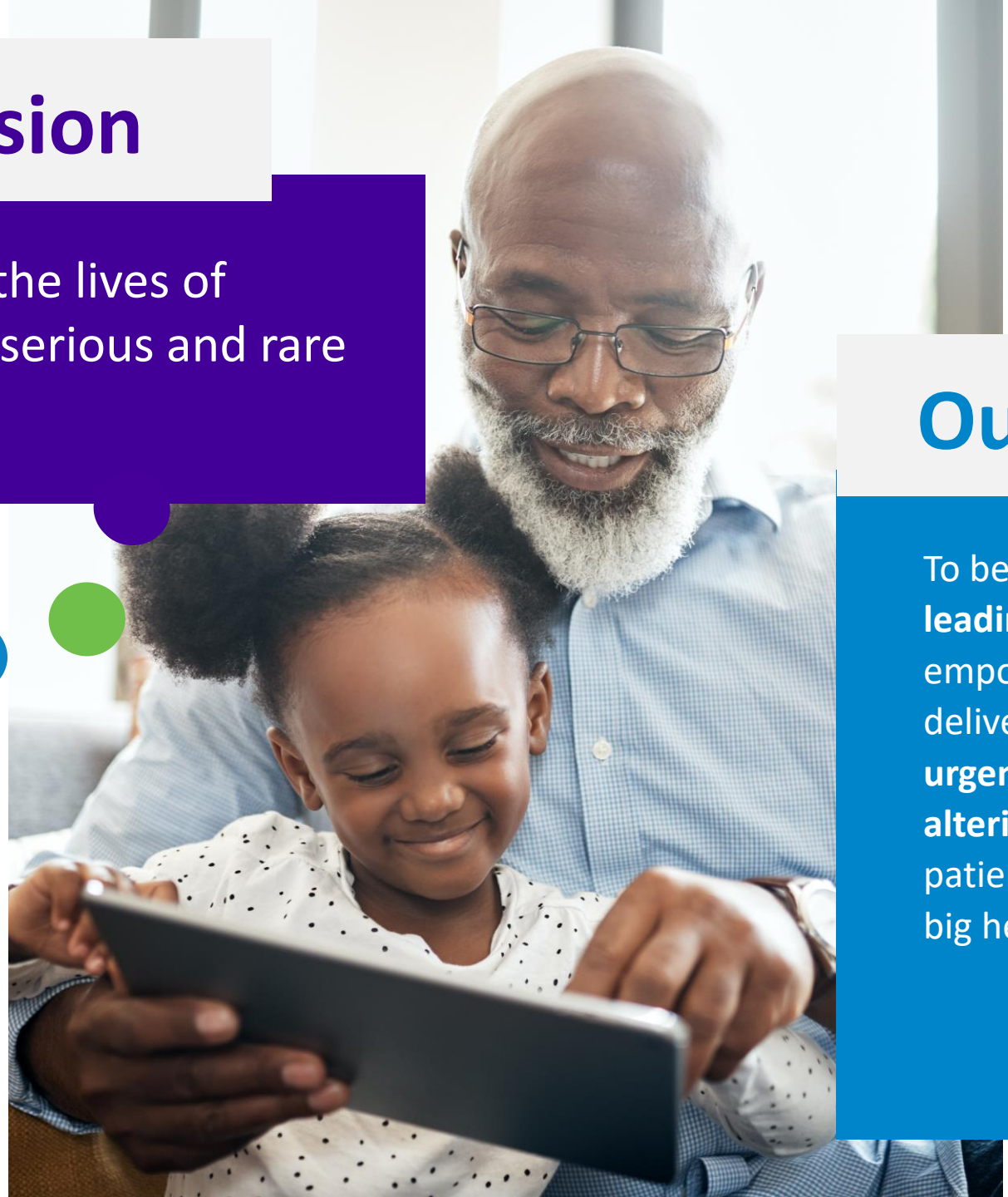
Treprostinil Palmitil Inhalation Powder (TPIP)

One Year Ago …	Today….
? Unknown…	✓ Animal data shows **disease modifying profile** in PAH models
	✓ Phase 1: First in human dosing & **trial completed**

** For treatment of patients with refractory MAC lung disease*
*** To our knowledge, first respiratory compound to receive PRIME designation*

Our Mission

To transform the lives of patients with serious and rare diseases



Our Vision

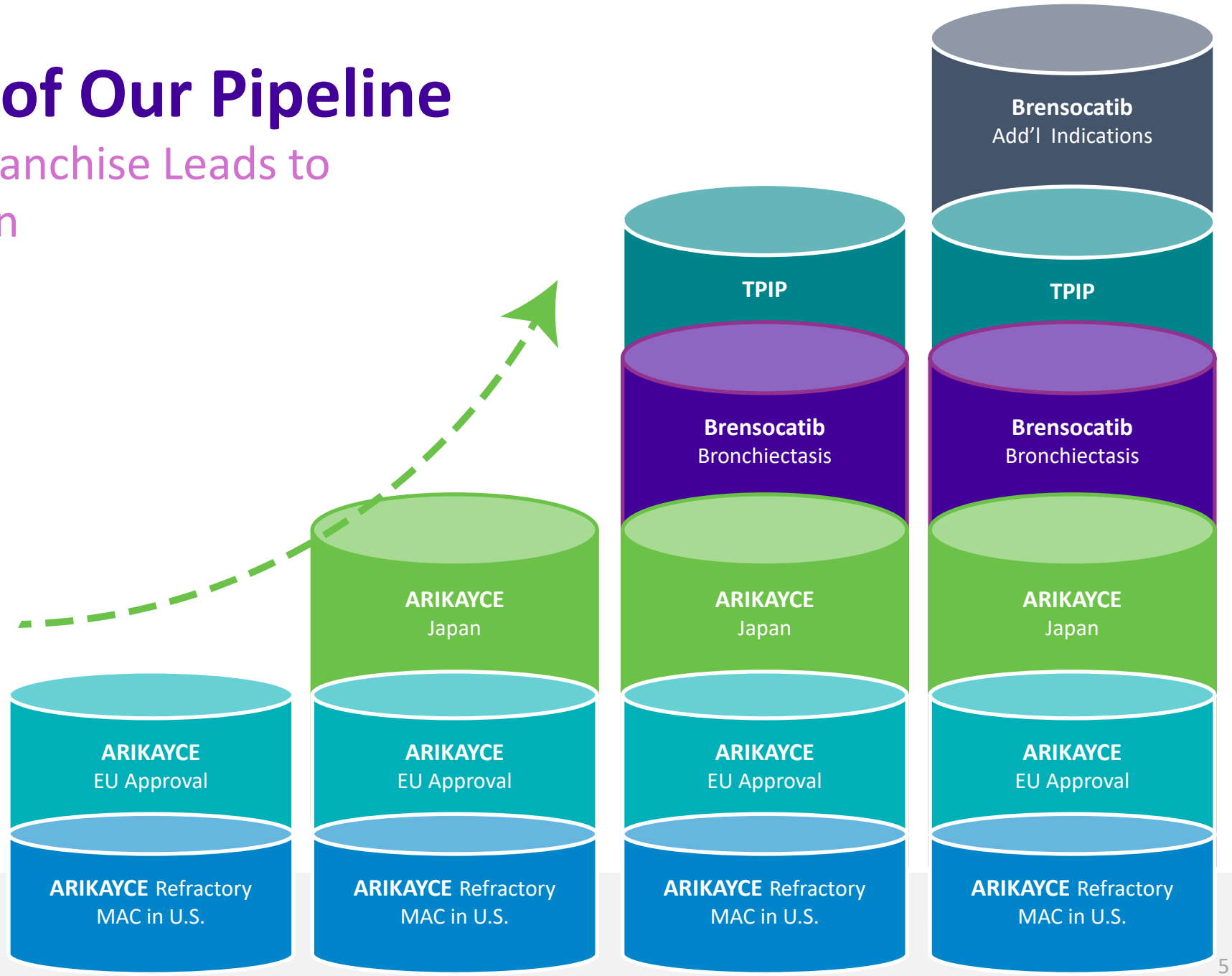
To be **a globally-recognized leading biotech company** that empowers great people to deliver, with a profound sense of **urgency and compassion, life-altering therapies** to small patient populations experiencing big health problems

Ongoing Success of Our Pipeline

Coupled with Our Core Franchise Leads to Compelling Value Creation

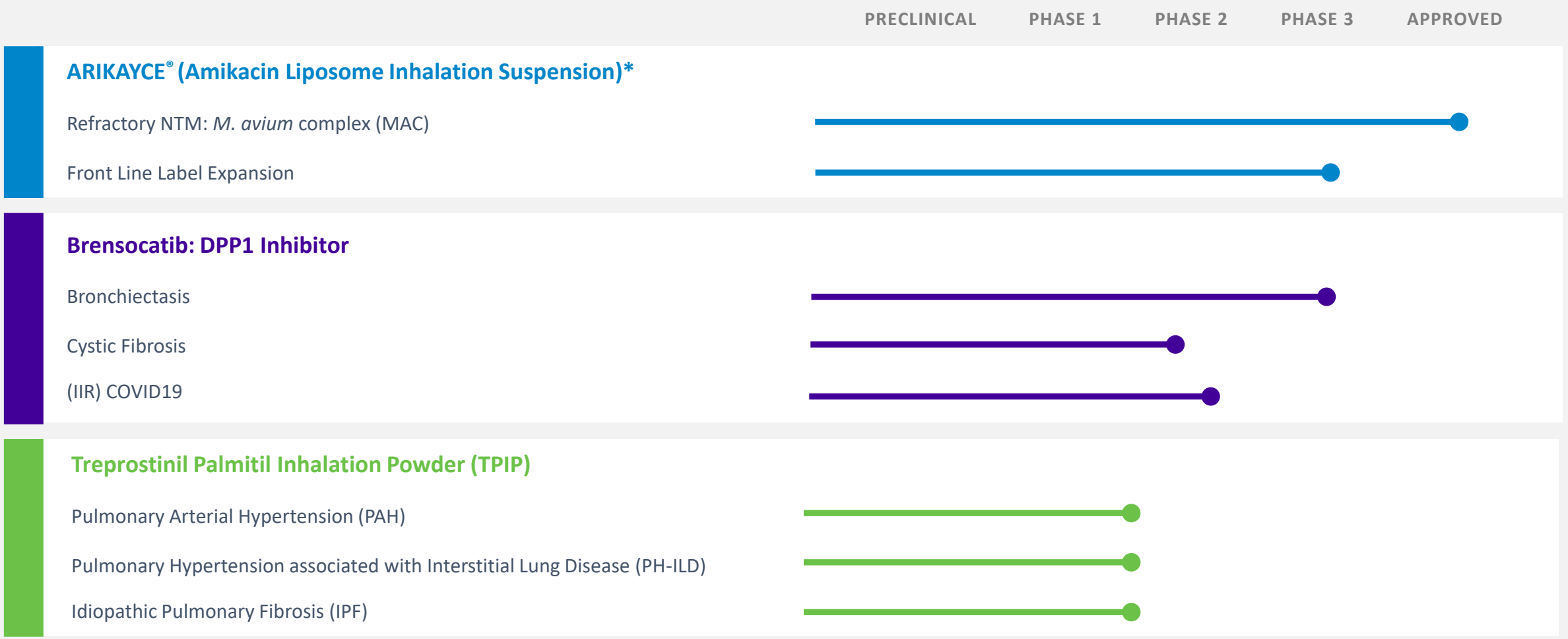
World Class Team

- Research & Development Expertise
- Global Commercial Presence
- Business Development Strength



Only approved product currently is ARIKYACE in both U.S. and EU

Three Pillars of Value Creation



** In the U.S., as a condition of accelerated approval, Insmed is conducting an additional clinical study to support full approval. Full approved has been granted by the European Commission.*

Treprostinil Palmitil Inhalation Powder (TPIP)

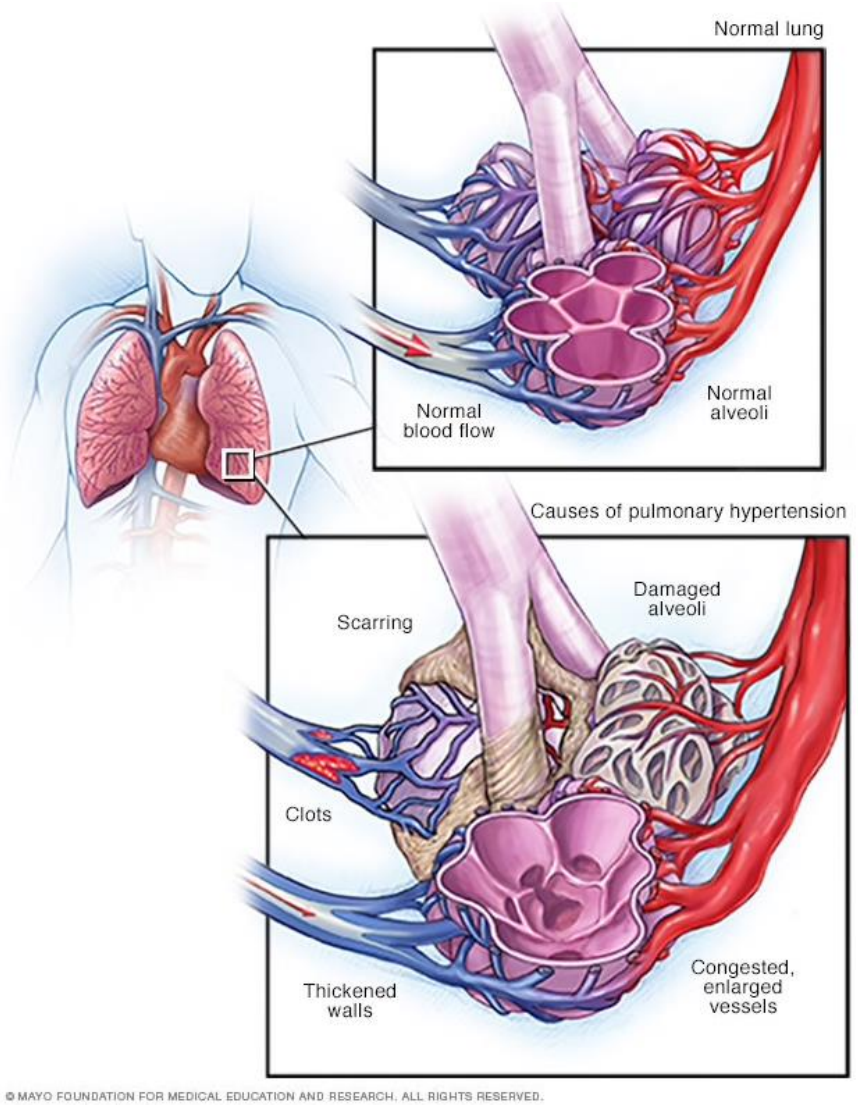
Harnessing the Full Potential

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
- Enabling greater and prolonged localized vasodilatory activity and disease-modifying efficacy due to high local concentrations in the lung



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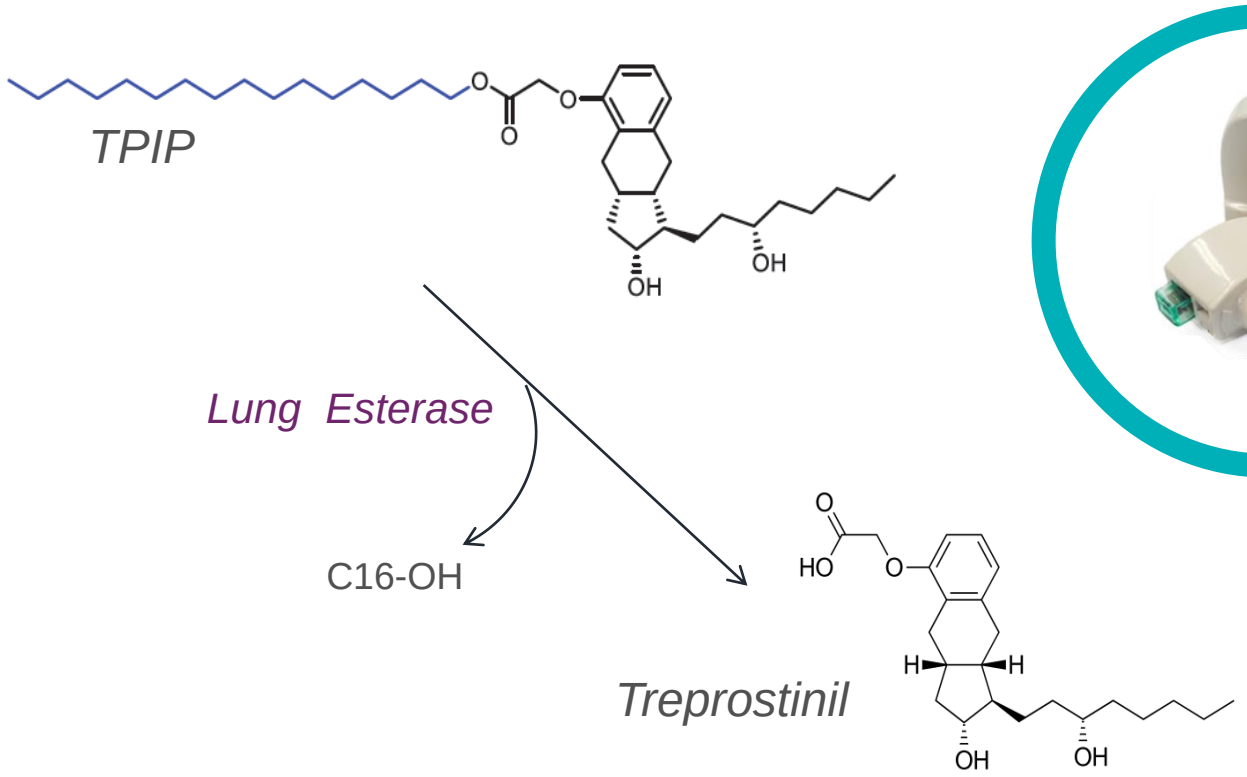
Treprostinil Palmitil Inhalation Powder (TPIP)

A Potentially Differentiated Prostanoid



Convenience

Portable, dry powder inhaler

QD or BID dosing

Potentially 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

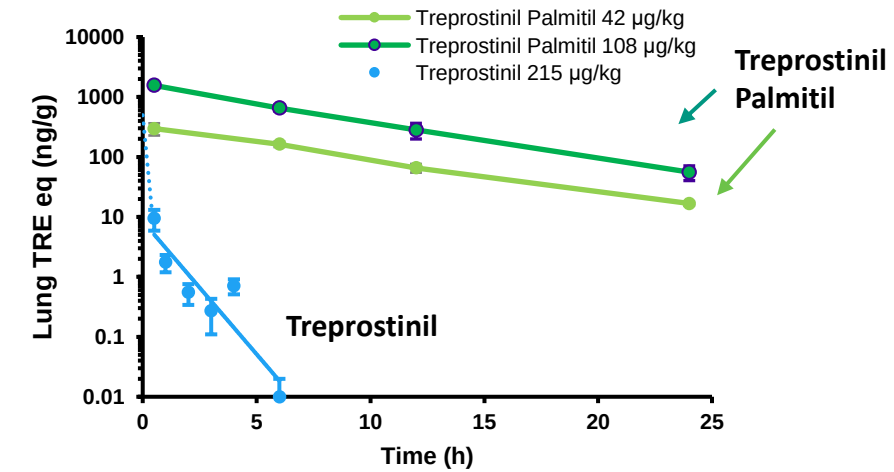
Potential disease modifier

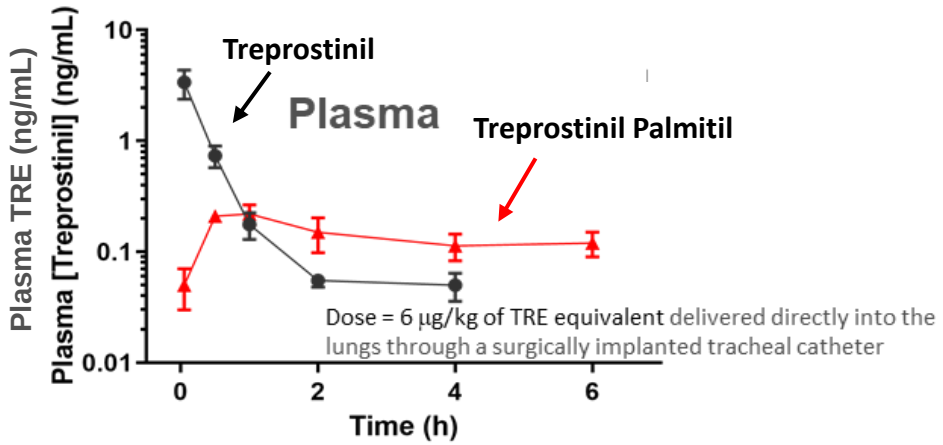
May be able to benefit the histopathologic process, whereas Tyvaso®, due to transient local exposure, cannot

Improved Pharmacokinetics:

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

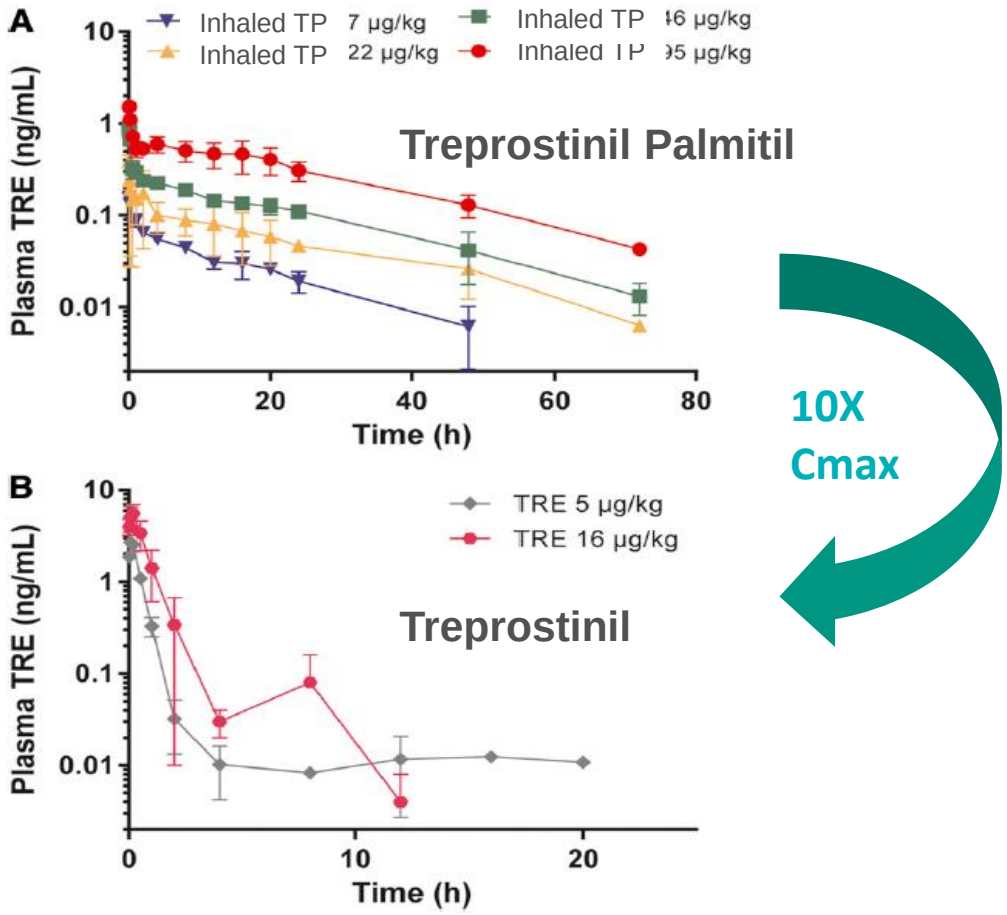
RAT Lung and Plasma Levels





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

DOG Plasma Levels



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

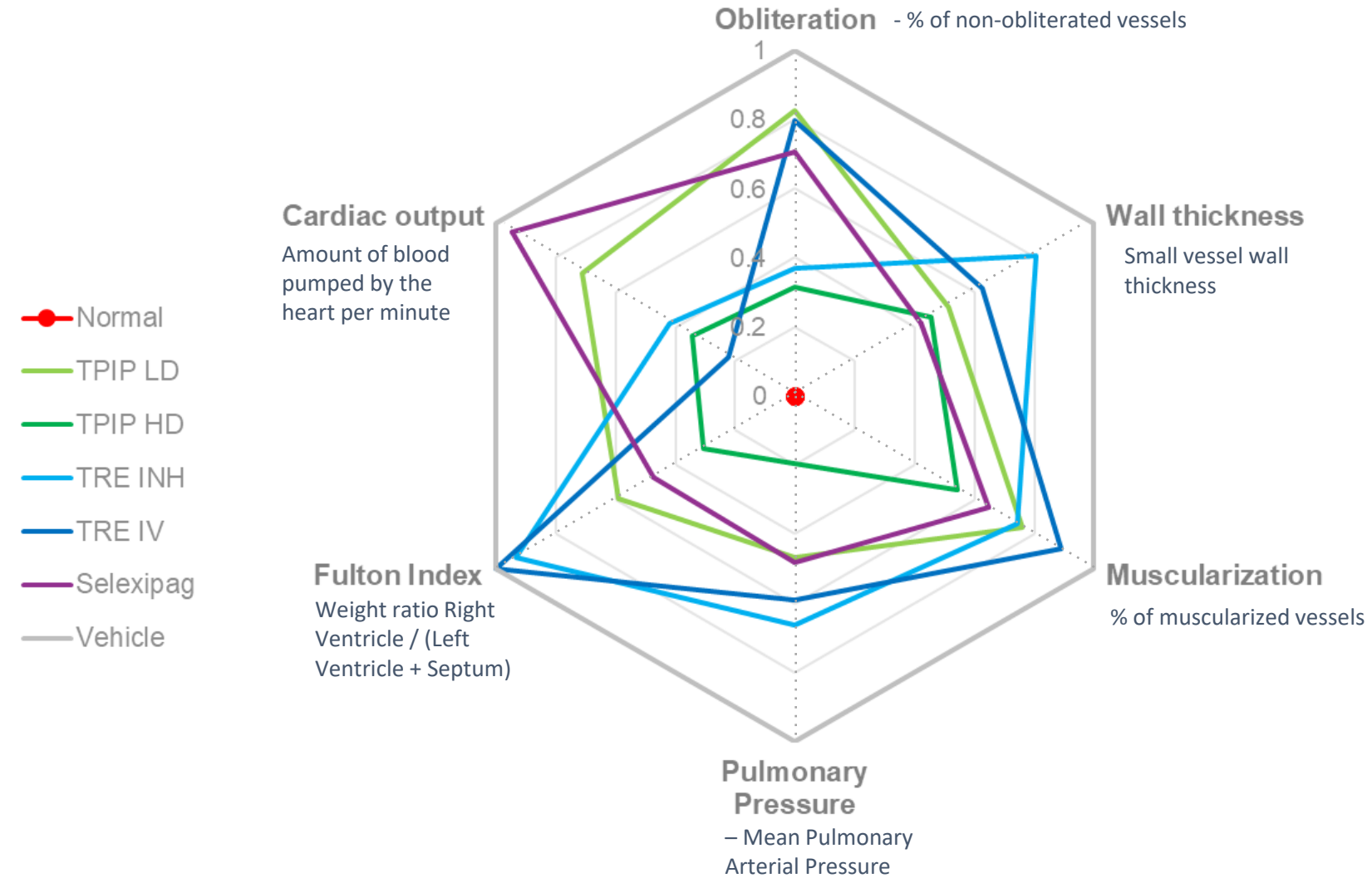
TPIP at High Dose

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

Parameter value =

(Value – Value of Normal) /

(Value of Vehicle – Value of Normal)



Data on file, Insmed Inc.

Comparison of Prostacyclin Analogs/Agonists

Approved Therapies vs. TPIP (investigational product candidate)

	Remodulin®	Tyvaso®	Orenitram®	Uptravi®	TPIP
Route of administration	IV or Subcutaneous	Inhaled (nebulized)	Oral	Oral	Inhaled **(dry powder)**
Dosing frequency	Continuous	4x per day	2x or 3x per day	2x per day	Once-to-twice daily
Dose-limiting side effects	Yes	Yes	Yes	Yes	To be evaluated in Phase 2 (encouraging preclinical data)
Efficacy in PAH (WHO Group 1)	Yes	Yes	Yes	Yes	
Proven to slow disease progression in PAH	No	No	Yes (but only as add-on to monotherapy)	Yes	To be evaluated in Phase 3 (encouraging preclinical data)
Efficacy in PH-ILD (WHO Group 3)	No data	Yes	No data	No data	Potential to pursue in parallel to PAH?
Efficacy in IPF	No data	TBC in upcoming TETON study	No data	No data	

Market Opportunity

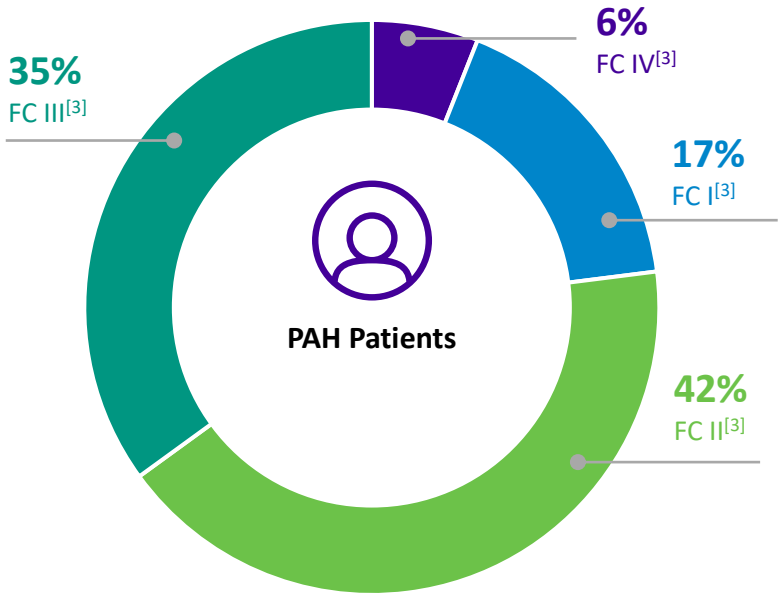
United Therapeutics' Viewpoint… Building On Their Precedent

Innovate → Grow → Expand

Current PAH Landscape

Prevalence of PH[1] WHO Group 1[2]

[in U.S. as of 2019]

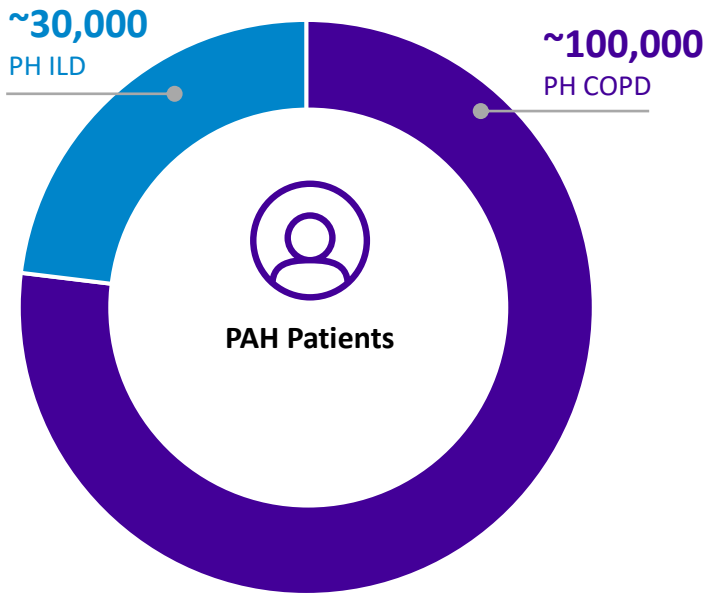


>45,000 Patients in U.S.

New PH Opportunities

Prevalence of PH ILD[4] & PH COPD[5] in WHO Group 3[2]

[in U.S. as of 2019]

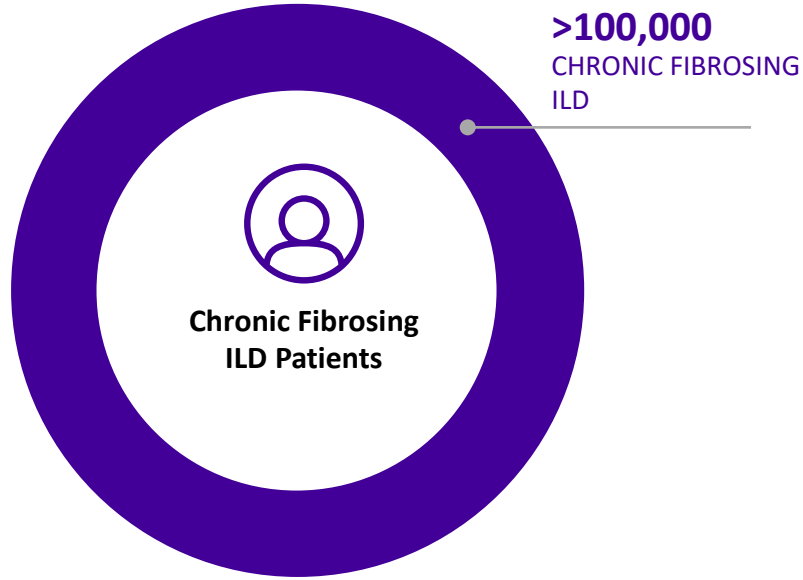


>130,000 Patients in U.S.

Opportunities Beyond PH

Prevalence of Chronic Fibrosing ILD[2]

[in U.S. as of 2019]



>100,000 Patients in U.S.

Slide information sourced from United Therapeutics November 2020 Corporate Presentation

[1] PH – Pulmonary Hypertension [2] Estimated patient populations based on United Therapeutics internal market research [3] The World Health Organization [WHO] created a system of four functional classes [FC] for patients with PAH. Class I means fewer symptoms and less restriction of activity. Class I symptoms are considered the least severe, and Class IV symptoms the most severe. [4] ILD=Interstitial Lung Diseases. [5] COPD] Chronic Obstructive Pulmonary Disease

Next Steps for TPIP Development

Phase 1 Complete

SAD/MAD Study

Objective
Establish PK and tolerability profile

Top line results expected in Q1 2021

Expect to Initiate Phase 2a in Early 2021

Exploratory, single dose study

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

Preliminary data expected in 2H 2021

Expect to Initiate Phase 2b in 2H 2021

Objective
Demonstrate hemodynamic effect size, inform design for pivotal program

Brensocatib

Pathogenesis of Bronchiectasis:

A 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

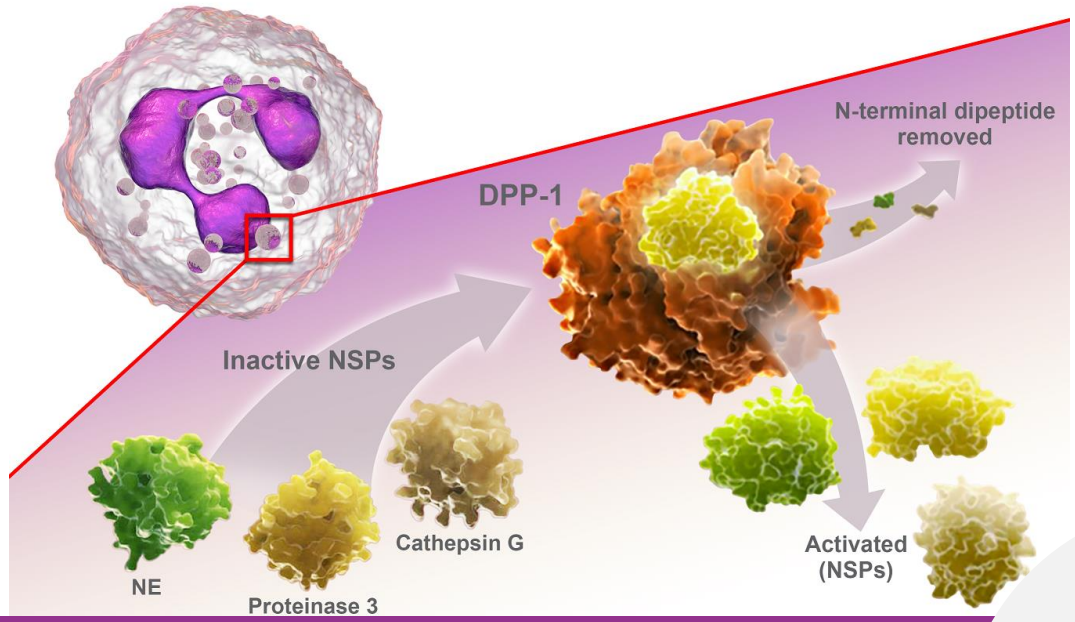
ABNORMAL MUCOCILIARY CLEARANCE

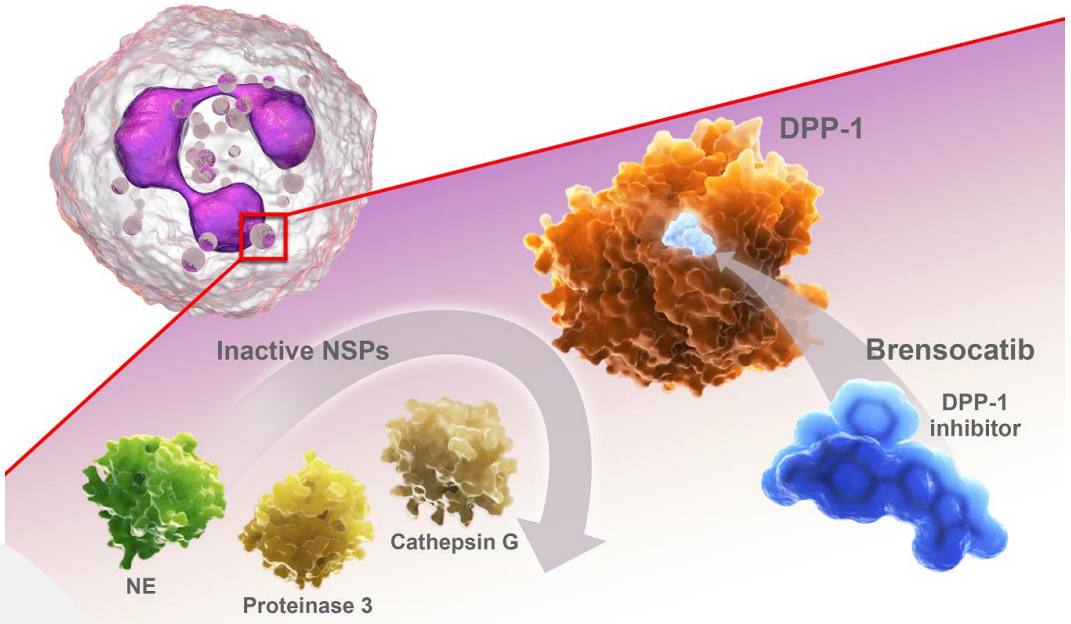
Structural damage impairs protective mucociliary clearance

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.

By Inhibiting the Activation of NSPs,

Brensocatib May Offer Applicability in a Range of Neutrophil-mediated Diseases





DPP1 is an enzyme that catalyzes the activation of NSPs in neutrophils when they are formed in the bone marrow

Neutrophils are the most common type of white blood cell and play an essential role in pathogen destruction and inflammatory mediation

Brensocatib

Novel once-a-day pill, reversible inhibitor of dipeptidyl peptidase 1 (DPP1)

Positive Phase 2 Data in bronchiectasis underscore potential of brensocatib

Strong rationale for further development in neutrophil-driven inflammatory conditions

WILLOW Study Success Recognized Worldwide

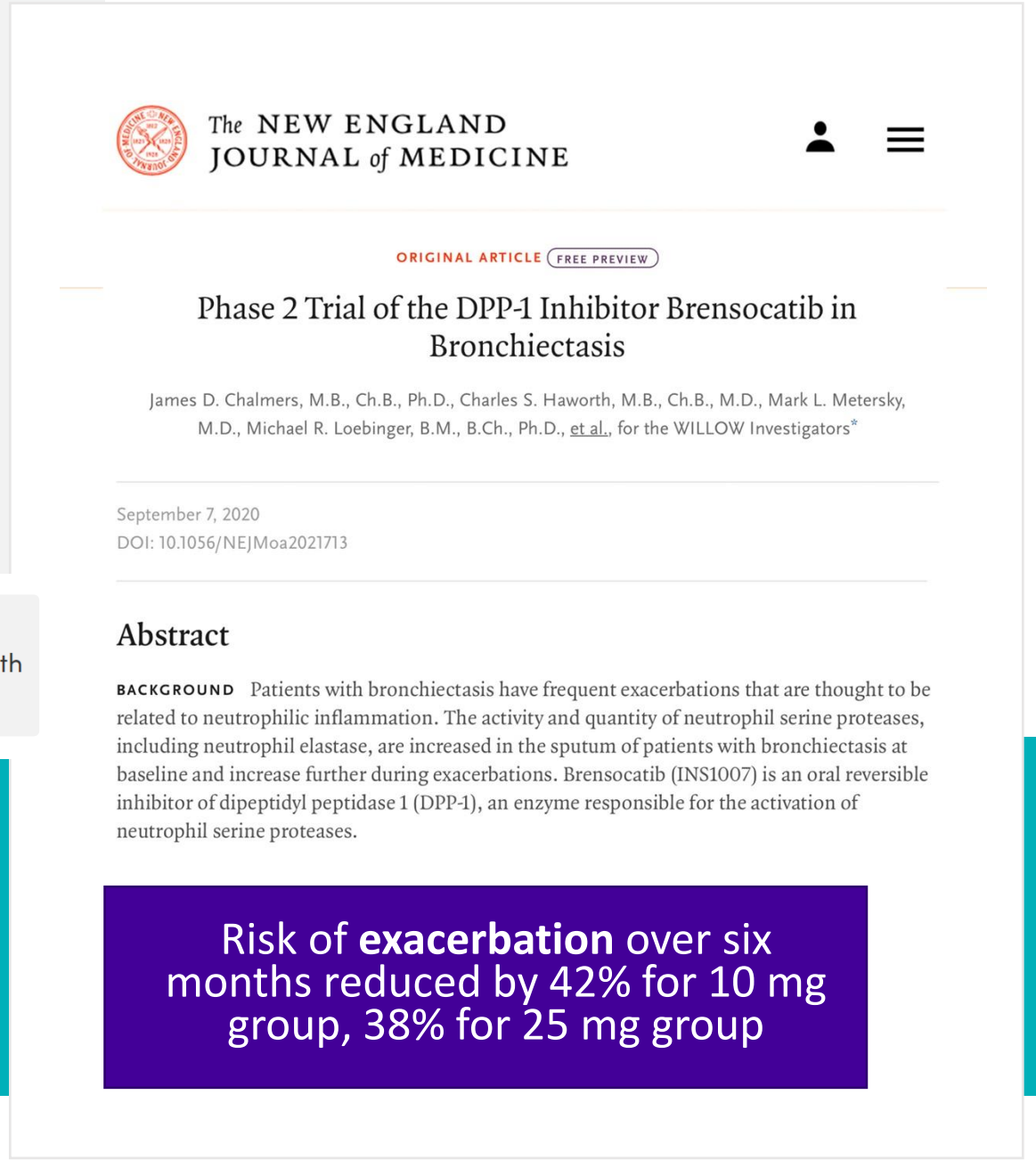
Insmed Receives FDA Breakthrough Therapy Designation for Brensocatib in Patients with Non-Cystic Fibrosis Bronchiectasis (NCFBE)

--Full Results from Phase 2 WILLOW Study of Brensocatib in NCFBE to be Presented at Virtual ATS Session on June 24, 2020--

Insmed Receives Priority Medicines (PRIME) Designation from European Medicines Agency (EMA) for Brensocatib in Patients with Non-Cystic Fibrosis Bronchiectasis (NCFBE)

Both 10 mg & 25 mg group met **primary endpoint** with **statistical significance**

Exacerbation-related hospitalization rates was higher & duration of hospitalization was longer in the placebo arm



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.

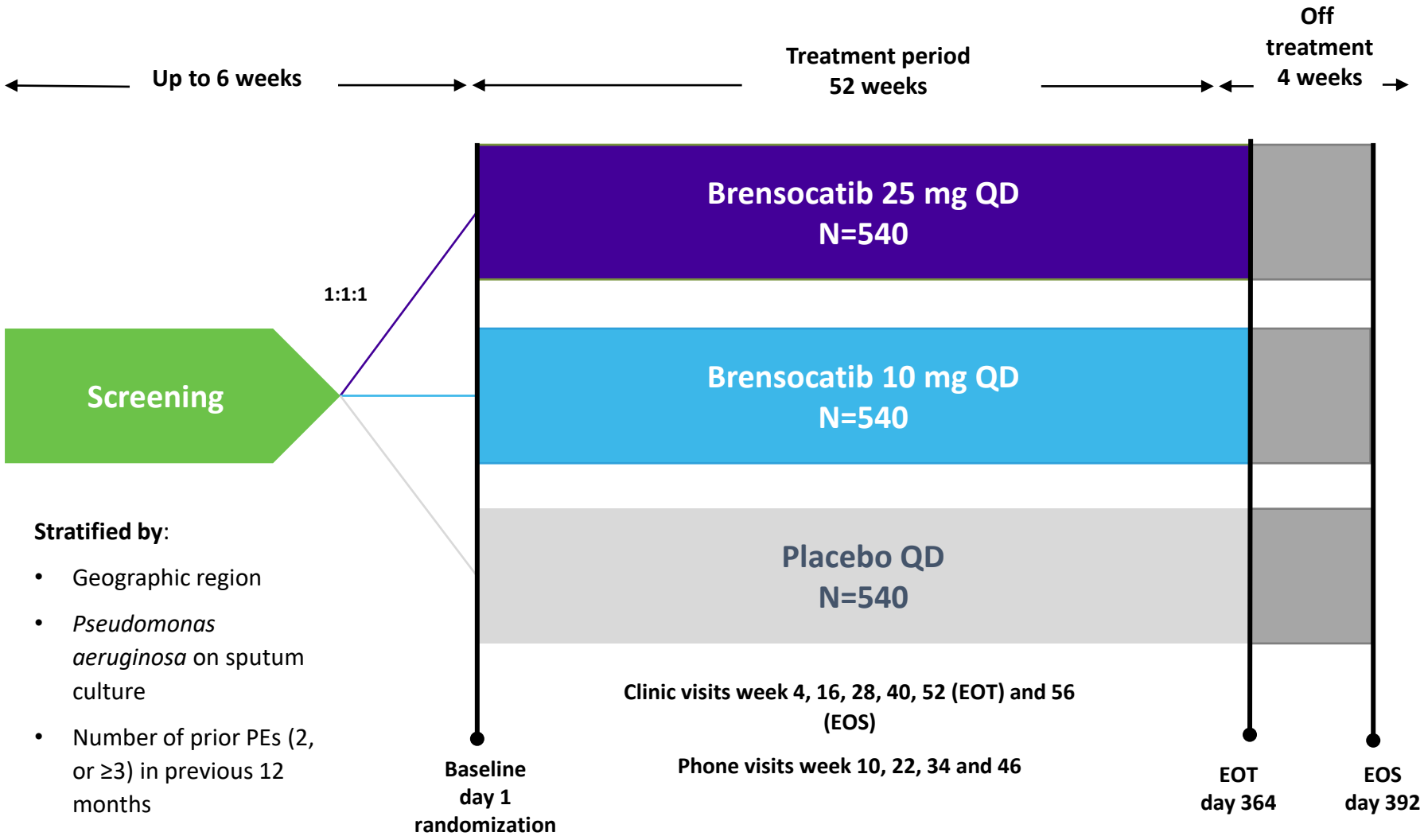
Risk of **exacerbation** over six months reduced by 42% for 10 mg group, 38% for 25 mg group

Strong Phase 2 Data Lead to Confidence in Phase 3

WILLOW vs. ASPEN Trial Details

	WILLOW	ASPEN
Sample Size	**256 Pts** (~85 pts/arm)	**1,620 Pts** (540 pts/arm)
Powering Assumptions	80% for a 40% reduction	90% for a 30% reduction
Robust Definition of Pulmonary Exacerbation	Consistent	Consistent
Duration of Therapy	6 months	12 months
Primary Endpoint	Time to first exacerbation	Rate of pulmonary exacerbation
Key Secondary Endpoint	Rate of pulmonary exacerbation	Time to first exacerbation

ASPEN Phase 3 Study Design



40 Countries

~480 sites

Patient Enrollment Initiated December 2020

EOS, end of study; EOT, end of treatment; QD, once daily; PE, pulmonary exacerbation

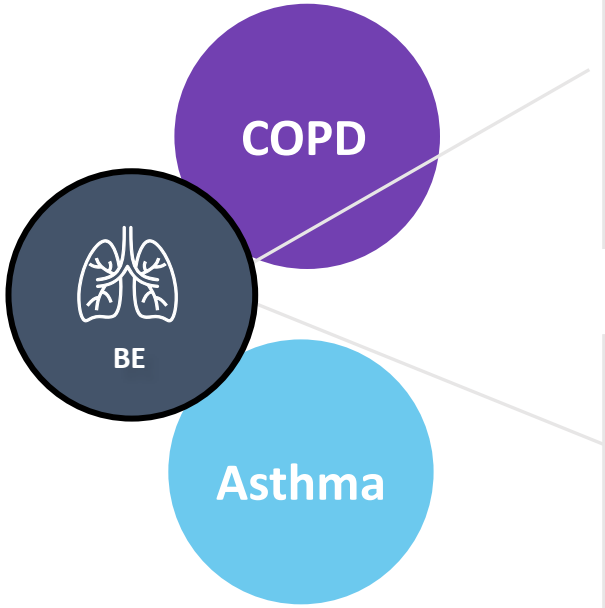
The Unmet Need in Bronchiectasis

No Available Treatment Options for 1.7M – 6M Diagnosed Bronchiectasis Patients

Total Diagnosed BE Patients

~340K – ~520K *	U.S.
~350K – ~500K **	EU5†
~1M to ~5M	Asia-Pacific◊
~1.7M – 6M	TOTAL

Additional Market Opportunity



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

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

**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; ◊ Studies indicate lack of consensus on prevalence rates. 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*

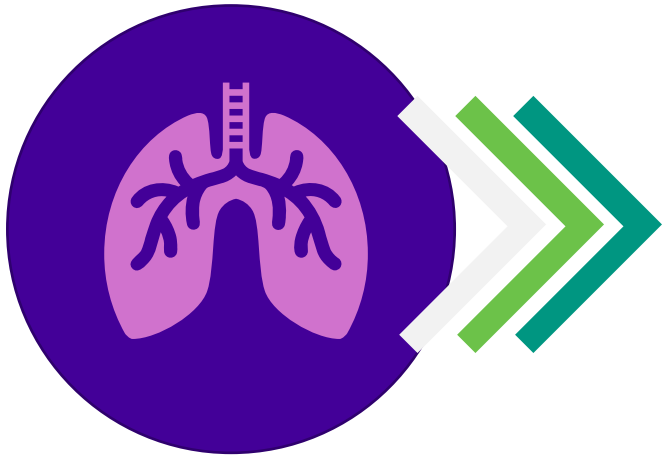
1. Agusti, A., Calverley, P.M., Celli, B. et al. Characterisation of COPD heterogenecity in the ECLIPSE cohort. Respir Res. 2010; 11: 122

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.

Strategically Building a Portfolio of Treatments for Neutrophil-mediated Diseases

Bronchiectasis Program



Bronchiectasis to Serve as 'Launch Pad' for Neutrophil-mediated Portfolio

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.

ARIKAYCE

Not for promotional use

First-in-Disease Therapy

for Refractory MAC Lung Disease Gaining Global Momentum

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

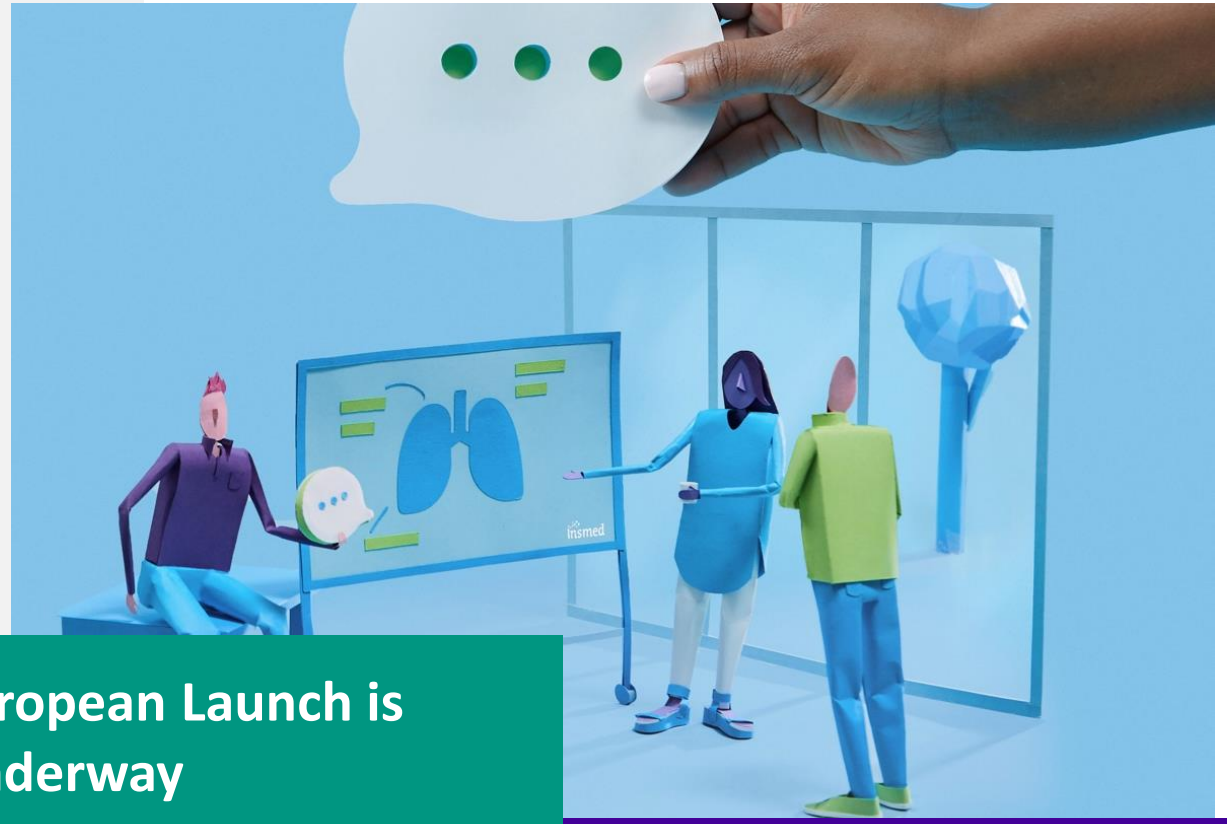
PULMOVANCE® liposomal technology delivers drug directly to the lungs

Prolongs release of amikacin in the lungs while limiting systemic exposure

Not for promotional use

Building on the Success of the Launch with Recent Advancements

- International guideline inclusion with a **strong recommendation** for use [1]
- U.S. sNDA approval adding **Culture Conversion Data** Beyond 12 Months to Label
- **Approved in Europe in late 2020**
- **Planned expansion into Japan by mid-2021**



European Launch is Underway

Reimbursement achieved in Germany

Netherlands Healthcare Assessment **recommends reimbursement**

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

[1] For adult patients with limited or no treatment options after six months of failed treatment.

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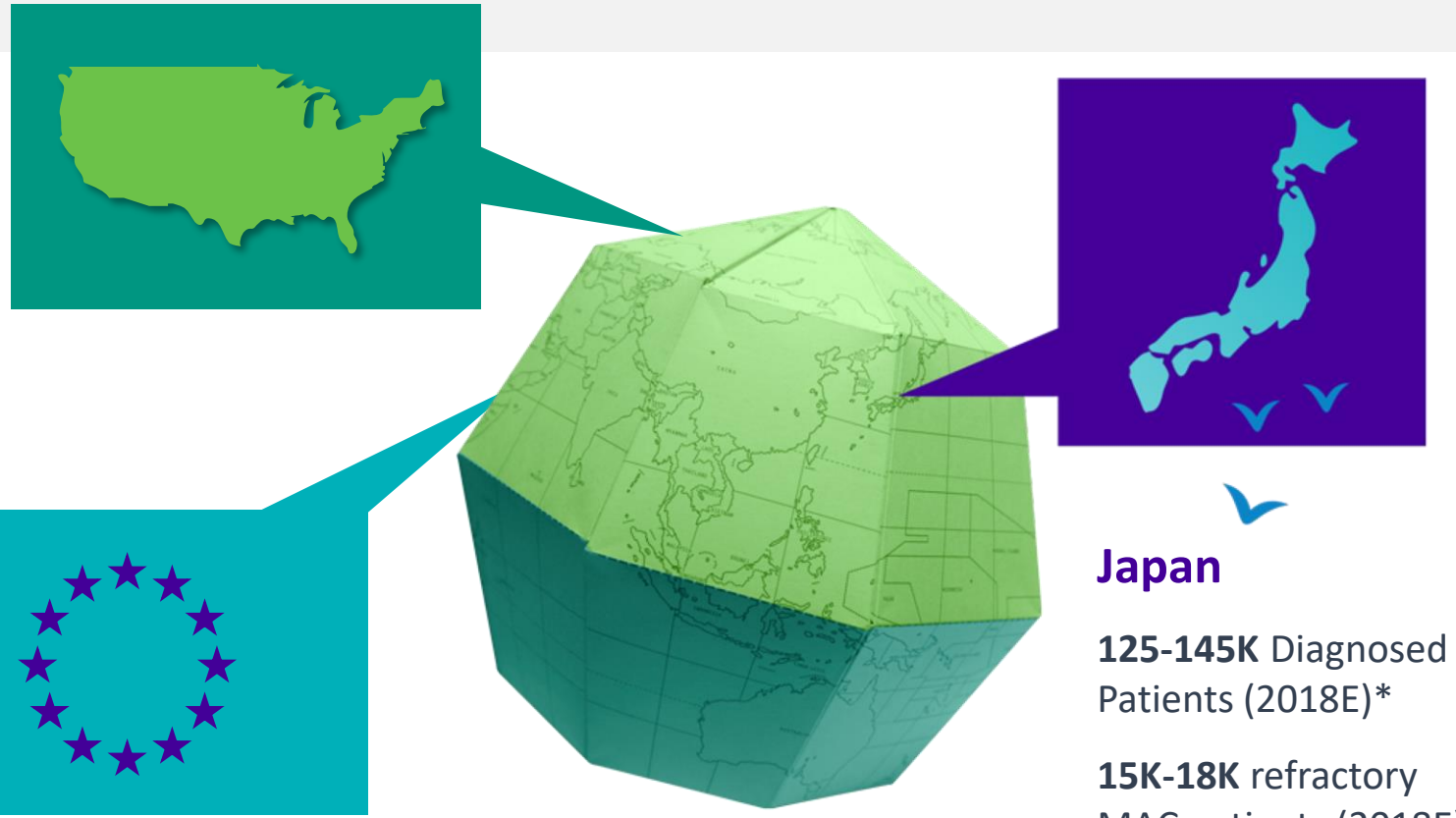
Clear Vision for Label Expansion & Global Market

U.S.

95-115K Diagnosed NTM Patients (2019E)*

12K-17K refractory MAC patients (2019E)*



EU† Market

14K Diagnosed NTM Patients (2018E)*

1,400 refractory MAC patients (2018E)*

Japan

125-145K Diagnosed NTM Patients (2018E)*

15K-18K refractory MAC 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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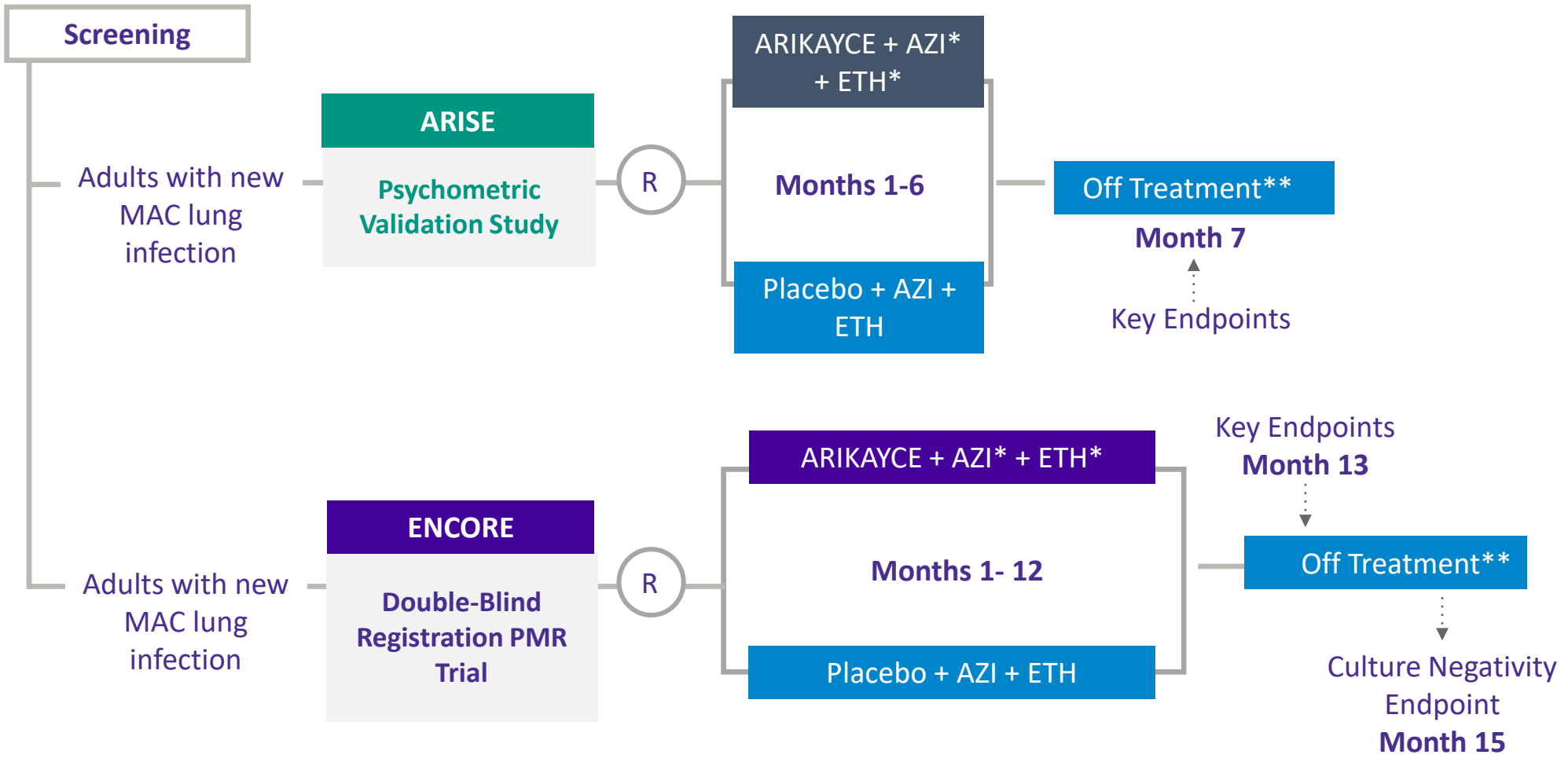
ARIKAYCE Front Line Program Ongoing

Trial Summary



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

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)

Not for promotional use

Financial Strength to Achieve Our Objectives

$588.8M
as of 9/30/20

Cash and Cash Equivalents

102M*
as of 9/30/20

Common Shares Outstanding

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

Building on Our Global Momentum to Create Shareholder Value

2018

ARIKAYCE
Top 10 Launch

2019

Brensocatib
Completed enrollment in WILLOW

2020

ARIKAYCE
EU launch

Brensocatib
NEJM publication of WILLOW data

TPIP
Positive preclinical data & initiated clinical studies

2021 (anticipated)

ARIKAYCE
Japan approval / launch

Brensocatib
Development in additional indications

TPIP
Data in P2a & advance into P2b

Anticipated Near-Term Events

Support All Three Pillars of Value Creation Strategy

ARIKAYCE: Commercial Expansion And Label Extension

EU Approval And Launch	4Q 2020	☑
Frontline Program Initiation (ARISE / ENCORE)	YE 2020	☑
Japan Approval	1Q 2021	☐
Japan Launch	Mid-2021	☐

Brensocatib: Unlocking Options For Neutrophil-mediated Diseases

ASPEN Trial Initiation (P3 Bronchiectasis)	YE 2020	☑
STOP-COVID19 Data	1H 2021	☐
Cystic Fibrosis PK Study Initiation	Mid-2021	☐

TPIP: Changing The Prostacyclin Paradigm

Phase 1 Data (PK and safety)	1Q 2021	☐
Phase 2a Trial Initiation	1Q 2021	☐
Phase 2a Preliminary Data	2H 2021	☐
Phase 2b Trial Initiation	4Q 2021	☐

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

Investor Relations
investor.relations@insmed.com
646-351-0954

Powered by Purpose

Appendix

Robust Development Cycle Capabilities

with Clear Commercialization Path

Pipeline Highlight: Populations with Urgent Unmet Patient Needs

Drug Discovery Research

- ARIKAYCE®
- Treprostinil Palmitil Inhalation Powder (TPIP)

Business Development *(Licensing and Acquisition)*

- Brensocatib

Clinical Development

Management of the Regulatory Pathway

Global Commercialization

An advanced research and development pipeline has potential to **address the unmet needs of patients with serious and rare diseases**.

Successfully brought a first-in-disease therapy independently from concept to market and has expertise in **every stage of the development cycle**.

Insmed Differentiated

With ARIKAYCE, Brensocatib and TPIP, we have developed three value drivers, plus

Robust Pipeline and Development Capabilities:

- Clinical Development
- Drug Discovery Research
- Business Development
- Management of the Regulatory Pathway
- Global Commercialization

Strong expertise and potential across the development cycle. Many companies succeed at part of this equation. We do it all, well.

Protected with Significant, Global IP

Brensocatib

US, Europe, Japan, China
In-licensed compound patent exclusivity until 2035

Non-CF Bronchiectasis Treatment Methods patent application filed, projected to expire in 2037

Oral formulation and ANCA vasculitis patent applications filed, projected to expire in 2039

PTE could extend patent term of select US patents by 3-5 years for first approved indication.

ARIKAYCE

U.S. multiple issued patents to 2035 *12-year regulatory exclusivity*

EU patent to 2035
10-year regulatory exclusivity

Japan patent exclusivity to 2035

Approval has been granted in both U.S. and EU for ARIKAYCE

TPIP

US 4 patents issued to 2034

Japan, EU, Australia, China
counterpart patents issued to 2034

Manufacturing

Brensocatib

API

ESTEVE

Spain
300kg capacity

Drug Product

ThermoFisher SCIENTIFIC

Canada
2mm capacity

ARIKAYCE

API

therapure BIOMANUFACTURING

Canada
200L capacity

Drug Product

patheon

UK
450L capacity

TPIP

API

CHIROGATE

Taiwan
50g capacity

Drug Product

Lonza

US
10,000 capsules capacity

• WILLOW STUDY •

Data Demonstrate Potential for First-in-Class Bronchiectasis Treatment

Randomized, double-blind, Phase 2 study; tested 10 mg, 25 mg and placebo

CT scan-confirmed NCFBE; ≥2 pulmonary exacerbations in past 12 months

Risk of **exacerbation** over six months **reduced by 42%** for 10 mg group, **38%** for 25 mg group

Primary and secondary **endpoints met** with **statistical significance**

Data demonstrate **positive correlation** between **neutrophil elastase reduction** and risk of **exacerbation** in 10mg group

ASPEN Phase 3 program initiated in late 2020

AstraZeneca Exercises First Option in License Agreement Validating Potential for COPD and Asthma

2020: PRIME Designation (EMA) & Breakthrough Therapy Designation (FDA) Granted

Willow Study Summary

Study Schema

NCFBE confirmed by CT scan

With documented history of ≥2 pulmonary exacerbations in prior 12 months

Randomized 1:1:1
Double Blind
256 Patients

Screening up to 6 weeks for sputum evaluation and periodontal evaluation

- **Brensocatib** 10 mg once daily
- **Brensocatib** 25 mg once daily
- **Placebo**

Primary Efficacy: Time to first pulmonary exacerbation

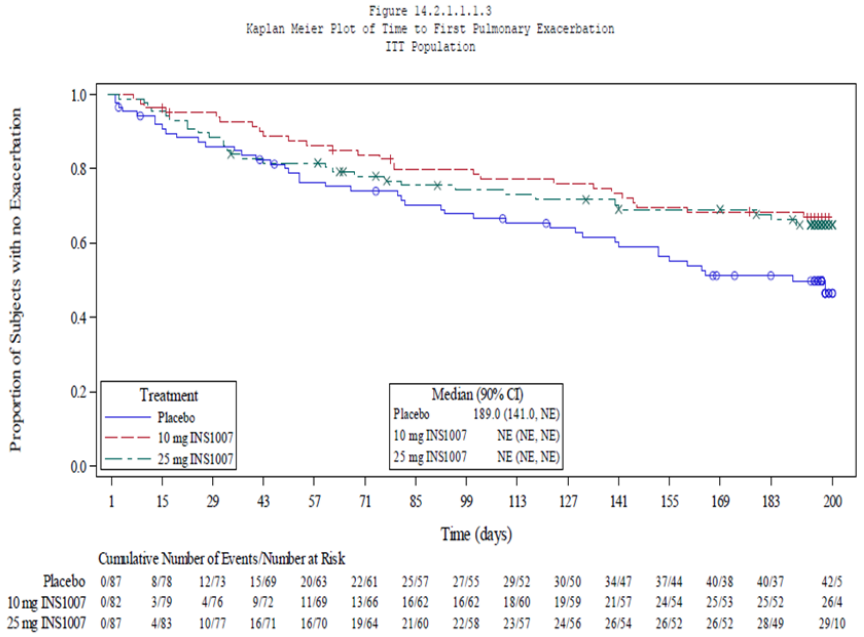
Secondary Efficacy:

- Rate of pulmonary exacerbations*
- Change in the Respiratory Symptoms Domain Score of the Quality of Life
- Bronchiectasis questionnaire
- Change in post-bronchodilator FEV1
- Change in concentration of active neutrophil elastase in sputum

Safety: Tolerability (e.g., AEs and AEs of special interest – infection, skin, and periodontal conditions)

Efficacy

Top-Line Data: WILLOW Study Achieves Primary Endpoint



Risk of having an exacerbation over the course of six months reduced by up to 40% with Brensocatib

Time to First Exacerbation vs. Placebo	Brensocatib 10 mg	Brensocatib 25 mg
p-value ^	0.027	0.044
Hazard Ratio	0.58	0.62
p-value ^	0.029	0.046

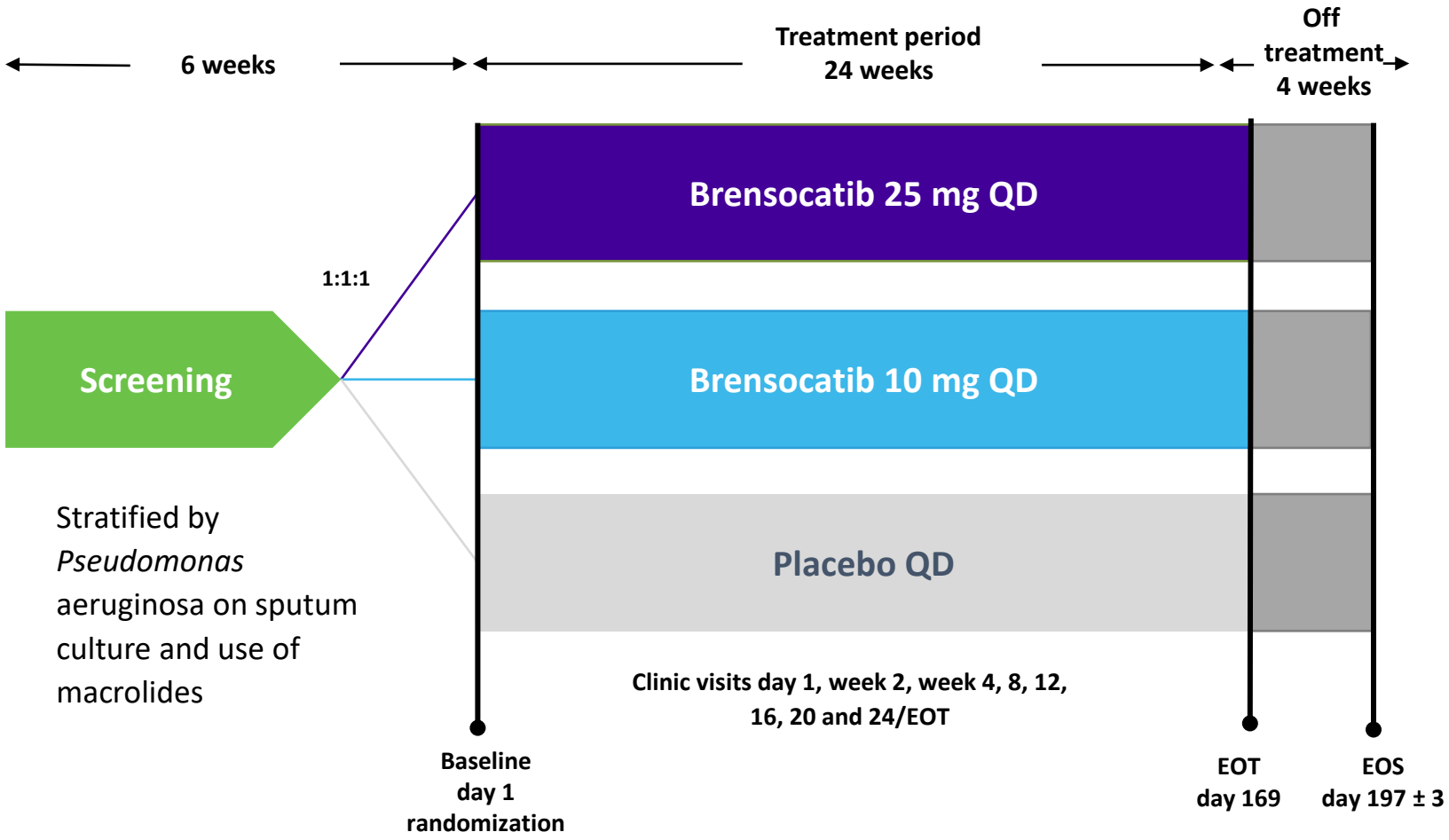
Safety

Brensocatib was generally well-tolerated in the WILLOW study

Most common adverse events (AEs) in patients treated with Brensocatib were cough, headache, sputum increase, dyspnea, fatigue, and upper respiratory tract infection

	Placebo	Brensocatib 10 mg	Brensocatib 25 mg
Rates of (AEs) leading to discontinuation	10.6%	7.4%	6.7%
Rates of adverse events of special interest (AESIs)			
Periodontal disease	2.4%	7.4%	10.1%
Hyperkeratosis	0%	3.7%	1.1%
Infections that were considered AESIs	18.8%	16.0%	16.9%

Brensocatib Phase 2 WILLOW Study Design



Primary objective

Time to first exacerbation over 24 weeks in patients with non-cystic fibrosis bronchiectasis (NCFBE)

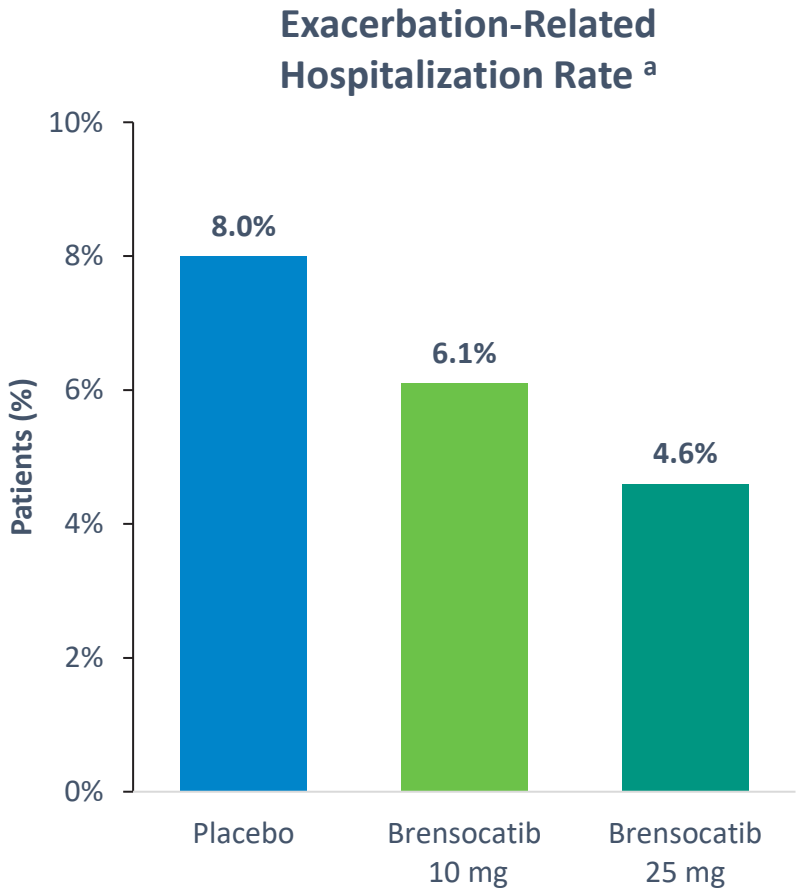
Secondary objective

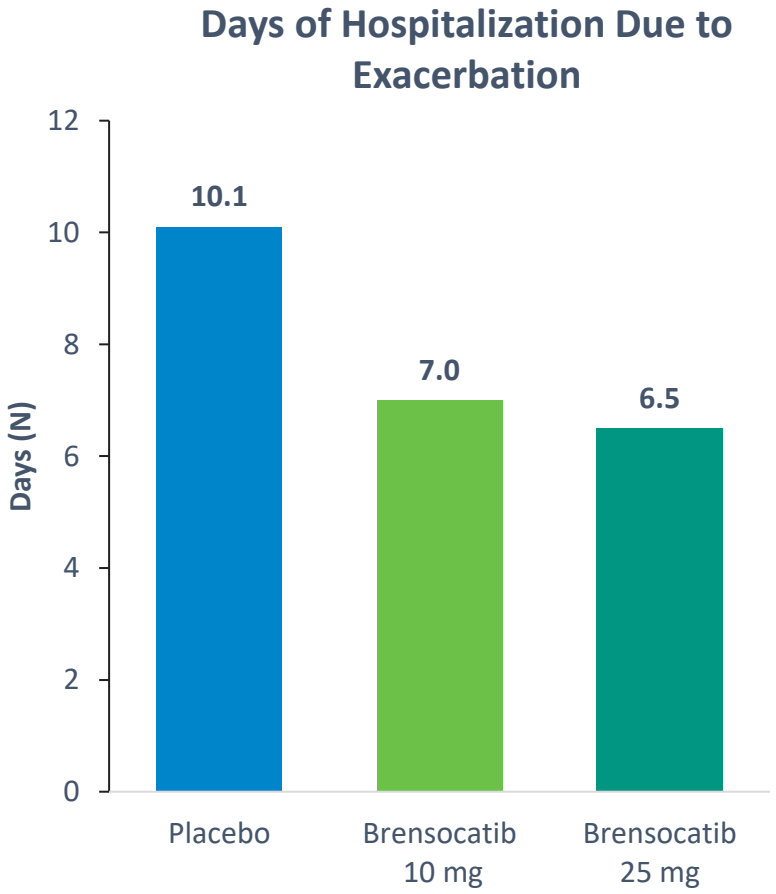
- Pulmonary exacerbation rate over 24 weeks
- Change in QOL-Bronchiectasis questionnaire respiratory symptoms domain over 24 weeks
- Change in post-bronchodilator ppFEV1 over 24 weeks
- Change in sputum NE activity from pretreatment to on-treatment

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

WILLOW:

Hospitalization Rate due to Exacerbations





Exacerbation-related hospitalization rates was higher & duration of hospitalization was longer in the placebo arm

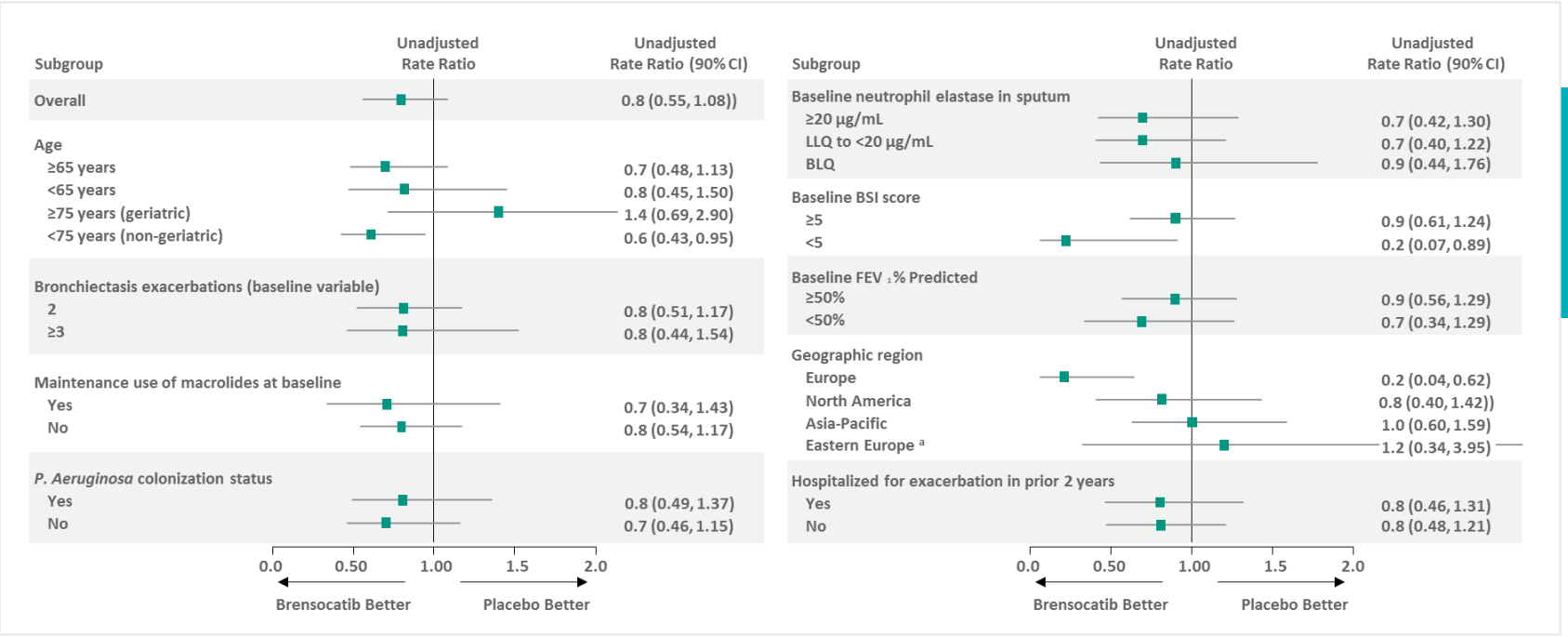
[a] *Exacerbations cited by investigator as primary reason for hospitalization.*

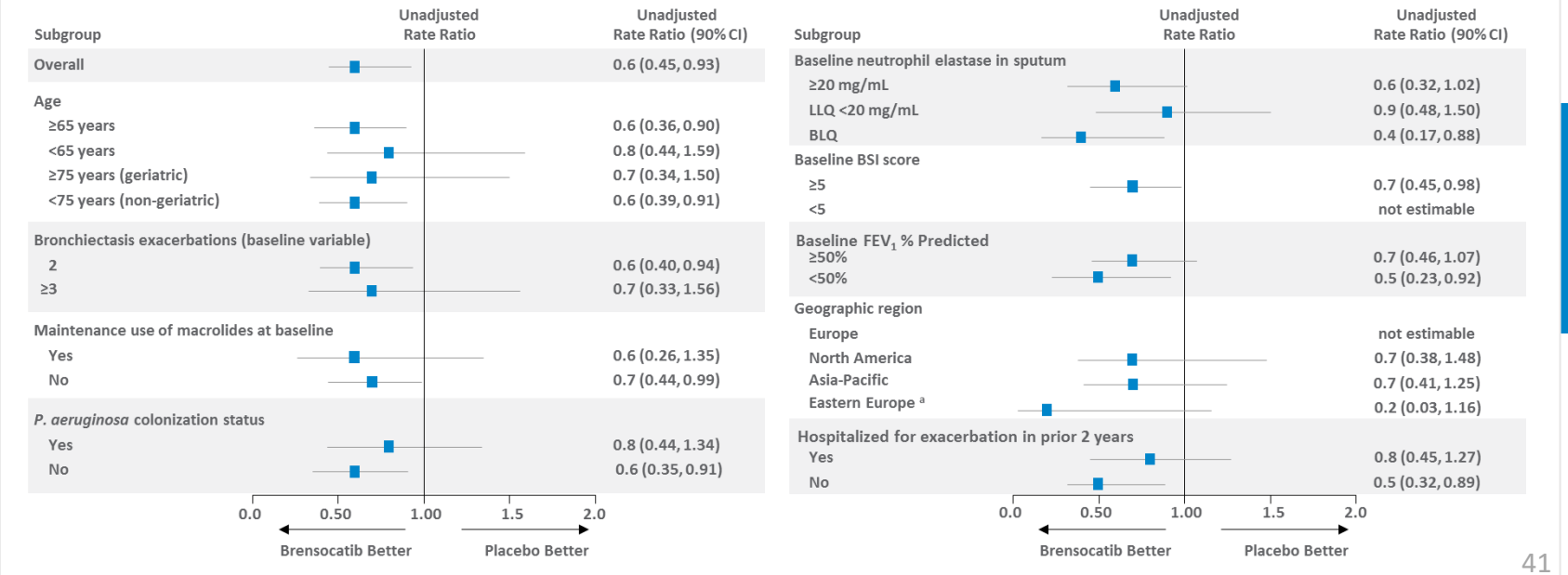
25 mg
brensocatib vs. placebo

Rate of Exacerbations

by Patient Subgroups

10 mg
brensocatib vs. placebo



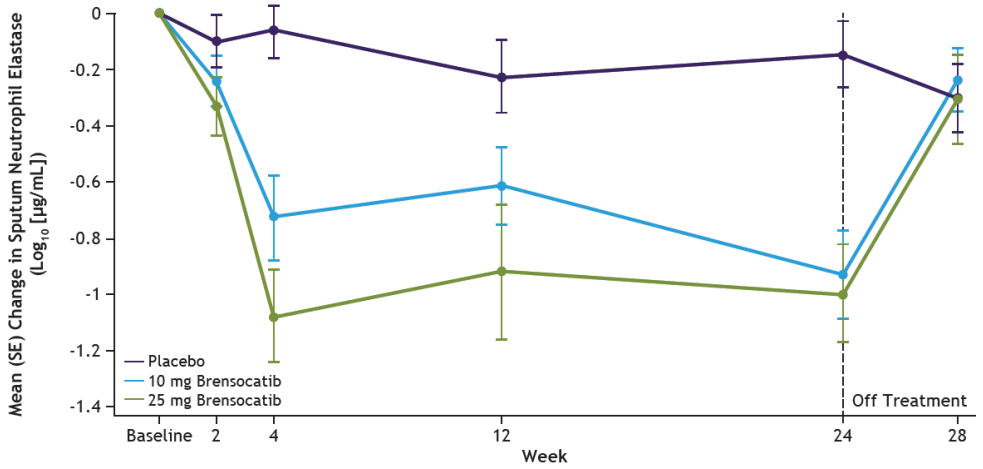


Chalmers et al, ERS International Congress 2020, 7-9 September. RCT4135
BSI, bronchiectasis severity index; FEV1, forced expiratory volume in 1 second
[a]Bulgaria/Poland

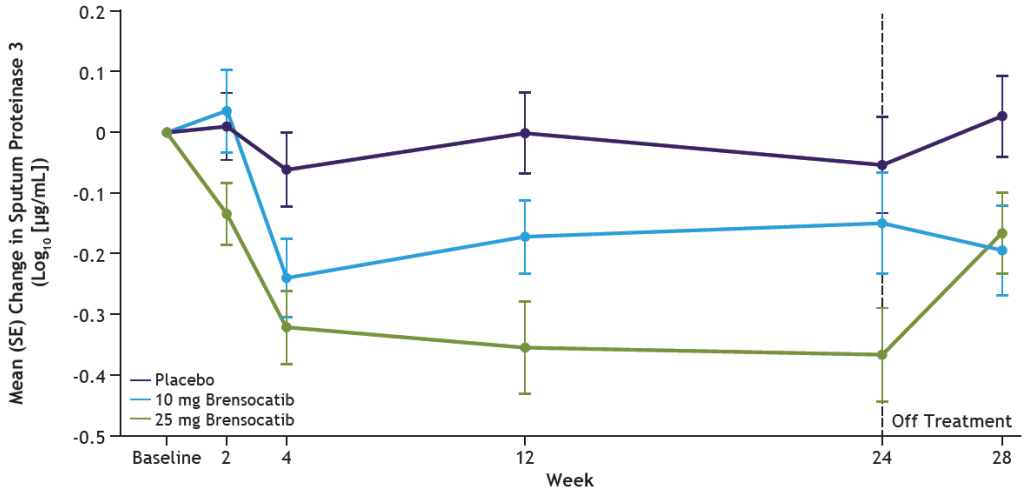
Dose Response Effect Seen Consistently Across Sputum Neutrophil Serine Proteases (NSPs)

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

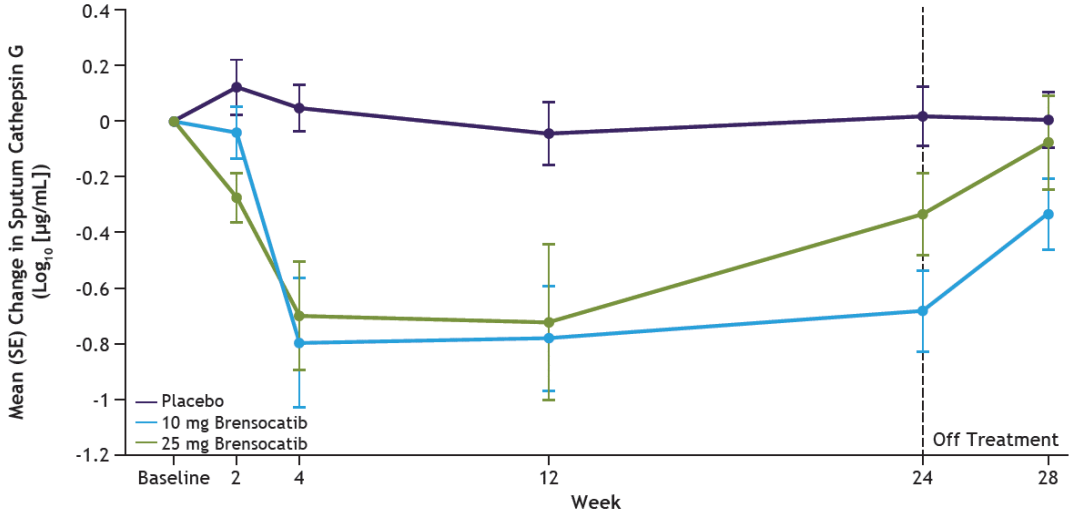
Neutrophil Elastase



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)

ASPEN Study: Phase 3 Pivotal Program Ongoing

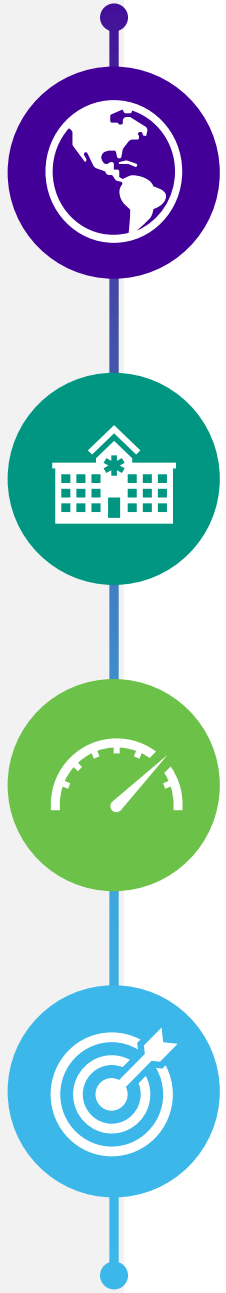
Single Trial Designed to Support Global Filing

Breakthrough Therapy Designation & PRIME designation granted for brensocatib in non-cystic fibrosis bronchiectasis (NCFBE)

Robust efficacy endpoints, supported by WILLOW results

Integrates feedback from Health Authorities

ASPEN Timeline Considerations



40 Countries

~480 sites

6 Fast Track Countries

Targeting WILLOW study sites

Well Positioned to Support a Successful Global Launch in Bronchiectasis

Uniquely positioned to commercialize brensocatib given the synergies that exist between bronchiectasis and NTM lung disease

Proven US launch capabilities with ARIKAYCE

Geographic and target HCP overlap with current US Sales structure

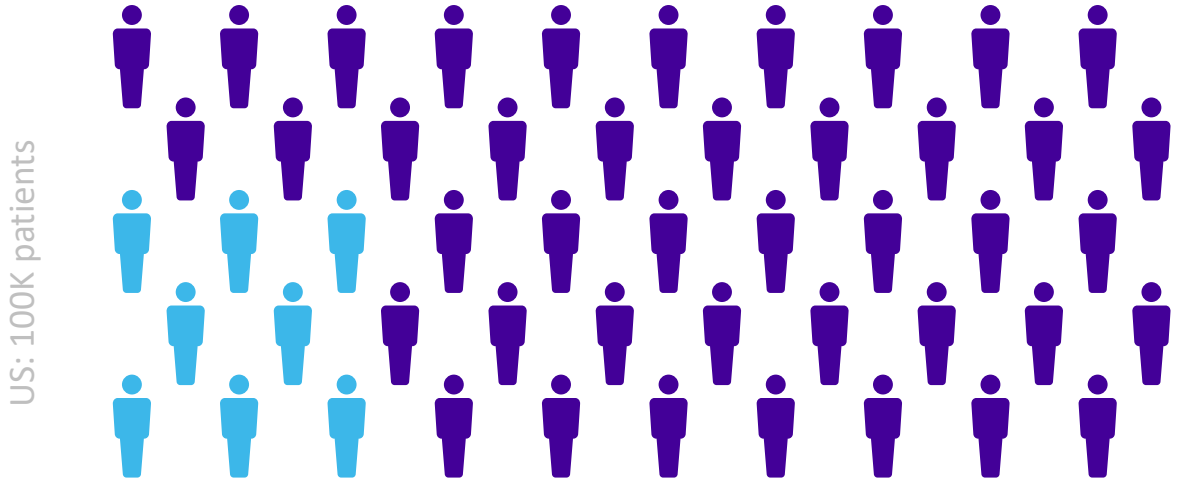
Experience with patient finding and activation

EU/Japan teams mobilized for launch success

Advocacy and patient support

ARIKAYCE Treats Refractory MAC Lung Disease

Potential Progression
Toward Use as Front-line and/or Maintenance Therapy



12-17 K refractory

ARIKAYCE approved in the United States for refractory *Mycobacterium avium* complex (MAC) lung disease

Approved Treatment in MAC Lung Disease

First and only therapy approved in the United States as part of a combination antibacterial drug regimen for adult patients with limited or no alternative treatment options

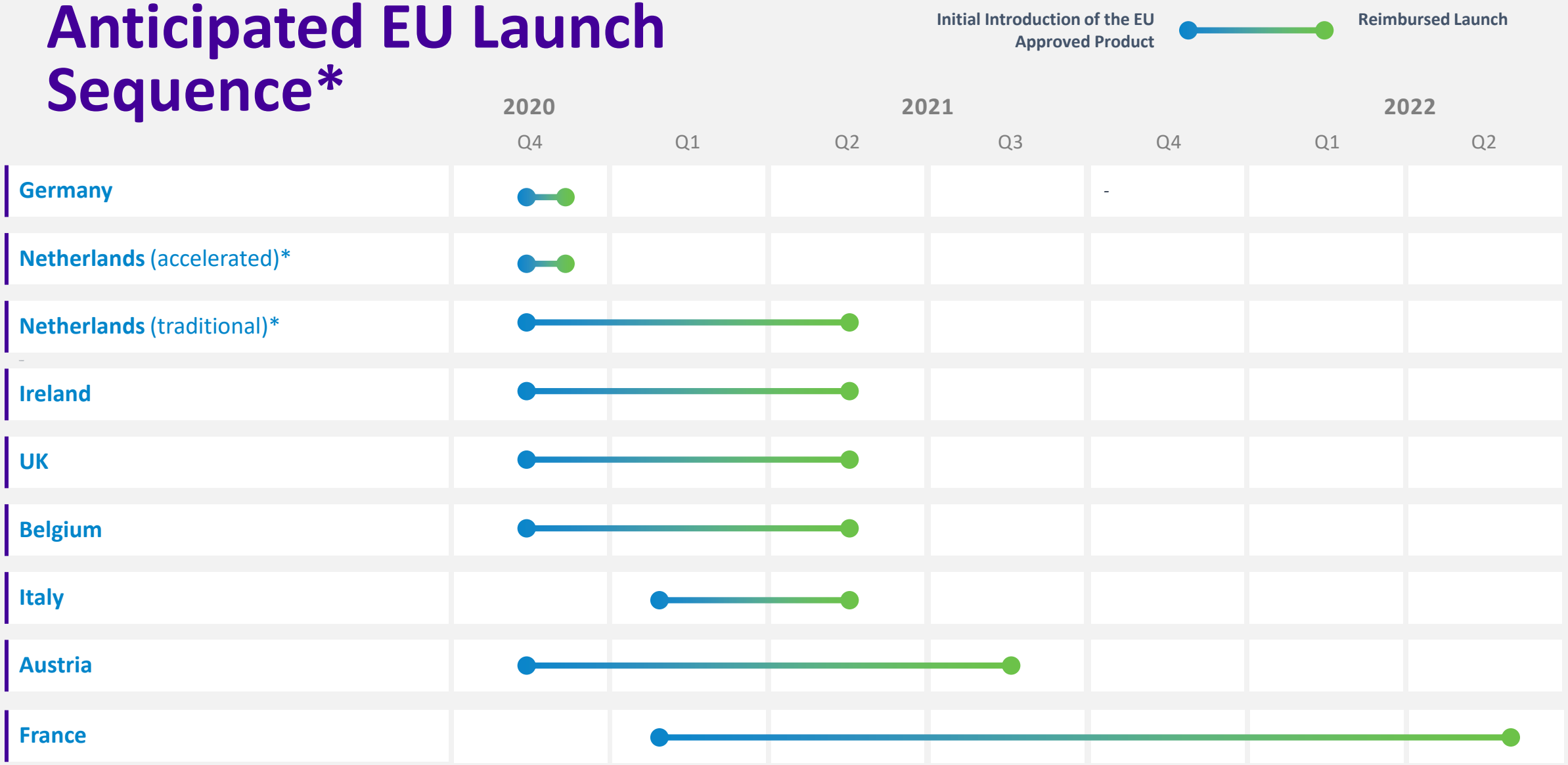
Received both breakthrough therapy & orphan drug designations

Label Expansion in Progress

Action
Front-line Phase 3 underway

Opportunity
Successful data and subsequent regulatory approval could result in a 5-fold increase in the addressable market

Anticipated EU Launch Sequence*

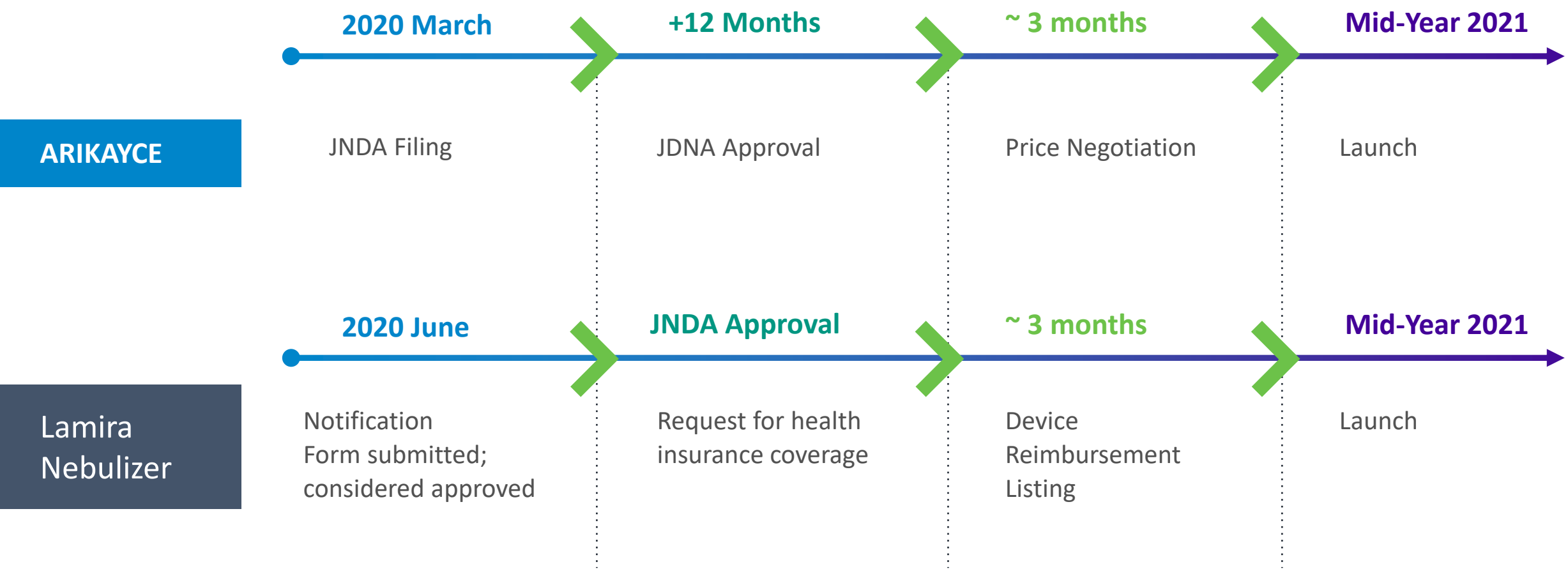


*If approved

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.

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



Future milestone dates are anticipated

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 inflow/ outflow tract obstructions, cardiomyopathies

no approved therapy

3. PH due to Lung Diseases and/or Hypoxemia

3.1. Chronic obstructive pulmonary disease

3.2. Interstitial lung disease

3.3. Other pulmonary disease 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

no approved therapy

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

no approved therapy

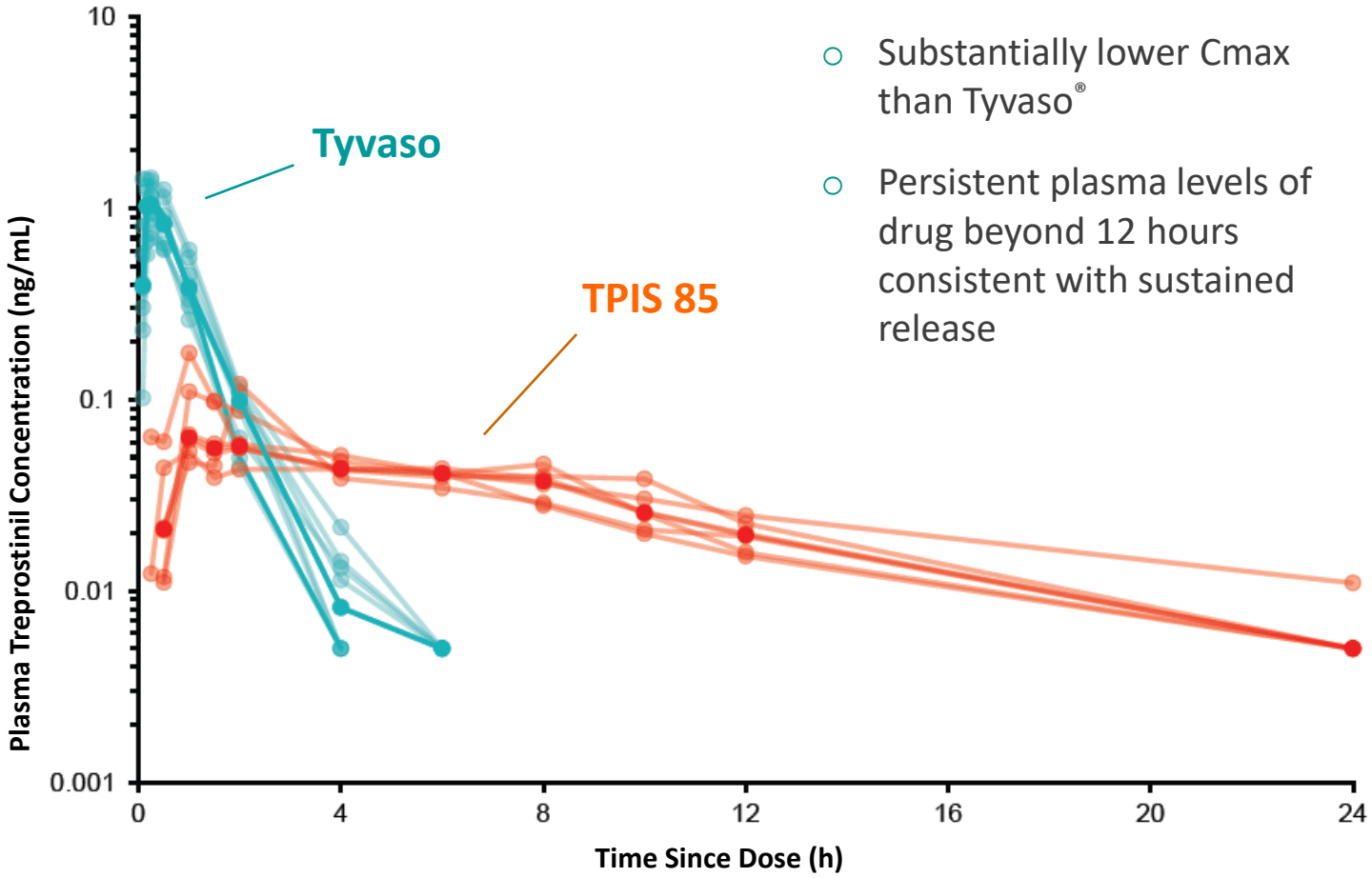
Treprostinil Palmitil Inhalation Solution

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).