



Investor Presentation

February 2024



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 timings discussed, projected, anticipated or indicated in any forward-looking statements. Such risks, uncertainties and other factors include, among others, the following: failure to obtain, or delays in obtaining, regulatory approvals for ARIKAYCE outside the U.S., Europe or Japan, or for the Company’s product candidates in the U.S., Europe, Japan or other markets, including separate regulatory approval for the Lamira® Nebulizer System in each market and for each usage; failure to continue to successfully commercialize ARIKAYCE, the Company’s only approved product, in the U.S., Europe or Japan (amikacin liposome inhalation suspension, Liposomal 590 mg Nebuliser Dispersion, and amikacin sulfate inhalation drug product, respectively), or to maintain U.S., European or Japanese approval for ARIKAYCE; business or economic disruptions due to catastrophes or other events, including natural disasters or public health crises; risk that brensocatib or TPIP does not prove to be effective or safe for patients in ongoing and future clinical studies, including, for brensocatib, the ASPEN study; uncertainties or changes 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 successfully or in a timely manner validate a PRO tool and complete the confirmatory post-marketing clinical trial 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, brensocatib, TPIP or the Company’s other product candidates; inaccuracies in the Company’s estimates of the size of the potential markets for ARIKAYCE, brensocatib, TPIP or the Company’s other 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 risks and uncertainties associated with, and the perceived benefits of, the Company’s secured senior loan with certain funds managed by Pharmakon Advisors, LP and the Company’s royalty financing with OrbiMed Royalty & Credit Opportunities IV, LP, including the Company’s ability to maintain compliance with the covenants in the agreements for the senior secured loan and royalty financing and the perceived impact of the restrictions on the Company’s operations under these agreements; the Company’s inability to create or maintain 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; risk that the Company’s competitors may obtain orphan drug exclusivity for a product that is essentially the same as a product the Company is developing for a particular indication; failure to successfully predict the time and cost of development, regulatory approval and commercialization for novel gene therapy products; failure to successfully conduct future clinical trials for ARIKAYCE, brensocatib, 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 its potential inability to enroll or retain sufficient patients to conduct and complete the trials or generate data necessary for regulatory approval of our product candidates or to permit the use of ARIKAYCE in the broader population of patients with MAC lung disease, among other things; risks that the Company’s clinical studies will be delayed, that serious side effects will be identified during drug development, or that any protocol amendments submitted will be rejected; risks that topline, interim or partial data sets are not representative of a complete or larger data set and are subject to change as more patient data becomes available or that blinded data will not be predictive of unblinded data; 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 successfully integrate its recent acquisitions and appropriately manage the amount of management’s time and attention devoted to integration activities; risks that the Company’s acquired technologies, products and product candidates are not commercially successful; the Company’s inability to adapt to its highly competitive and changing environment; the Company’s inability to access, upgrade or expand its technology systems or difficulties in updating our existing technology or developing or implementing new technology; risk that the Company is unable to maintain its significant customers; risk that government healthcare reform materially increases the Company’s costs and damages its financial condition; risk that our current and potential future use of artificial intelligence and machine learning may not be successful; deterioration in general economic conditions in the U.S., Europe, Japan and globally, including the effect of prolonged periods of inflation, affecting the Company, its suppliers, third-party service providers and potential partners; 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 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; risk that the Company’s operations are subject to a material disruption in the event of a cybersecurity attack or issue; 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; the Company’s history of operating losses, and the possibility that the Company may never achieve or maintain profitability; goodwill impairment charges affecting the Company’s results of operations and financial condition; 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 appropriate regulatory authorities 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, 2023 and any subsequent Company filings with the Securities and Exchange Commission (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.

With respect to the blended and blinded data observed from the ongoing TPIP studies, the dose titration, efficacy, and safety analyses were based on data available as of August 28, September 12, and October 23, 2023, respectively. These findings may not be representative of results after the studies are completed and all data is collected and analyzed. As a result, later interim data readouts and final data from these studies may be materially different than the observations described above, including with respect to efficacy, safety and tolerability of TPIP.

insmed[®]

5-YEAR VISION

Build a sustainable biotechnology company by leveraging revenue generation from a portfolio of life-altering therapies for small patient populations experiencing big health problems





2024: The Year of Insmed's Transformation

Brensocatib ASPEN Readout in Bronchiectasis

First Phase 2 TPIP Readout in PH-ILD

Advance ARIKAYCE® Toward Label Expansion

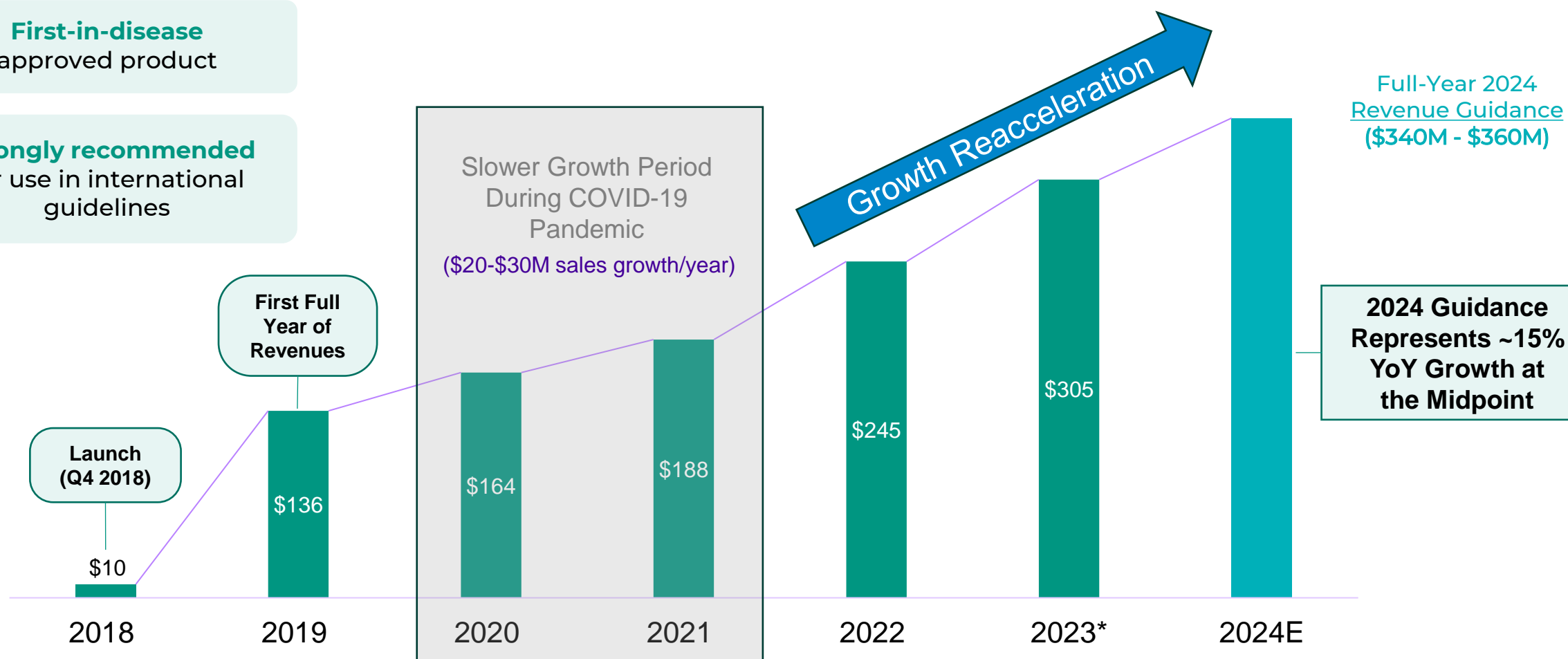
Continued Progress on Cutting-Edge Early Pipeline

***The Stage is Set for a
Breakout Year
Rarely Seen in Biotech***

ARIKAYCE Expected to Continue to Deliver Strong Double-Digit Revenue Growth Globally in 2024

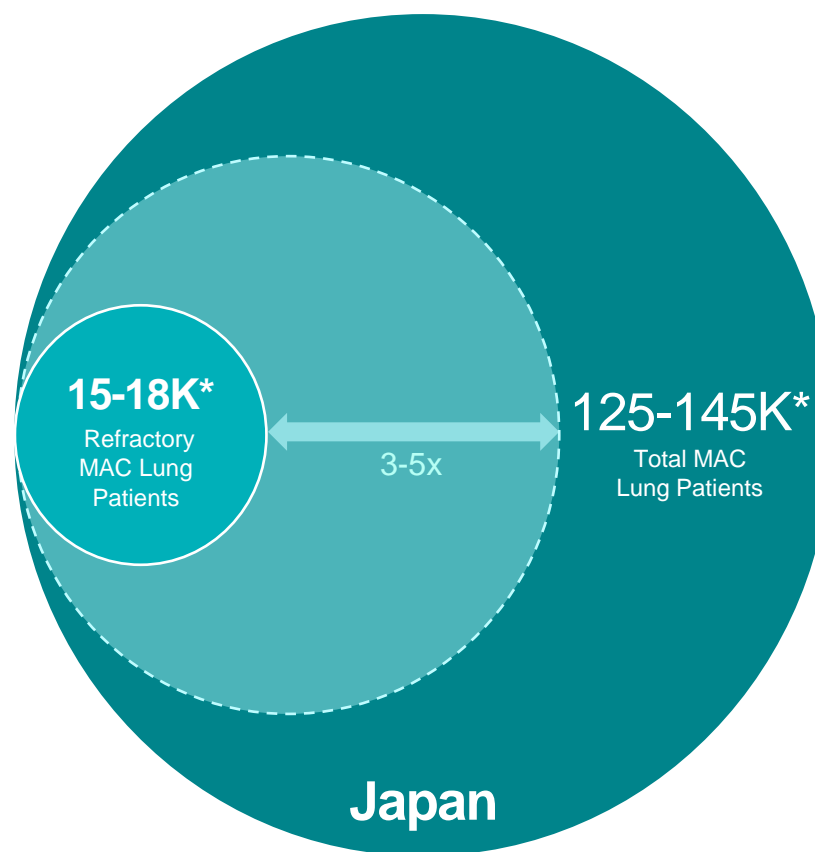
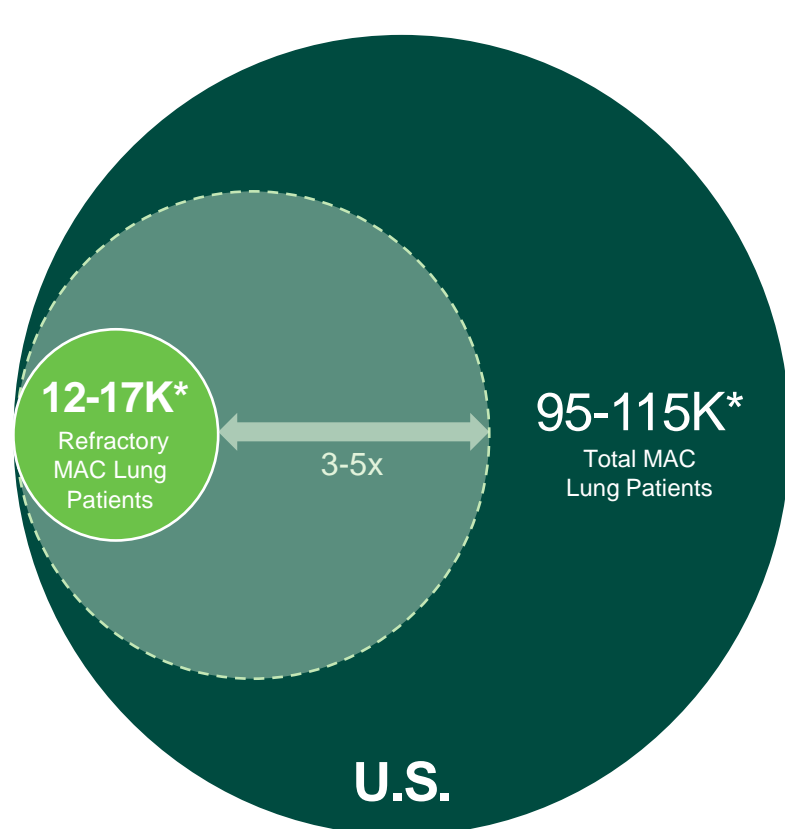
First-in-disease
approved product

Strongly recommended
for use in international
guidelines

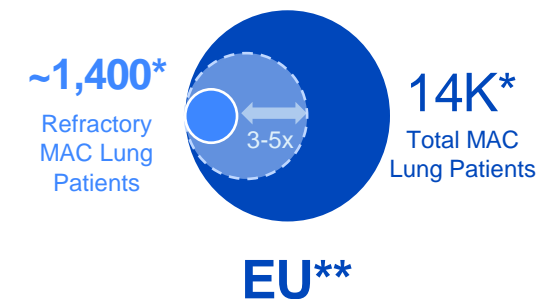


ARIKAYCE Expected to be a >\$1 Billion Peak Sales Product Assuming Label Expansion to Include All Patients with MAC Lung Disease

Newly diagnosed NTM MAC could expand the ARIKAYCE commercial opportunity by 3-5 times

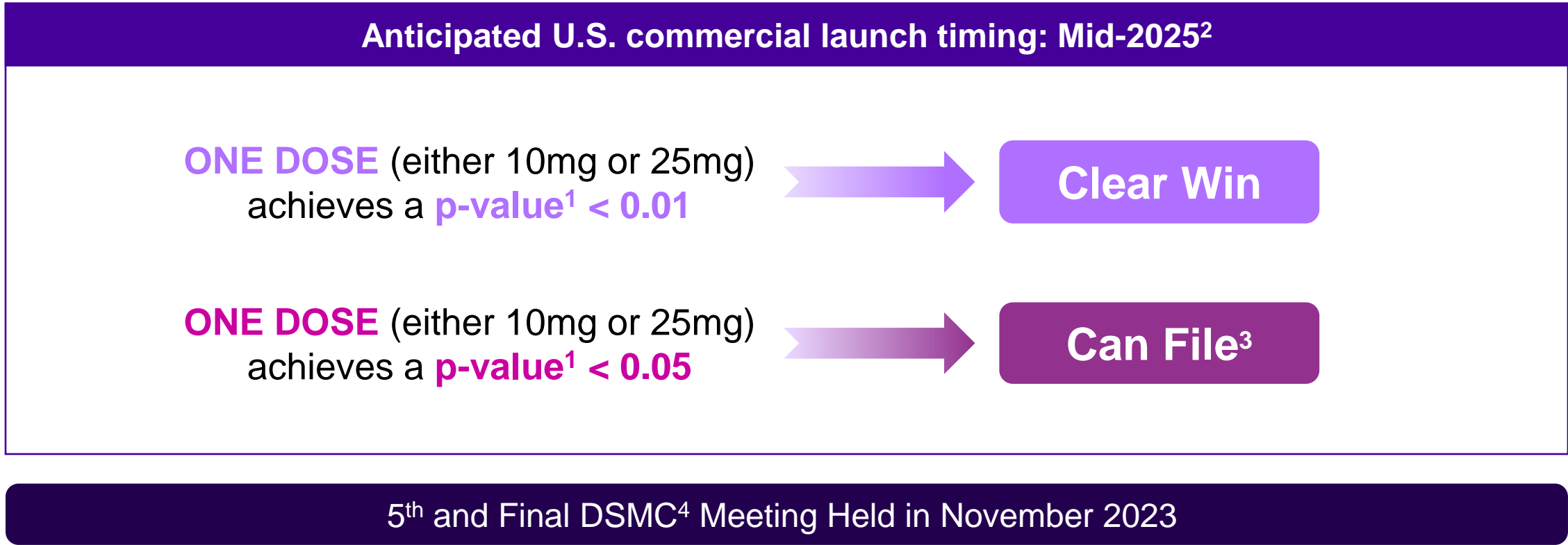


Topline results from the ongoing Phase 3 ENCORE trial **expected in 2025**



Brensocatib: ASPEN on Track to Read Out in 2Q24

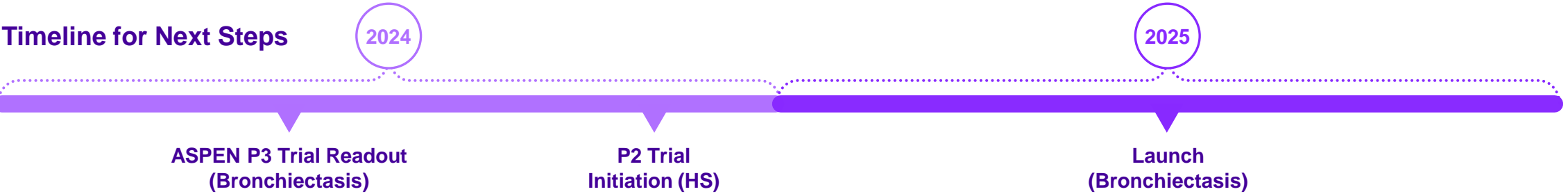
Need One Dose to Win for Regulatory and Commercial Success



¹Refers to the p-value for the primary endpoint, adjusted for multiplicity. ²Timing assumes one dose (either 10mg or 25mg) achieves a p-value <0.01. Brensocatib has been granted Breakthrough Therapy Designation in the US and PRIME designation in the EU. ³FDA indicated that this data result could be filed for review. ⁴DSMC: Data Safety Monitoring Committee.

If ASPEN Succeeds, Brensocatib Expected to Become a \$5+ Billion Peak Sales Product

	Total Addressable Market (global)	Current Treatment Landscape
Bronchiectasis ^{1,2,3}	~1M	No approved treatments
Chronic Rhinosinusitis w/o Nasal Polyps (CRSsNP) ^{4,5,6,7}	~400K	
Hidradenitis Suppurativa (HS) ^{8,9}	~250K	Treatment includes multiple therapies and/or surgery



¹Assumes indication for non-cystic fibrosis bronchiectasis and approval in US, European 5, and Japan. ²Weycker, et al. Prevalence and incidence of NCFBE among US adults in 2013. Chronic Respiratory Disease. 2017. ³Insmad: Patient Level Claims Data Analysis and Internal Market Research; Ex-US estimates based on published epidemiology research, Insmad market research, and extrapolation of US-focused claims and epi data analysis (sourced from swoop/ipm.ai). ⁴Cho et. al, Chronic Rhinosinusitis without Nasal Polyps J Allergy Clin Immunol Pract. 2016 ; 4(4): 575–582. doi:10.1016/j.jaip.2016.04.015. ⁵Benjamin et. al, Clinical Characteristics of Patients with Chronic Rhinosinusitis without Nasal Polyps in an Academic Setting, J ALLERGY CLIN IMMUNOL PRACT VOLUME 7, NUMBER 3, MARCH 2019. ⁶Patient level claims data analysis US ONLY (Komodo Health), proportion of actively managed CRS patients with no Dx codes for Nasal Polyps in patient history; Extrapolated to European 5 and Japan. ⁷Patient level claims data analysis US ONLY (Komodo Health), proportion of actively managed CRSsNP patients with ESS; Extrapolated to European 5 and Japan. ⁸Phan et al, Global prevalence of hidradenitis suppurativa and geographical variation—systematic review and meta-analysis Biomedical Dermatology (2020) 4:2. ⁹Puri, Ajay: Hidradenitis Suppurativa Executive Insights, DRG Nov 2019.

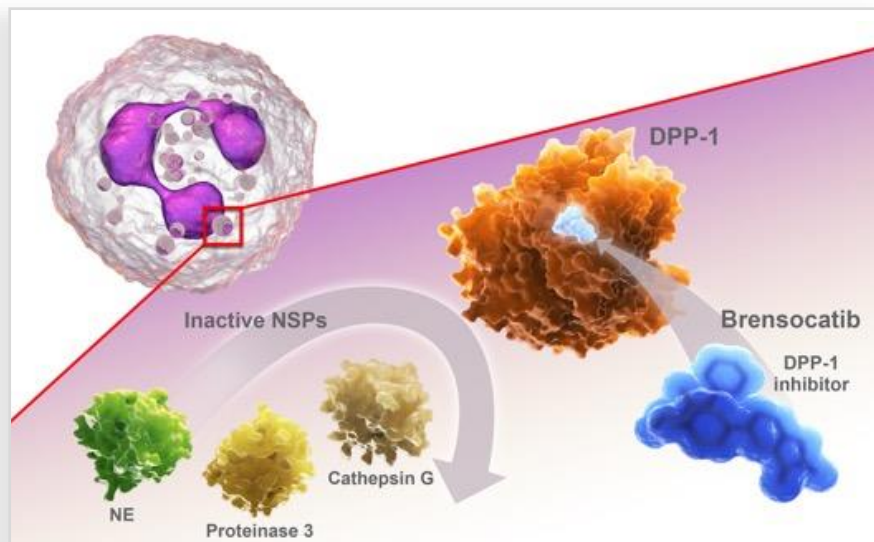
Brensocatib (DPP1 Inhibitor) has potential in a broad range of neutrophil-mediated diseases

Neutrophils play an **essential role** in pathogen destruction and **inflammatory mediation**

Neutrophils contain the **NSPs that have been implicated in a variety of inflammatory diseases** such as bronchiectasis, CRS, CF and HS

DPP1 catalyzes activation of NSPs
Brensocatib shows inhibition of NSPs in multiple clinical studies

Phase 2 data published in NEJM showed **potential clinical benefits of directly reducing neutrophil-mediated inflammation**



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

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., Francesco Blasi, M.D., Ph.D., Oriol Sibila, M.D., Ph.D., Anne E. O'Donnell, M.D., Eugene J. Sullivan, M.D., Kevin C. Mange, M.D., M.S.C.E., Carlos Fernandez, M.D., M.P.H., Jun Zou, Ph.D., and Charles L. Daley, M.D. for the WILLOW Investigators*

Article Figures/Media

Metrics

November 26, 2020

N Engl J Med 2020; 383:2127-2137

DOI: 10.1056/NEJMoa2021713

23 References 81 Citing Articles

TPIP: Multiple Clinical Readouts Expected in 2024 and 2025

“The hemodynamic changes are stunning...” KOL comment on the blinded results shared in Oct. 2023

PH-ILD

- Phase 2 study fully enrolled (Nov. 2023)
- Topline readout expected **pre-ASPEN** (Q2 2024)

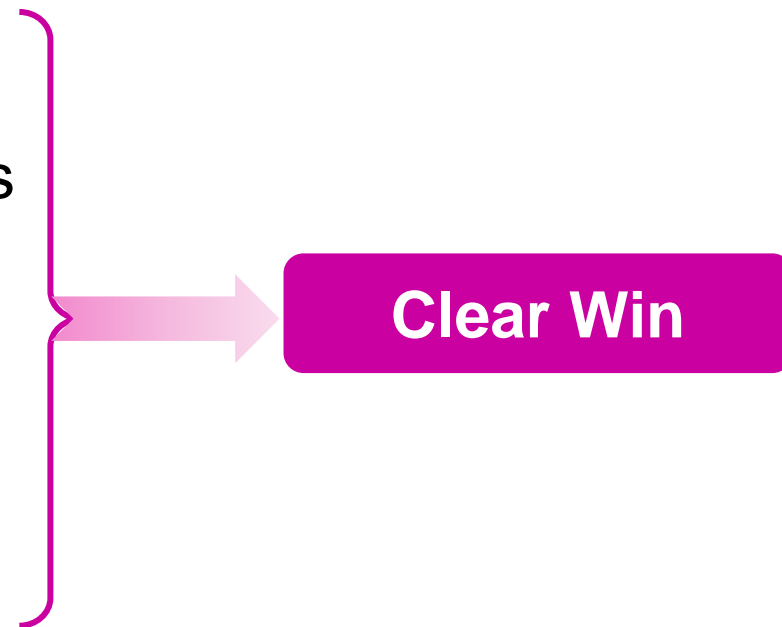
PAH

- 45 patients enrolled in Phase 2 study (YE 2023)
- ~47% average PVR reduction among responders*
- Updated blinded data from ~40 patients (Q2 2024)
- Phase 2 topline data in 2025
- Doubling dose ceiling to 1,280µg from 640µg

>80% of all study participants reached the maximum dose in just 5 weeks*

TPIP: Upcoming Phase 2 Data in PH-ILD Primarily Meant to Characterize Safety Profile

- Favorable tolerability profile in patients with PH-ILD
- Highest dose (640µg) achieved in majority of patients
- Treatment-emergent adverse events consistent with underlying disease
- Pharmacokinetic endpoints are consistent with preclinical data¹



**The PH-ILD Phase 2 is a SAFETY study
and is not powered to show statistical differences**

Inhalation delivery of a prostanoid is **more potent** than systemic delivery

We designed TPIP to chemically accomplish the **continuous delivery** of a prostanoid and its demonstrated benefits

Sheep Model of Sustained Acute Pulmonary Hypertension

“ ”

... aerosol delivery of the drug had a much greater vasodilatory effect than intravenous delivery.

At the highest dose, aerosol delivery of the drug returned both pulmonary vascular resistance and pulmonary artery pressure to baseline levels...

J Appl Physiol 99: 2363–2368, 2005.

First published September 1, 2005; doi:10.1152/japophysiol.00083.2005.

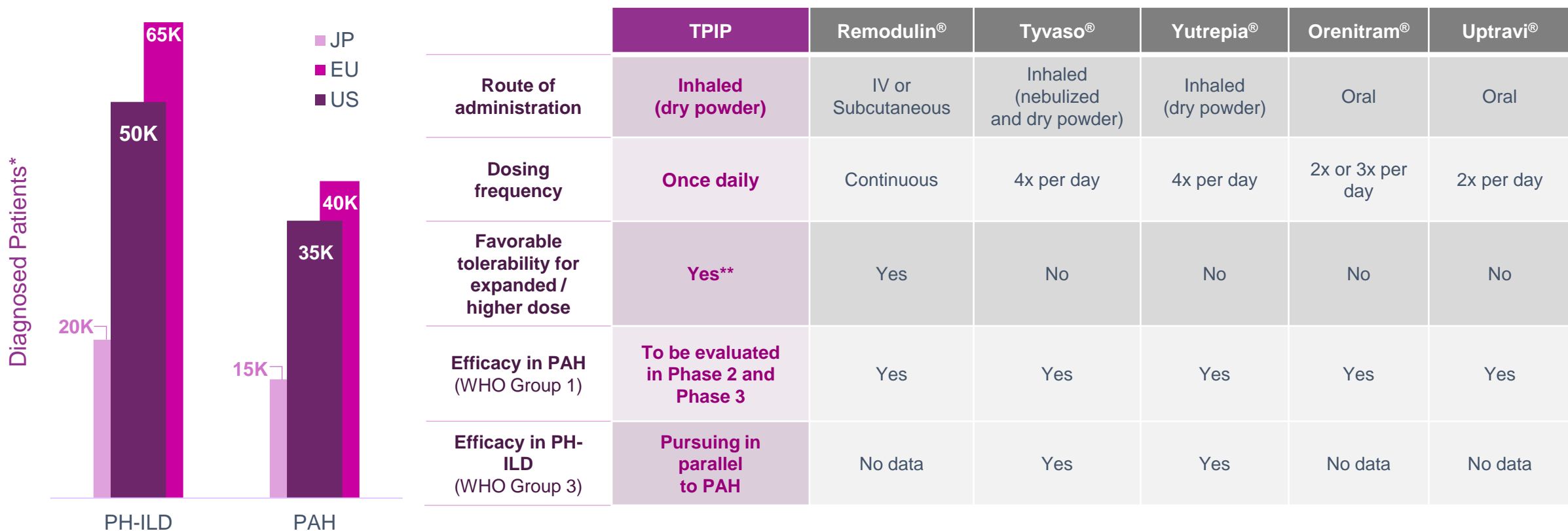
Potent effects of aerosol compared with intravenous treprostinil on the pulmonary circulation

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}

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

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

TPIP Has the Potential to be the Prostanoid of Choice in the Multi-Billion Dollar PH-ILD and PAH Markets



EU: European 5 comprised of France, Germany, Italy, Spain and the United Kingdom; *Coultais DB et al, "The epidemiology of interstitial diseases", Am J Respir Crit Care Med, 1994; Ryu et al., "Pulmonary hypertension in patients with interstitial lung disease." Mayo Clinic Proceedings, 2007; Anderson et al., "Pulmonary hypertension in interstitial lung disease: prevalence, prognosis and 6 min walk test." Respir Med, 2012; Kirson N et al, "Prevalence of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension in the United States", Jul 2011; Analysis of Compile Health claims; Meta-analysis of several Japan-based publications relating to interstitial lung diseases; Japan's Intractable Disease Database and Insmed internal analysis; Insmed Primary Quantitative Market Research Fielded September 2021; Duchemann et al., "Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris." European Respiratory Journal, 2017; 2019 National Audit of Pulmonary Hypertension Great Britain; Humbert M et al, "Pulmonary arterial hypertension in France: results from a national registry", Feb 2006; Hoeper M et al, "Incidence and prevalence of pulmonary arterial hypertension in Germany", Nov 2015; Escribano-Subias P et al, "Survival in pulmonary hypertension in Spain: insights from the Spanish registry", 2012. **Safety analysis based on data available as of the most recent data disclosure (October 23, 2023).

Encouraging Observations from Ongoing TPIP Phase 2 Studies in PH-ILD and PAH

Blended and Blinded Dose Titration and Safety and Tolerability Data

	PH-ILD	PAH
Dose Titration¹ Patients Titrated to Maximum Dose of 640 µg or Placebo (%)	80% of first 10 patients who reached Week 5 visit	83% of first 24 patients who reached Week 5 visit Insméd plans to seek to increase the maximum dose of TPIP from 640 µg to up to 1,280 µg, once a day, for the open-label extension portion of its PAH study
Pulmonary Vascular Resistance (PVR)² Average Reduction in PVR from Baseline (%)		21.5% of 22 patients who completed Week 16 of treatment 47% of 64% of patients who experienced PVR reductions Several patients experienced reductions >65%
Safety and Tolerability³	<ul style="list-style-type: none">• No new or unexpected safety concerns observed in either trial• Adverse events (AEs) consistent with those seen in PH-ILD or PAH patients and known effects of inhaled prostacyclins• AEs related to cough were mostly mild• DSMB meeting held in October 2023 approved continuation of both studies as planned	

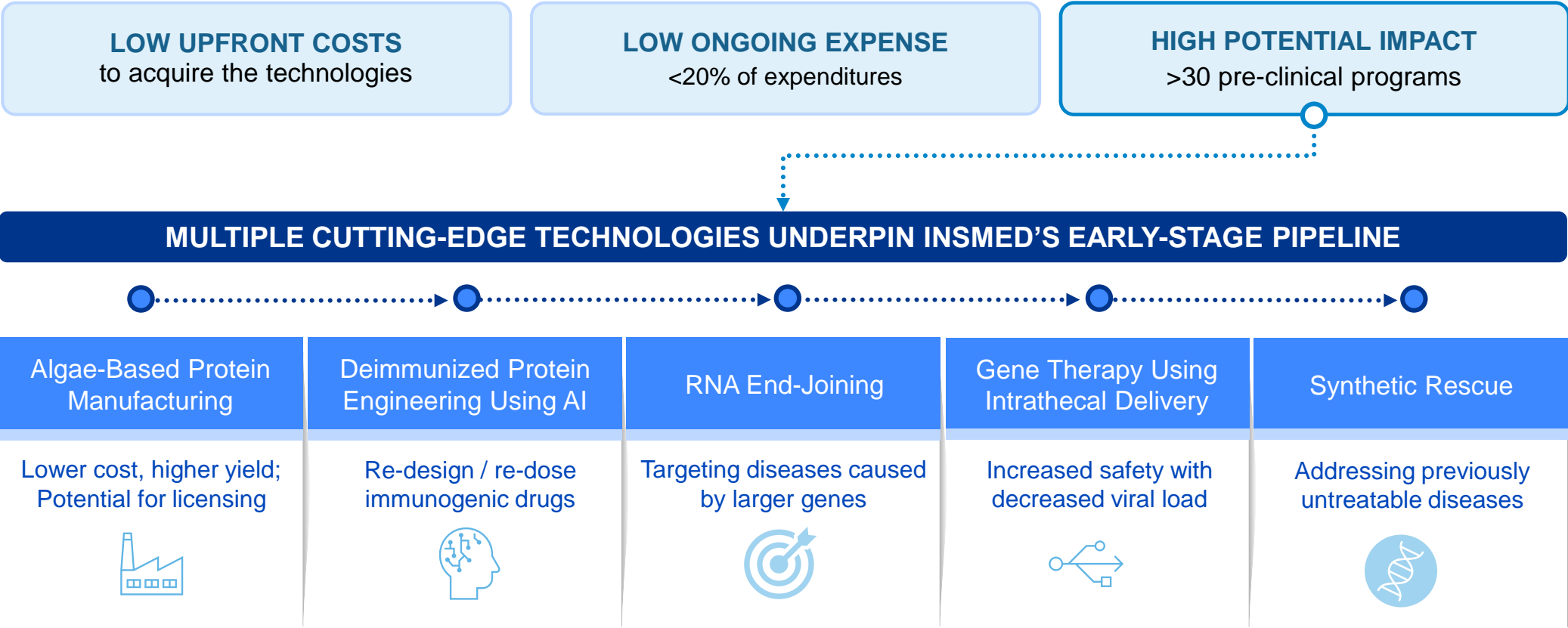


¹Dose titration analysis based on data available as of August 28, 2023. Dose titration data in both PH-ILD and PAH reflect first sets of patients in each trial who reached the Week 5 visit, which is the last possible point at which the dose can be increased in the trial.

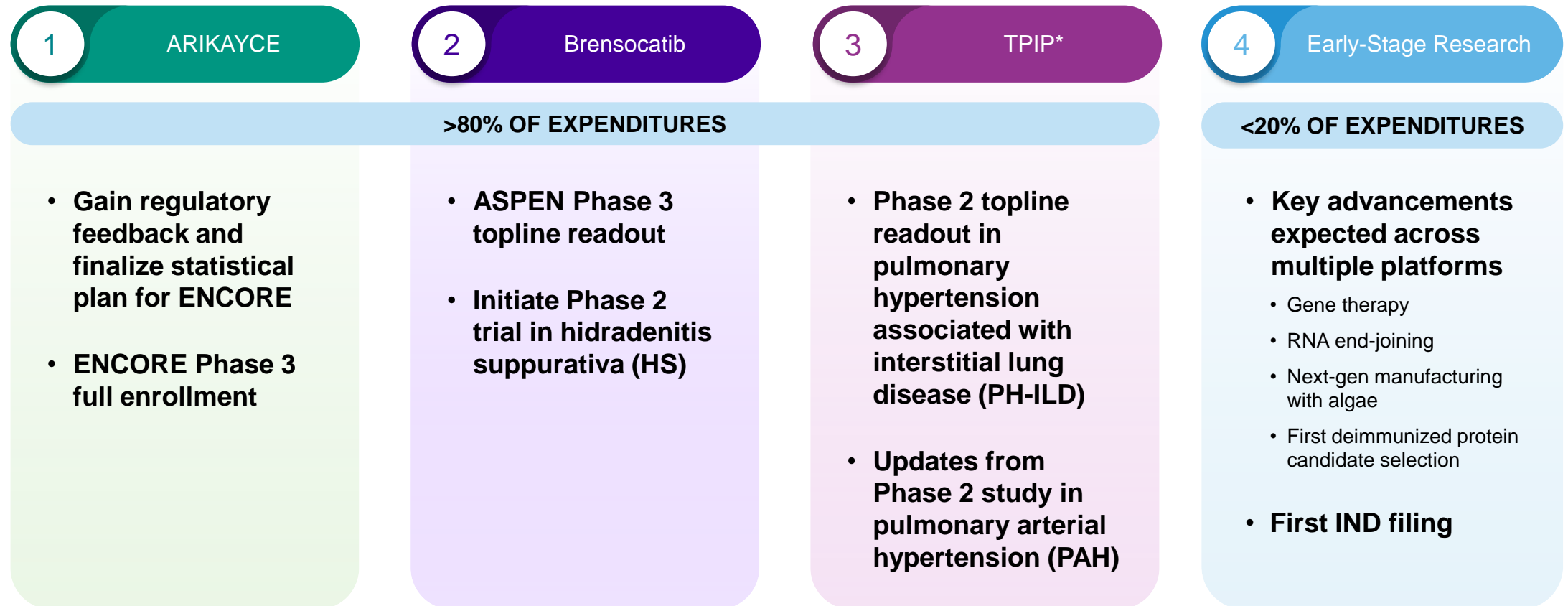
²Efficacy analysis based on data available as of September 12, 2023. PVR data in PAH based on a review of 22 patients who had completed 16 weeks of treatment.

³Safety analysis based on data available as of October 23, 2023.

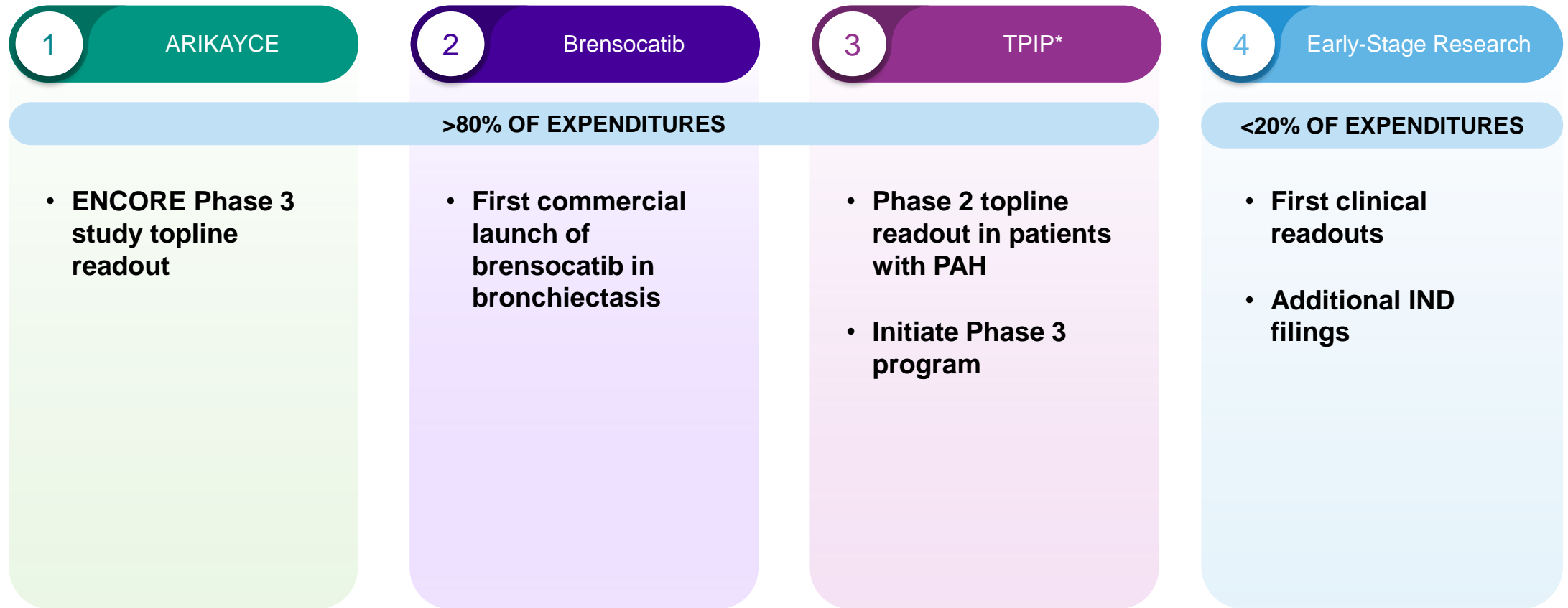
Early-Stage Research: An Assembly of Complementary Platform Technologies to Answer the Question: “What’s Next?”



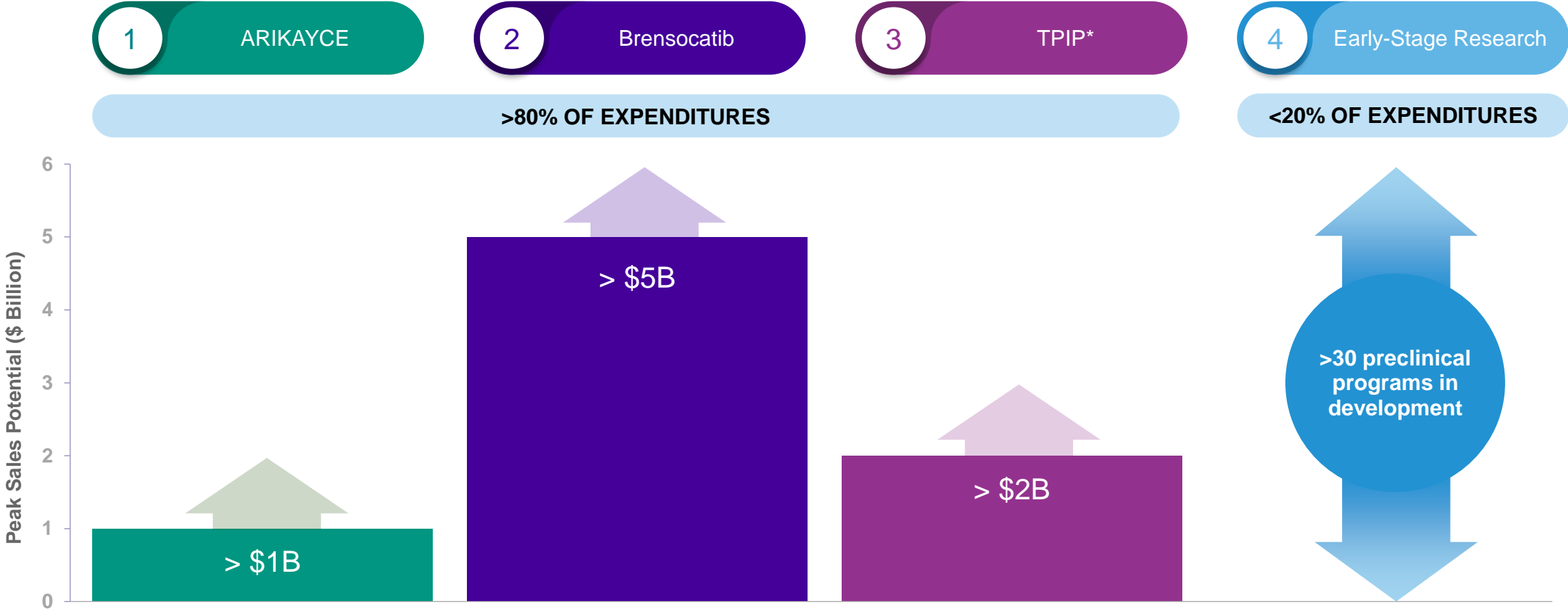
Key Catalysts Set to Transform Insmed in 2024**



...with Many More Important Catalysts Expected in 2025**

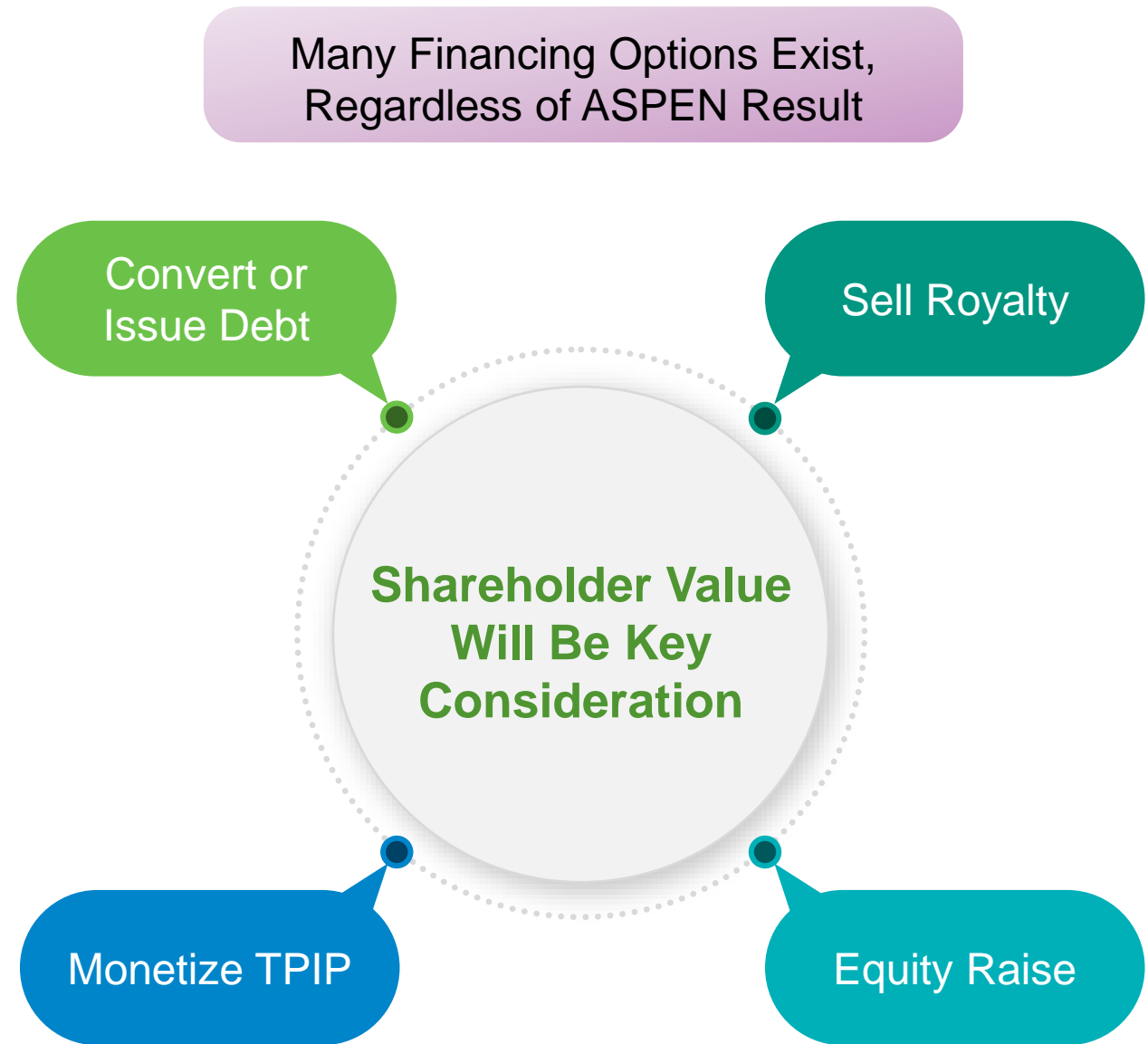


Three Programs with Peak Sales Potential > \$1 Billion Each



Current Cash Position Offers Insmed Flexibility on the Timing and Form of Any Future Capital Raise

- Rich event pipeline in next two years
- Financing options available under all scenarios



**Our Purpose and Values
Define our Culture at
Insmmed Where Employees
Are Empowered to do
their Best Work on Behalf
of Patients in Need**



*The 2023 annual Insmmed Pulse Survey included 91% participation across the organization.

In a recent survey*
>90% of employees
responded that...

*"I am proud to
work at Insmmed."*

*"I am inspired by
the work we do."*

*"I believe Insmmed
will be successful
in the future."*

*"I understand how my
job helps Insmmed
achieve success."*

#1 on Science's
Top Biopharma
Employers List
(3rd Year in a Row)



Certified
as a Great Place
to Work
(3rd Year in a Row)



Appendix

Protected with Significant, Global IP

Brensocatib

U.S., Europe, Japan, China
in-licensed compound patent
exclusivity until 2035

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 the
U.S., EU, and Japan for ARIKAYCE

TPIP

U.S. 4 patents issued to 2034

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

Manufacturing

ARIKAYCE

API



Drug Product



Brensocatib

API



Drug Product

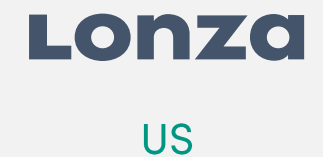


TPIP

API

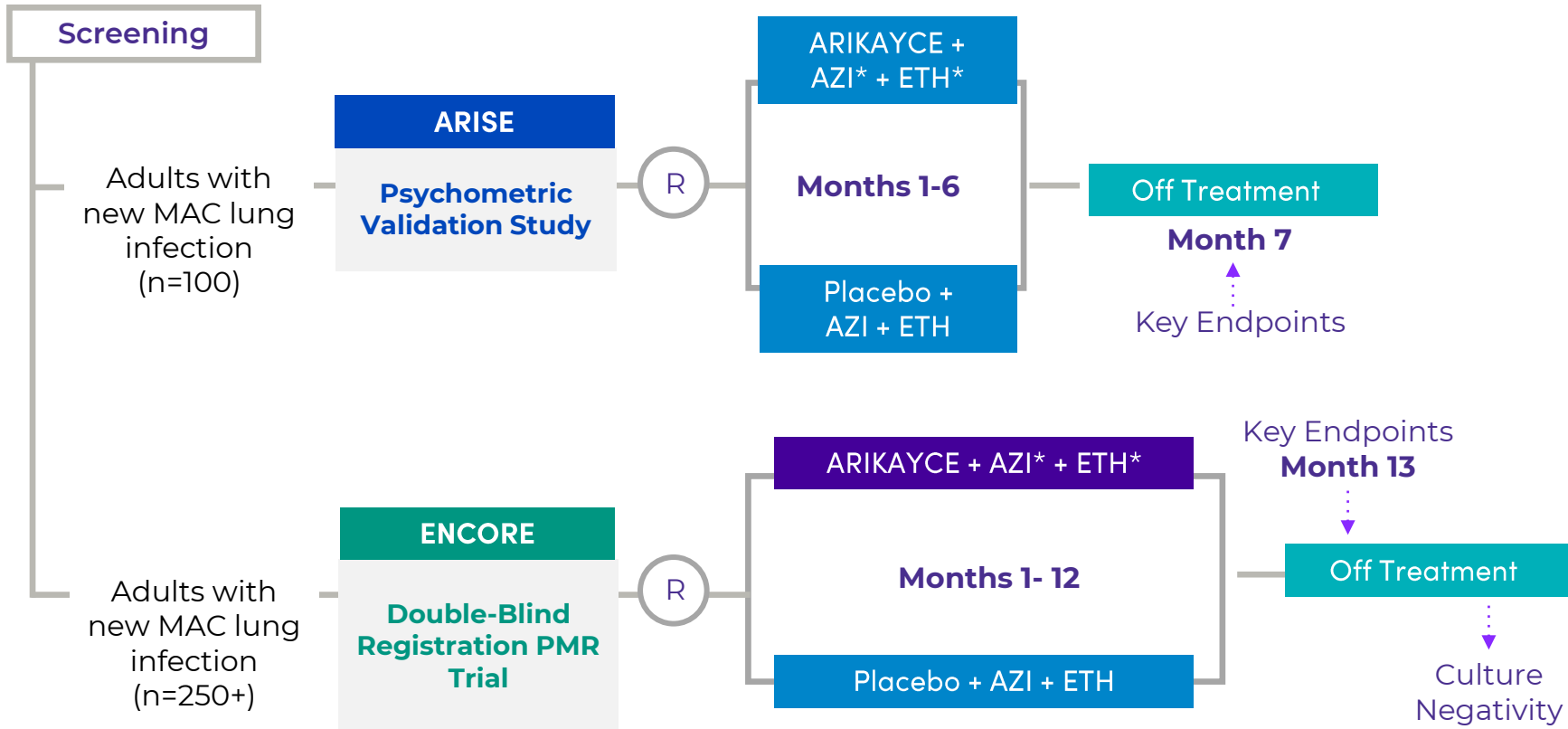


Drug Product



ARIKAYCE Clinical Program to Potentially Expand MAC Indication

TRIAL SUMMARY



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

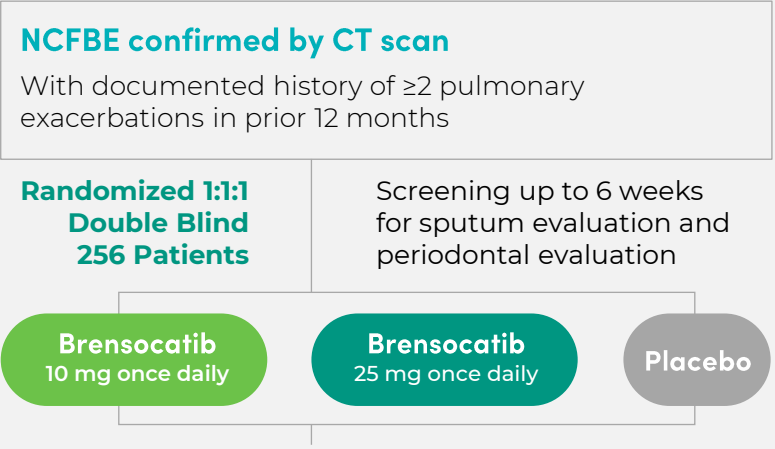
Key Secondary Endpoint

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

- Topline results from Phase 3 ENCORE trial expected in **2025**
- 3rd DSMC meeting approved ENCORE continuation in **November 2023**
- ENCORE enrollment to remain open after reaching 250 patients (**YE 2023**)
- **Positive topline results** from Phase 3 ARISE trial shared in **September 2023**

WILLOW Study Summary

Study Schema



Primary Efficacy: Time to first pulmonary exacerbation

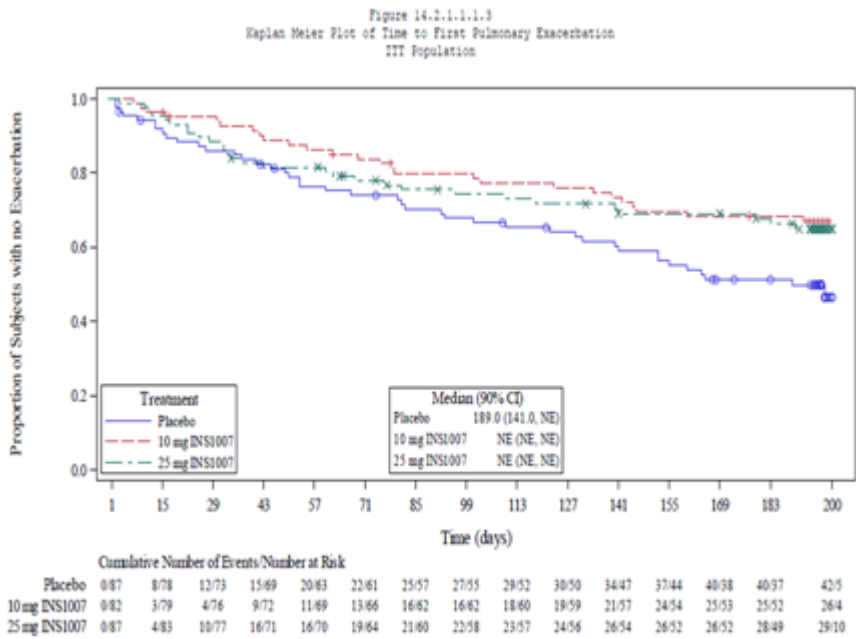
Secondary Efficacy:

- 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 Brensocaticb

Time to First Exacerbation vs. Placebo	Brensocaticb 10 mg	Brensocaticb 25 mg
p-value ^	0.027	0.044
Hazard Ratio	0.58	0.62
p-value ^	0.029	0.046
Rate of Exacerbation vs. Placebo	Brensocaticb 10 mg	Brensocaticb 25 mg
Reduction (%)	36	25
p-value ^	0.041	0.167

Safety

Brensocaticb was generally well-tolerated in the WILLOW study

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

	Placebo	Brensocaticb 10 mg	Brensocaticb 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%

WILLOW

PRE-SPECIFIED ANALYSIS

Time to First Pulmonary Exacerbation After Week 4

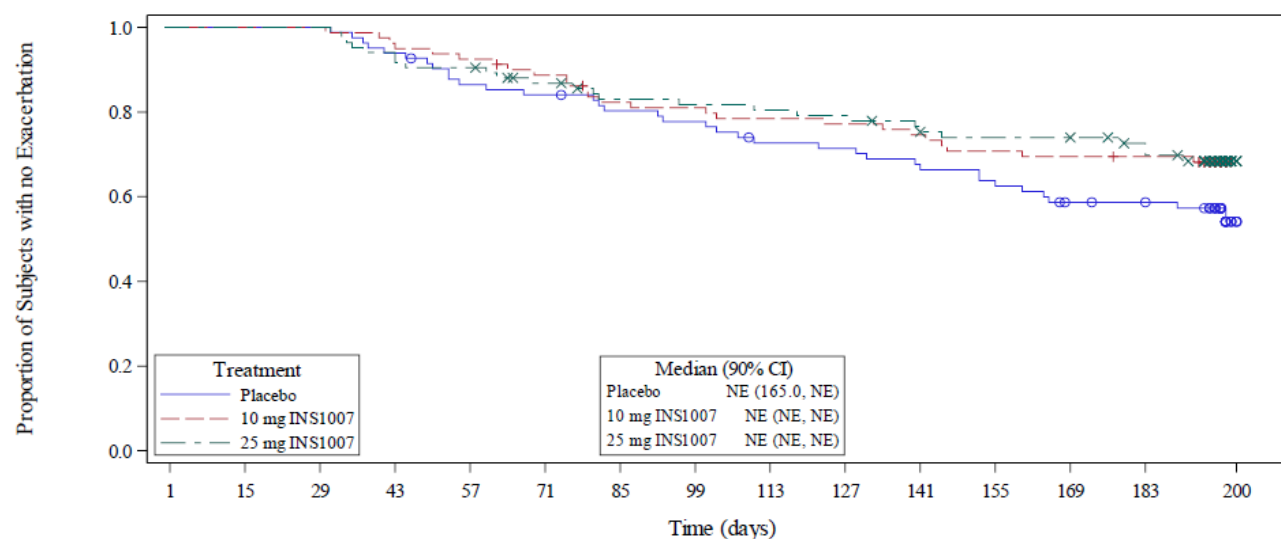
Inmed Incorporated
Protocol: INS1007-201 Version 5.0 Amendment #4.0
Syneos Health Study Number 1009113

CONFIDENTIAL

Page 1 of 1
Final

Figure 14.2.1.1.6.2

Kaplan Meier Plot of Time to First Pulmonary Exacerbation after Visit 4 (Week 4) (Sensitivity Analysis 5)
ITT Population



		Cumulative Number of Events/Number at Risk														
	Placebo	0/82	0/82	0/82	5/77	11/70	13/68	16/64	18/62	22/57	23/56	27/53	30/50	33/44	33/43	35/7
10 mg INS1007		0/80	0/80	0/80	4/77	6/74	9/70	14/64	15/63	17/61	18/60	20/58	23/55	24/54	24/53	25/4
25 mg INS1007		0/84	0/84	0/84	7/79	8/76	11/70	14/65	15/64	16/63	17/62	20/59	21/56	21/56	24/52	25/10

Notes: Time to first pulmonary exacerbation is defined as the time (days) from randomization to date of first documentation of pulmonary exacerbation which occurred from Visit 4 (Week 4) through Visit 9 (Week 24) or EOS, whichever is earlier. NE=Not Estimable. Pulmonary exacerbations that occurred before Visit 4 (Week 4) were not considered. Censored values are indicated on the graph.
Data Source: ADTTE, Corresponding Listing 16.2.6.1.1

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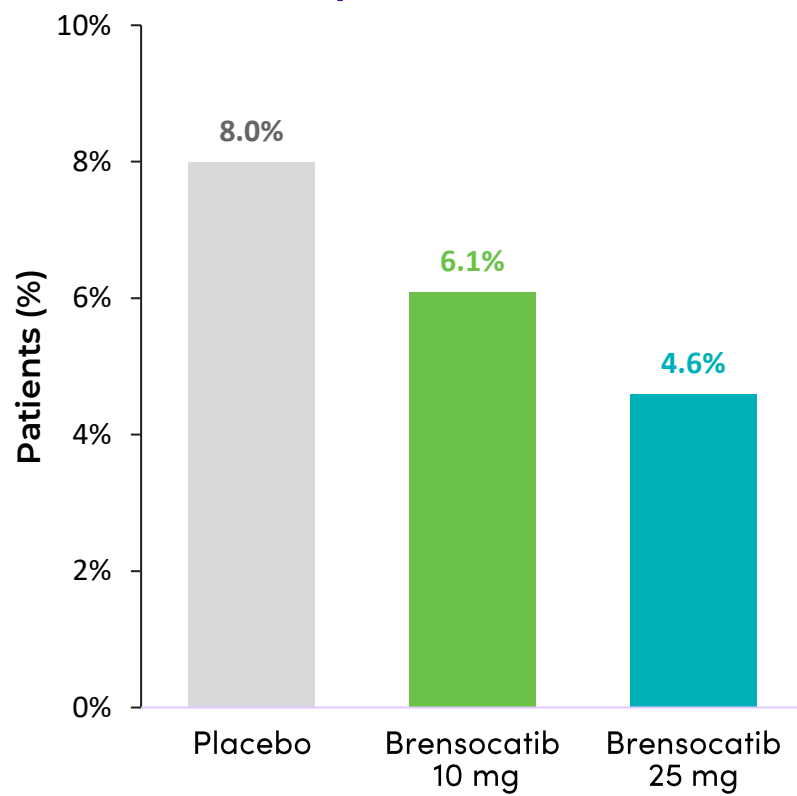
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Higher proportion of subjects experienced pulmonary exacerbations in the placebo group from day 29 to end of study

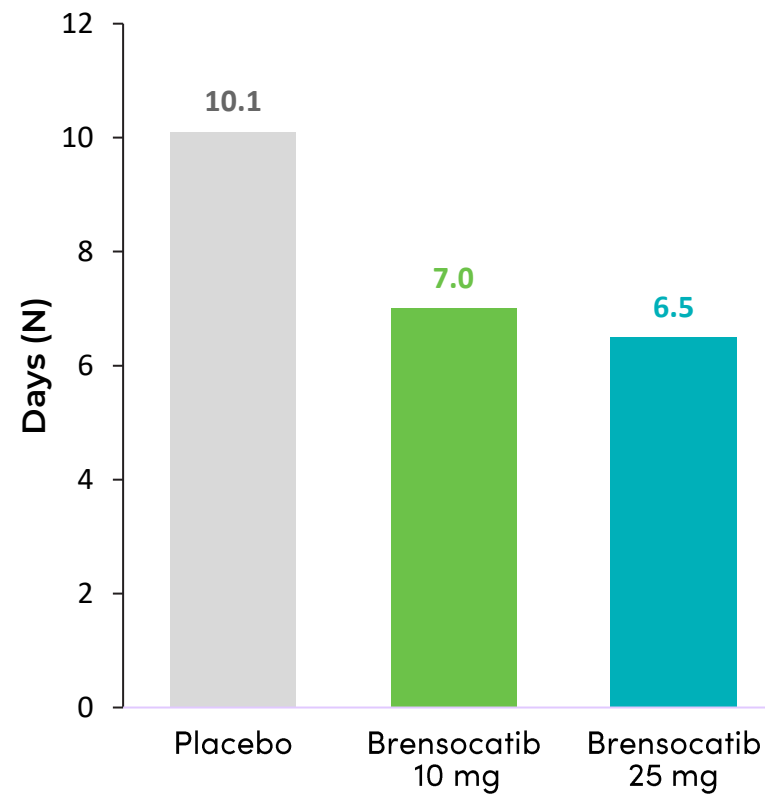
WILLOW:

HOSPITALIZATION RATE DUE TO EXACERBATIONS

**Exacerbation-Related
Hospitalization Rate ^a**



**Days of Hospitalization
Due to Exacerbation**

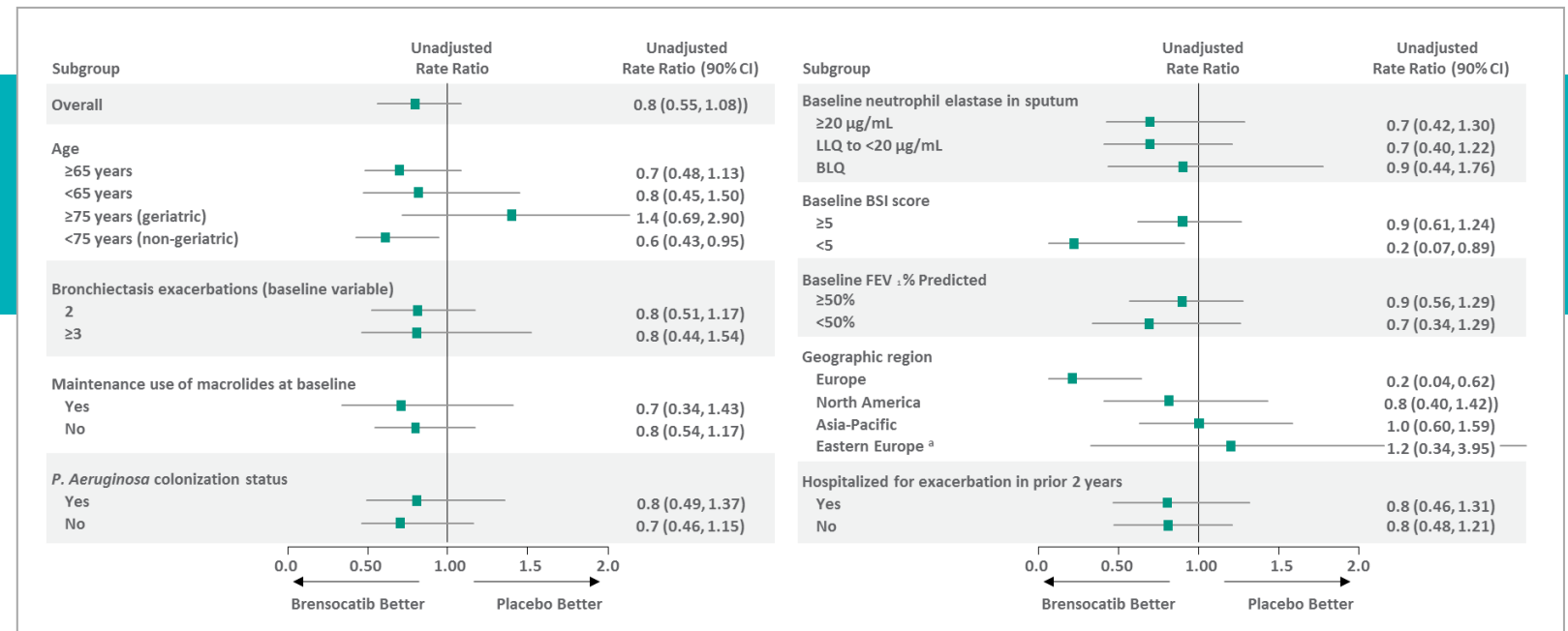


Exacerbation-related hospitalization rates was higher & duration of hospitalization was longer in the placebo arm

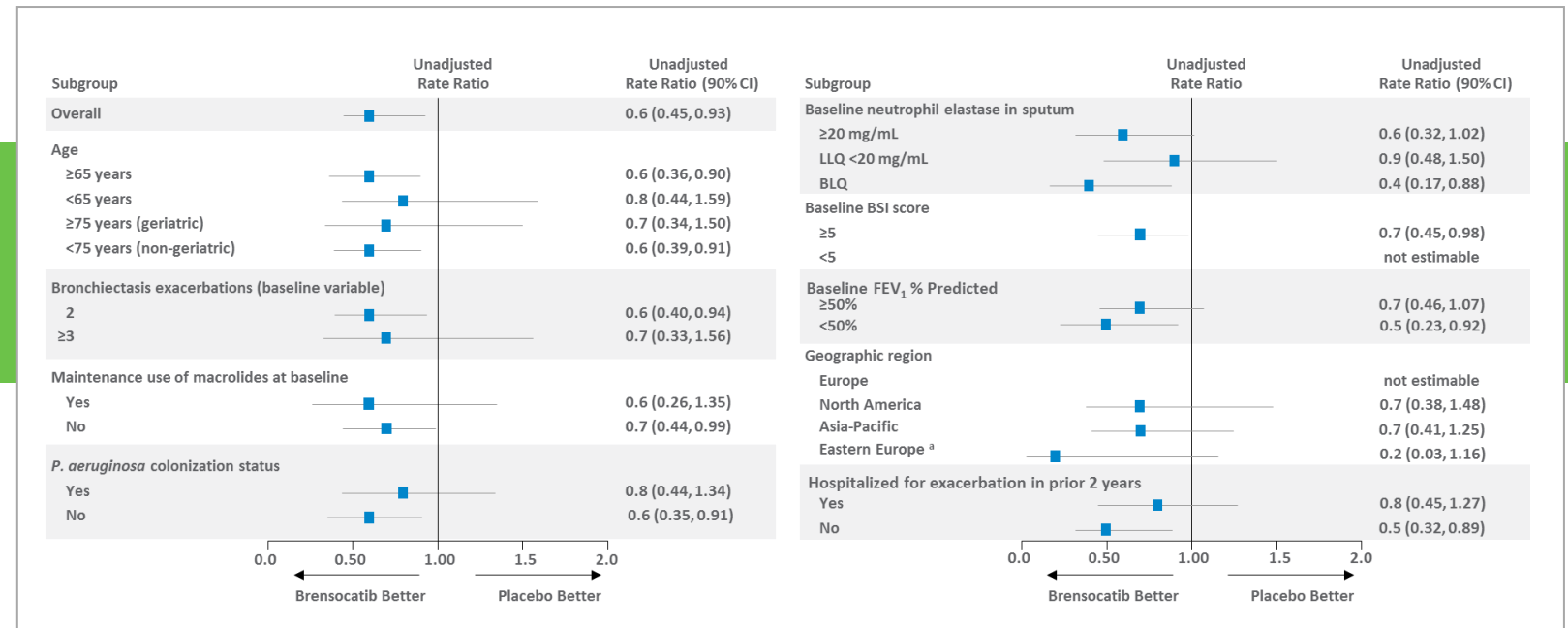
25 mg brensocatib vs. placebo

Rate of Exacerbations

BY PATIENT SUBGROUPS



10 mg brensocatib vs. placebo

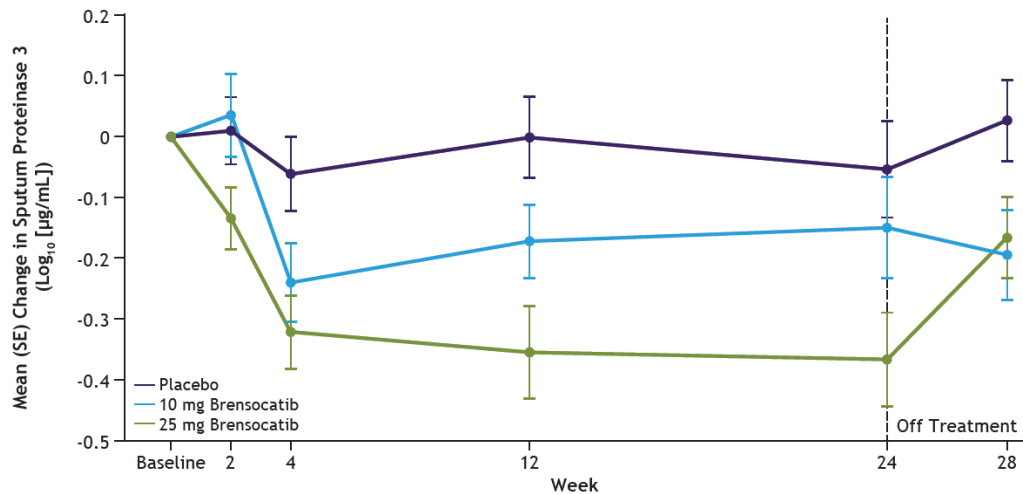


Chalmers et al, ERS International Congress 2020, 7-9 September. RCT4135
BSI, bronchiectasis severity index; FEV₁, forced expiratory volume in 1 second
^aBulgaria/Poland

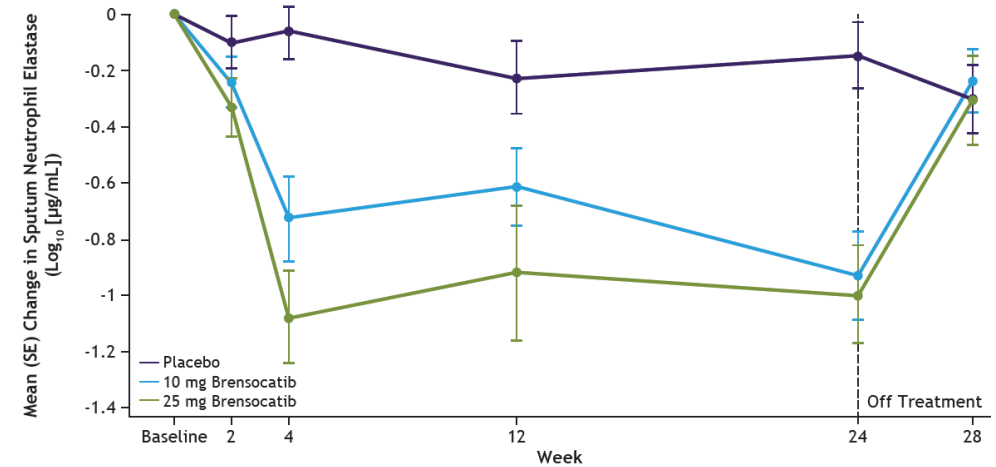
Dose Response Effect Seen Consistently Across Sputum Neutrophil Serine Proteases (NSPs)

MEAN (SE) CHANGE FROM BASELINE
TO WEEK 24 (LOG10 [MG/ML])

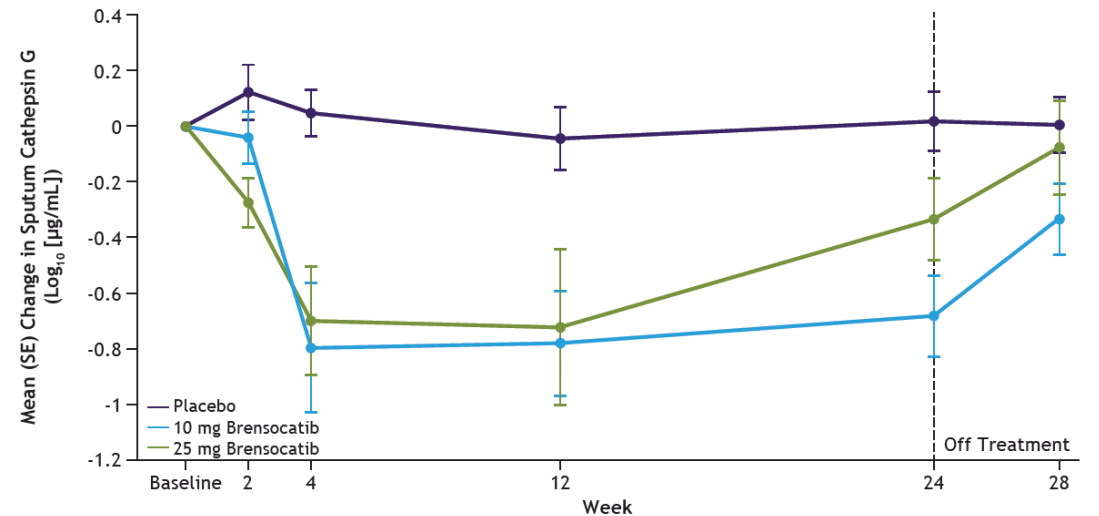
Proteinase 3



Neutrophil Elastase



Cathepsin G

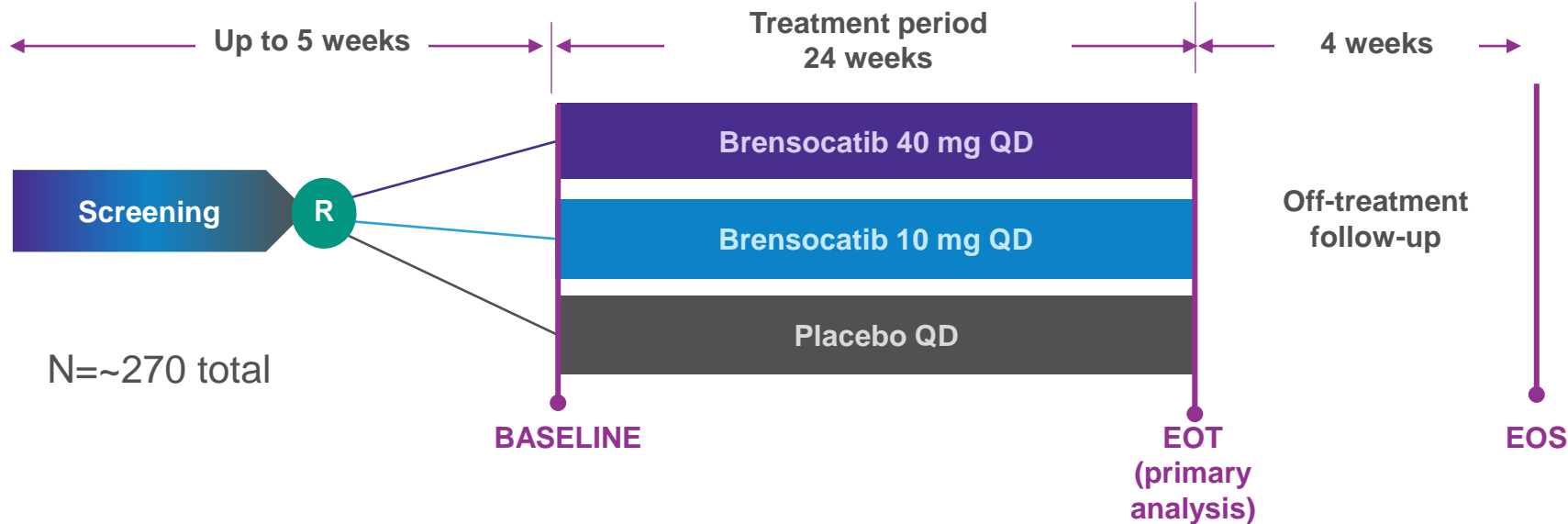


WILLOW

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 2 in CRSsNP: BiRCh Trial



Key eligibility criteria:

- Male or female ≥ 18 years old and ≤ 75 years old
- At least a 12-week history of CRSsNP and confirmed by endoscopy at Screening
- Ongoing CRS symptoms: nasal congestion score of at least 2, sTSS score of at least 5 and sino-nasal outcome test 22 score of at least 20 at screening and baseline
- Blood eosinophil count of ≤ 750 cells/ μ L at Screening
- Previous sinonasal surgery for CRS and/or treatment with systemic steroids or antibiotics for CRS within a year of Screening Visit

Primary Endpoint

Change in daily sinus total symptom score (sTSS)

Secondary Endpoint

- Change in percentage sinus opacification
- Change in modified LMK CT (Lund-MackKay computed tomography) score
- Proportion of participant requiring rescue
- Change in Sino-nasal Outcome Test 22 score

Exploratory Endpoint

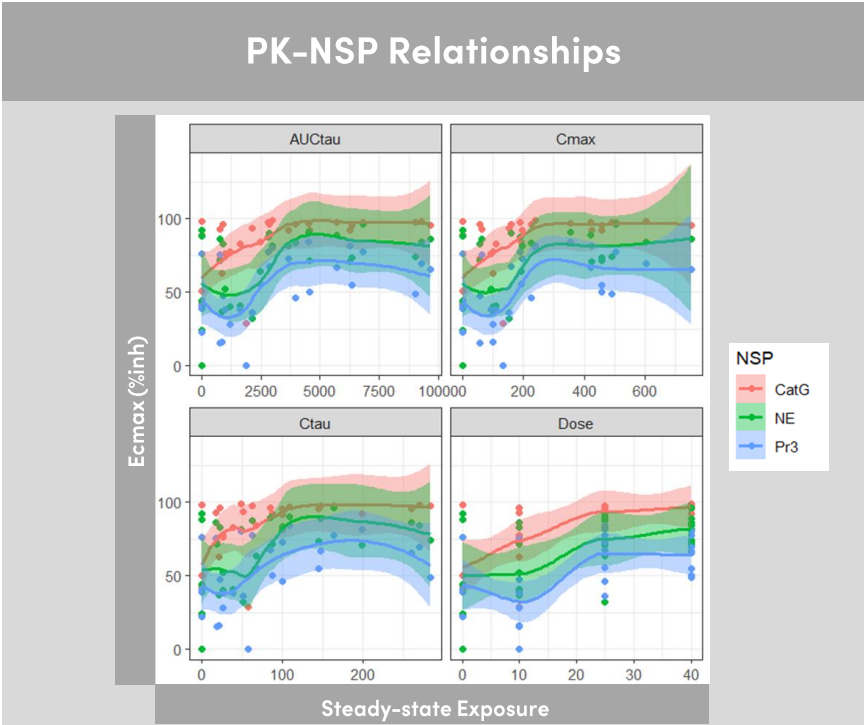
Neutrophil serine proteases (NSPs) in blood

EOS, end of study; EOT, end of treatment; QD, once daily.

CF Phase 2 Topline Data: Dose & Exposure Dependent Inhibition of Blood NSPs was Observed

NSP activity reduction relative to baseline on Day 29 (median):			
DOSE	Neutrophil Elastase (NE)	Cathepsin-G (CatG)	Proteinase 3 (Pr3)
placebo	-14.7%	11.3%	2.5%
10 mg	33.2%	69.5%	15.8%
25 mg	54.9%	86.9%	37.2%
40 mg	74.0%	95.6%	55.0%

Insmed Dataset: Nov 23, 2022



FINDINGS

- Measured NSP data were highly variable within and between subjects
- Average inhibition on NSP activity was dose dependent, and the degree of inhibition appeared to be CatG > NE > Pr3
- Brensocatib demonstrated inhibition of all 3 NSPs especially at the 25 and 40 mg dose levels
- Clear correlations between NSP activity and brensocatib exposure (Cmax, AUC, trough concentration) or dose were observed
- The Company concluded that an additional cohort evaluating a 65 mg dose of brensocatib is not needed in this patient population.

Brensocatib inhibited the NE activity in a dose dependent fashion in all populations tested

Blood/Plasma NE Data Comparison Between Studies

NE activity reduction relative to baseline (median) at 4 week* in Different Populations:			
DOSE	Insmed CF** (INS1007-211)	AstraZeneca Phase 1 Healthy Volunteers (D6190C00001***)	Insmed NCFBE (WILLOW)
placebo	-14.7%	16.5%	3.40%
10 mg	33.2%	34.8%	30.9%
25 mg	54.9%	42.6%	66.5%
40 mg	74.0%	55.1%	NA

* Day 29 data for INS1007-211 and INS1007-201, and Day 28 data for D6190C00001
**INS1007-211 PD Dataset: Nov 23, 2022
*** AZ Study; NE activity was normalized by ANC
Insmed Dataset: Nov 23, 2022

FINDINGS

- NE Inhibition in CF subjects was comparable to that in non-CF subjects
- The degree of NE activity inhibition at Week 4 was generally comparable between CF and non-CF populations

CF Phase 2 Topline Data: Brensocatib was well-tolerated with **no new safety signals** detected

	Brensocatib N:24			Pooled Placebo	Total
DOSE	10 mg QD n: 8 (%) AE	25 mg QD n: 8 (%) AE	40 mg QD n: 8 (%) AE	n: 5 (%) AE	29 (%) AE
Any TEAE	4 (50) 11	5 (62.5) 11	4 (50) 9	2 (40) 5	15 (51) 43
TEAE related to study treatment	0	1 (12.5) 1	1 (12.5) 2 ¹	1 (20) 1 ²	3 (10.3) 4
Serious TEAE	0	0	1 (12.5) 1 ³	0	1 (3.4) 1
Serious TEAE related to study treatment	0	0	0	0	0
TEAE resulting in Death	0	0	0	0	0
TEAE of Special Interest	0	0	0	0	0
TEAE leading to study withdrawal	0	0	0	0	0
TEAE related to COVID-19 ⁴	0	1 (12.5) 2 ⁴	1 (12.5) 1	0	2 (6.9) 3 ⁴

Insmed Dataset: Nov 23, 2022

¹Abdominal pain (temporal association), mild (3 event 2 participants)

²Chromaturia (temporal association), mild

³Pulmonary exacerbation

⁴Includes an TEAE of "fatigue" related to COVID-19

FINDINGS

- Thirteen participants in brensocatib arms and two in placebo reported 43 TEAEs
- One reported SAE of pulmonary exacerbation in brensocatib 40 mg arm (not related). Four TEAEs were related to study drug (3 in brensocatib and 1 in placebo arms).
- There were no deaths nor AESIs.

Strong Phase 2 Data Lead to Confidence in Phase 3

WILLOW VS. ASPEN TRIAL DETAILS

	WILLOW	ASPEN
Sample Size	256 Pts (~85 pts/arm)	1,682 Pts* (~560 pts/arm)
Powering Assumptions	80% for a 40% reduction	90% for a 30% reduction
Mean Exacerbation Rate (Events/Patient/Year)	1.37 (actual) 1.2 (planned)	1.2
Robust Definition of Pulmonary Exacerbation	Consistent	Consistent
Duration of Therapy	6 months	12 months
Primary Endpoint	Time to first exacerbation	Rate of pulmonary exacerbation

Consistent baseline characteristics across both the ASPEN and WILLOW trials

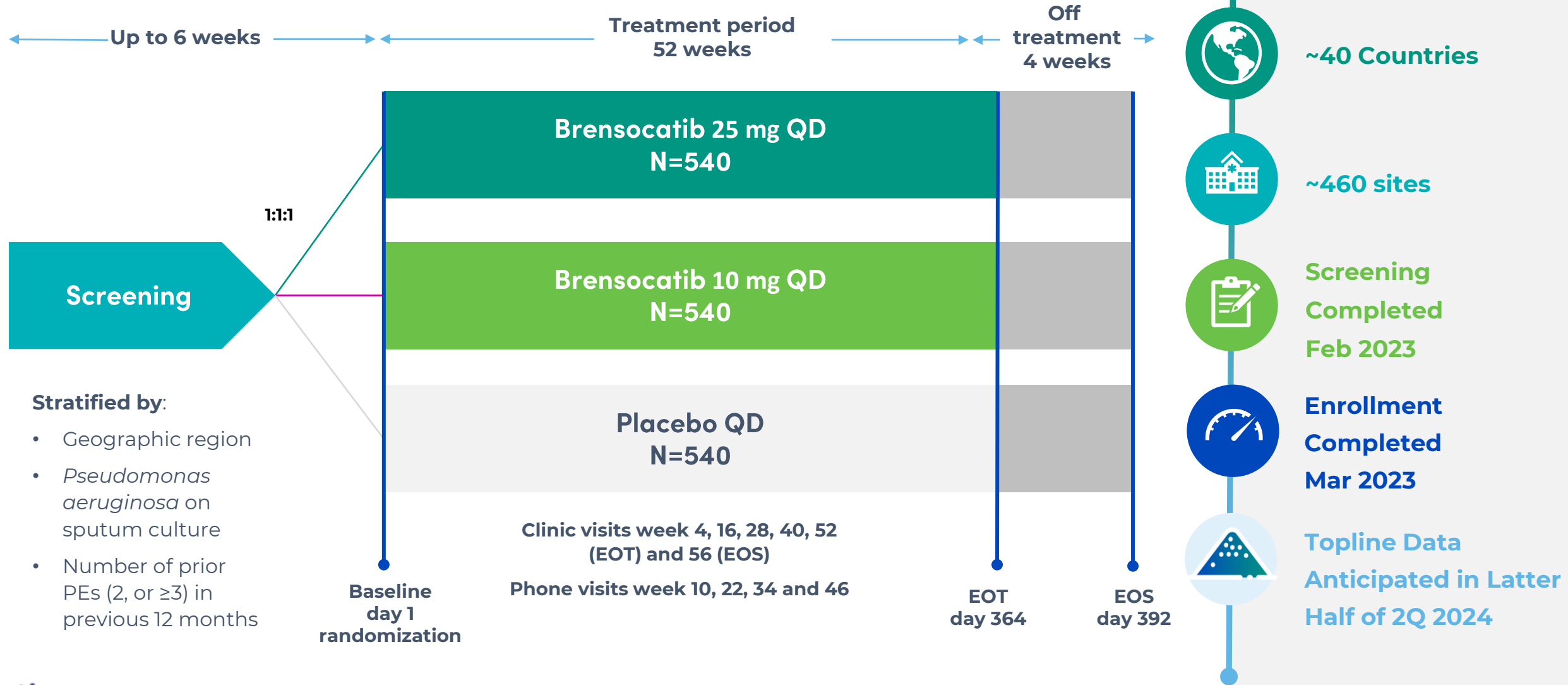
Characteristics	ASPEN ¹	WILLOW
Number of patients	1,682*	256
Mean age (yrs)	61.3	64.1
≥ 75 years (n, %)	262, 15.6%	48, 18%
Female (n, %)	1,089, 64.7%	174, 67.9%
Number of patients with history of COPD as secondary** (n, %)	241, 14.3%	42, 16.4%
Number of patients with history of asthma as secondary** (n, %)	302, 17.9%	64, 25%
Pseudomonas aeruginosa positive (n, %)	589, 35.0%	89, 34.8%
Chronic macrolide use (n, %)	285, 16.9%	40, 15.6%
≥3 exacerbations in prior 12 months (n, %)	492, 29.3%	84, 32.8%
2 exacerbations in prior 12 months (n, %)	1,190, 70.7%	172, 67.2%

* Evaluable adult subjects

** As reported by medical history

¹ Represents preliminary figures

ASPEN Phase 3 Study Design



TPIP at High Dose

SHOWED SUPERIOR EFFECT OVERALL IN
THE SUGEN-HYPOXIA RAT MODEL FOR PAH

Parameter value =
$$\frac{(\text{Value} - \text{Value of Normal})}{(\text{Value of Vehicle} - \text{Value of Normal})}$$

Fulton Index = weight ration
Right Ventricle / (Left Ventricle + Septum)

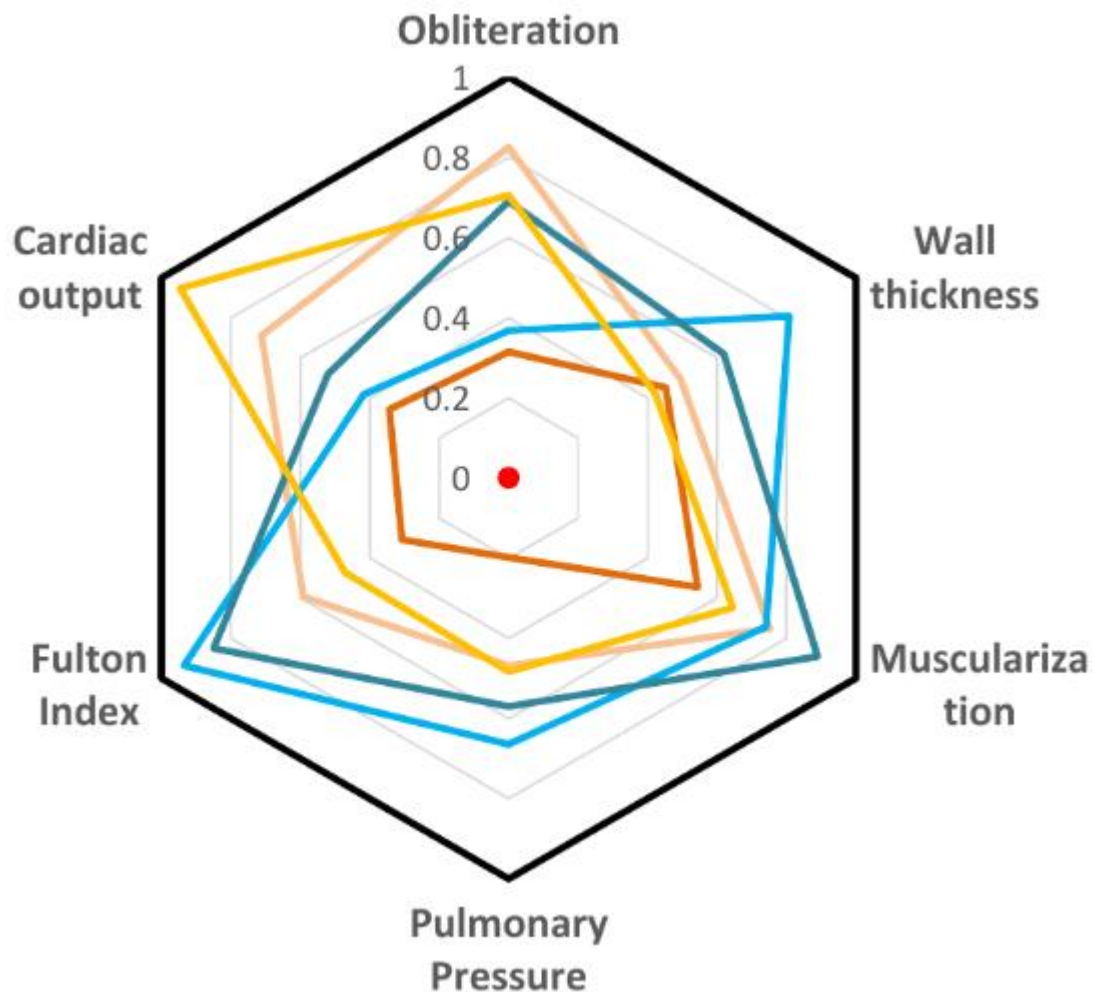
Pulmonary Pressure
mean Pulmonary Arterial Pressure

Obliteration
% of non-obiterated vessels

Wall thickness
Small vessel wall thickness

Muscularization
% of muscularized vessels

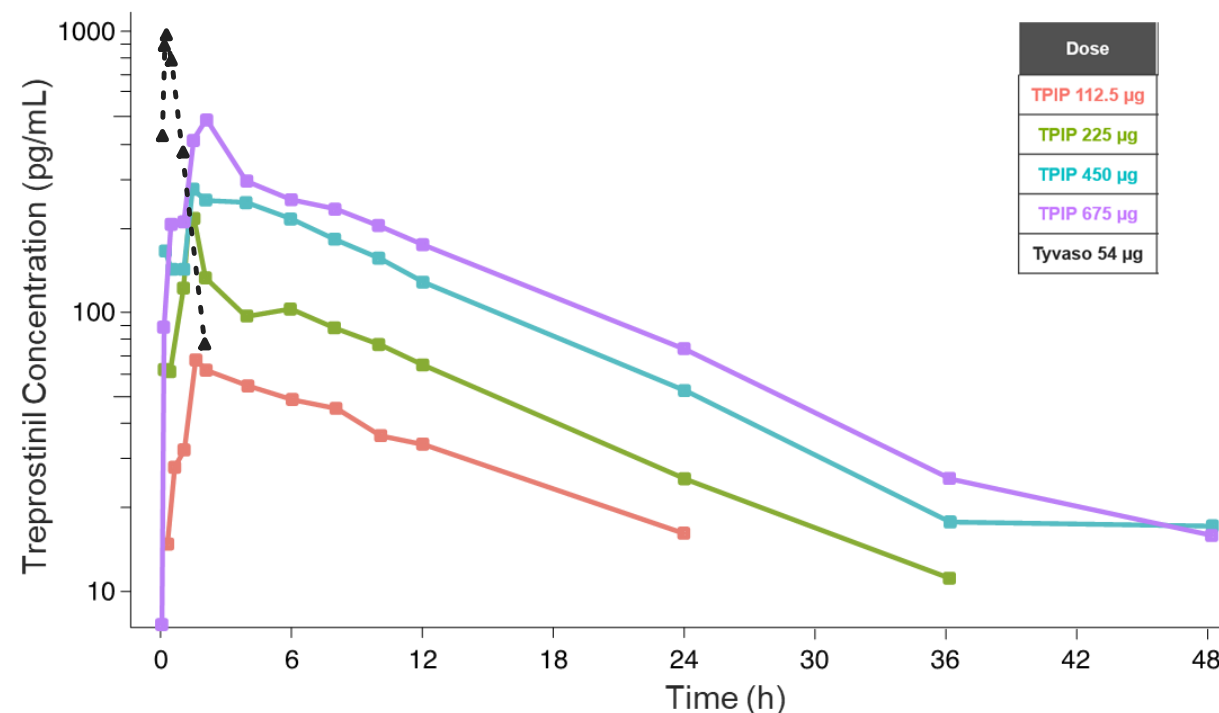
Cardiac Output
amount of blood pumped by the heart
per minute



Key Takeaways

from TPIP Phase 1 study

- Safety profile was generally **well tolerated**, AEs were mild and **consistent with inhaled prostanoid**
- Tolerability was improved with **an up-titration approach**
- Findings suggest TPIP may be safely **dosed at nominal doses far in excess of Tyvaso**
- PK supports development of TPIP with **once daily dosing**
- TPIP showed substantially **lower C_{max} and longer half-life** than that of Tyvaso
- Future studies would use an up-titration dosing schedule to the maximum individual tolerated dose **exceeding 600 μg once daily**



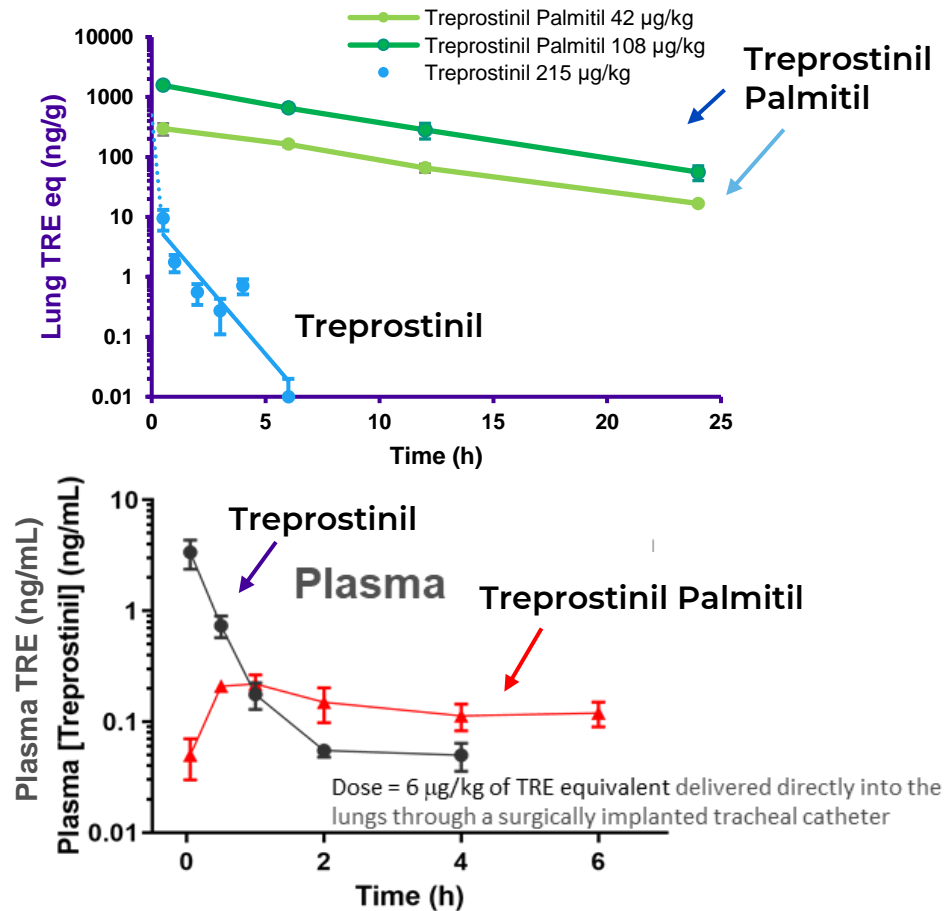
Supports the potential for improved tolerability, efficacy and convenience

TPIP showed substantially lower C_{max} and longer half-life

Improved Pharmacokinetics:

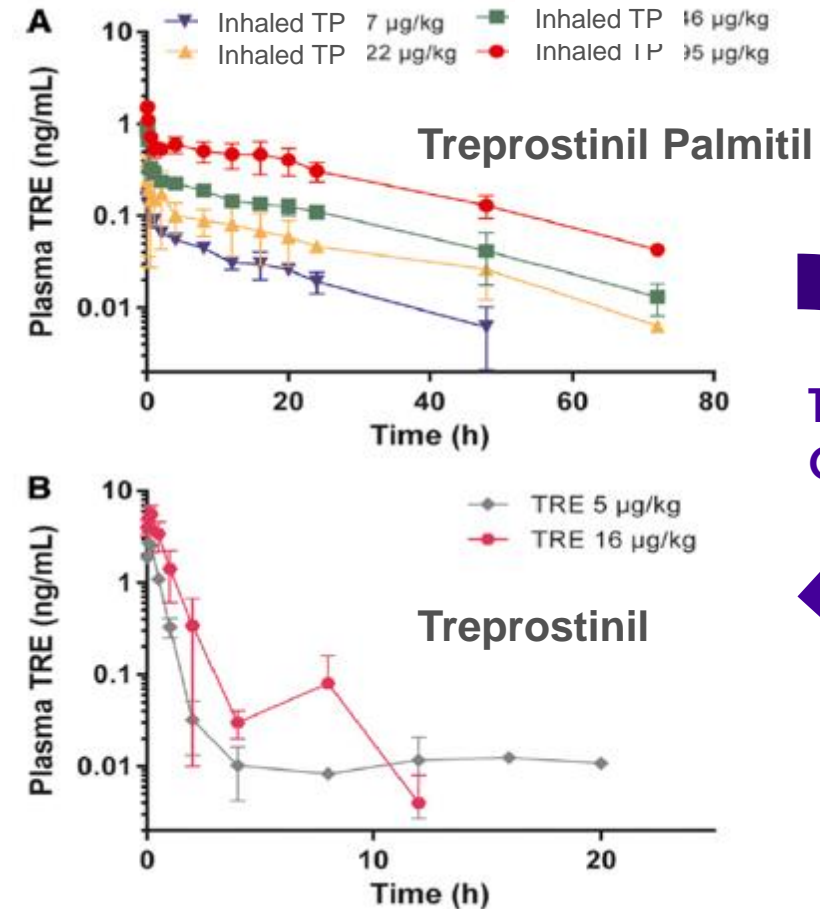
PROLONGED LUNG RESIDENCE, LOWER C_{MAX}, PROLONGED HALF LIFE (RAT AND DOG)

RAT Lung and Plasma Levels



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

DOG Plasma Levels



10X
C_{max}

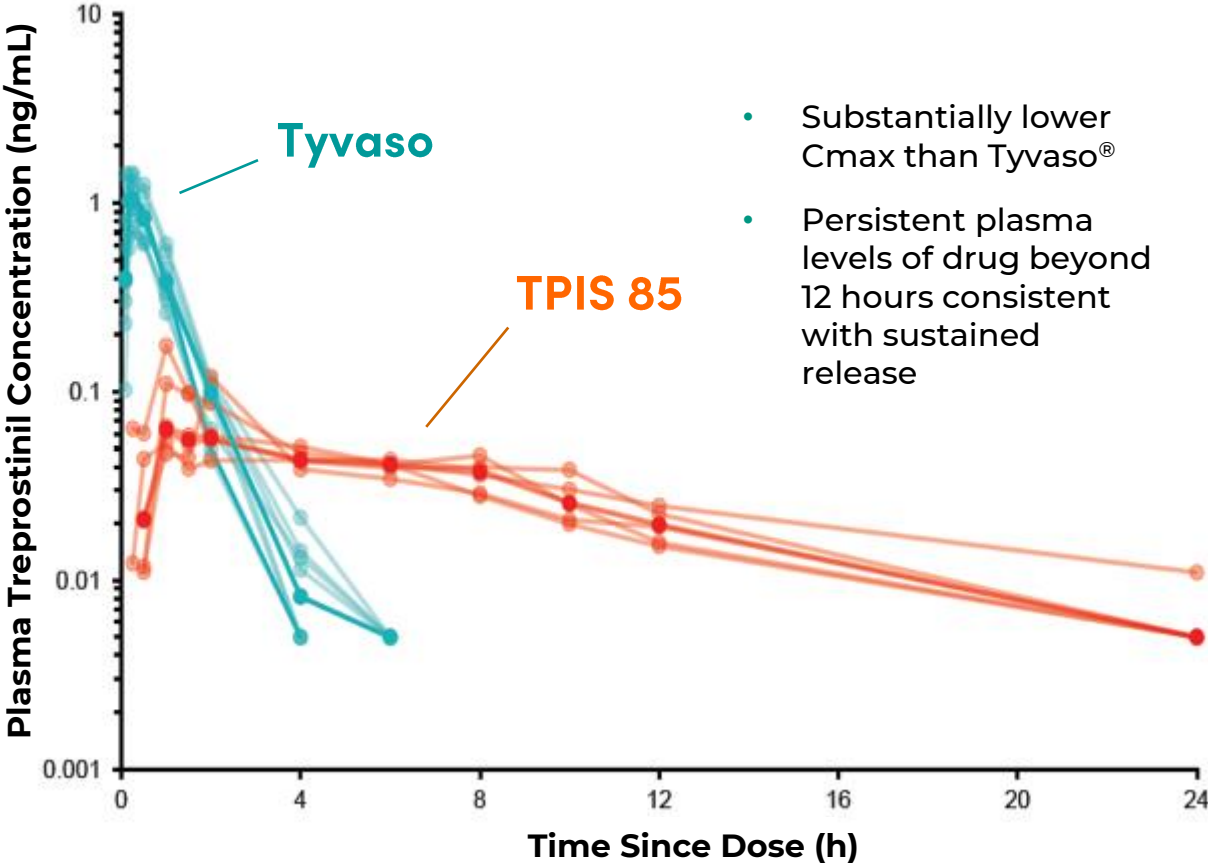
M. R. Corboz, et al. (2017) J. Pharmacol. Exp. Ther. 363:348-357.

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



SAD Cohorts:

TREATMENT EMERGENT ADVERSE EVENTS (TEAES)

TEAEs were Consistent with Inhaled Prostanoid and Mostly Mild

	112.5 µg (6)	225 µg (6)	450 µg (6)	675 µg (6)	Placebo (2)	Total (26)
Completed (%)	6 (100)	6 (100)	6 (100)	6 (100)	2 (100)	26 (100)
TEAEs (%)	4 (66.7)	3 (50.0)	4 (66.7)	6 (100)	0 (0.0)	17 (65.4)
Moderate TEAEs (%)	0 (0.0)	1 (16.7)	0 (0.0)	3 (50.0)	0 (0.0)	4 (15.4)
Prostanoid-Related AEs						
Dizziness (%)	1 (16.7)	1 (16.7)	2 (33.3)	3 (50.0)	0 (0.0)	7 (26.9)
Nausea (%)	0 (0.0)	1 (16.7)*	2 (33.3)	1 (16.7)	0 (0.0)	4 (15.4)
Hypotension (%)	0 (0.0)	1 (16.7)	1 (16.7)	2 (33.3)*	0 (0.0)	4 (15.4)
Headache (%)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	2 (7.7)
Vomiting (%)	0 (0.0)	1 (16.7)*	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
Respiratory / Other Notable AEs						
Cough (%)	2 (33.3)	2 (33.3)	3 (50.0)	4 (66.7)	0 (0.0)	11 (42.3)
Throat Irritation (%)	2 (33.3)	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	5 (19.2)
Chest Discomfort (%)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)*	0 (0.0)	3 (11.5)
Low O ₂ Saturation	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)*	0 (0.0)	1 (3.8)
Dyspnea	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (3.8)

* Moderate TEAEs: 225 µg – 1 subject with nausea and vomiting; 675 µg – 2 subjects with hypotension, 1 subject with chest discomfort, low oxygen saturation and dyspnea
Includes all AEs that occurred in more than two subjects, as well as others of interest

MAD Cohorts:

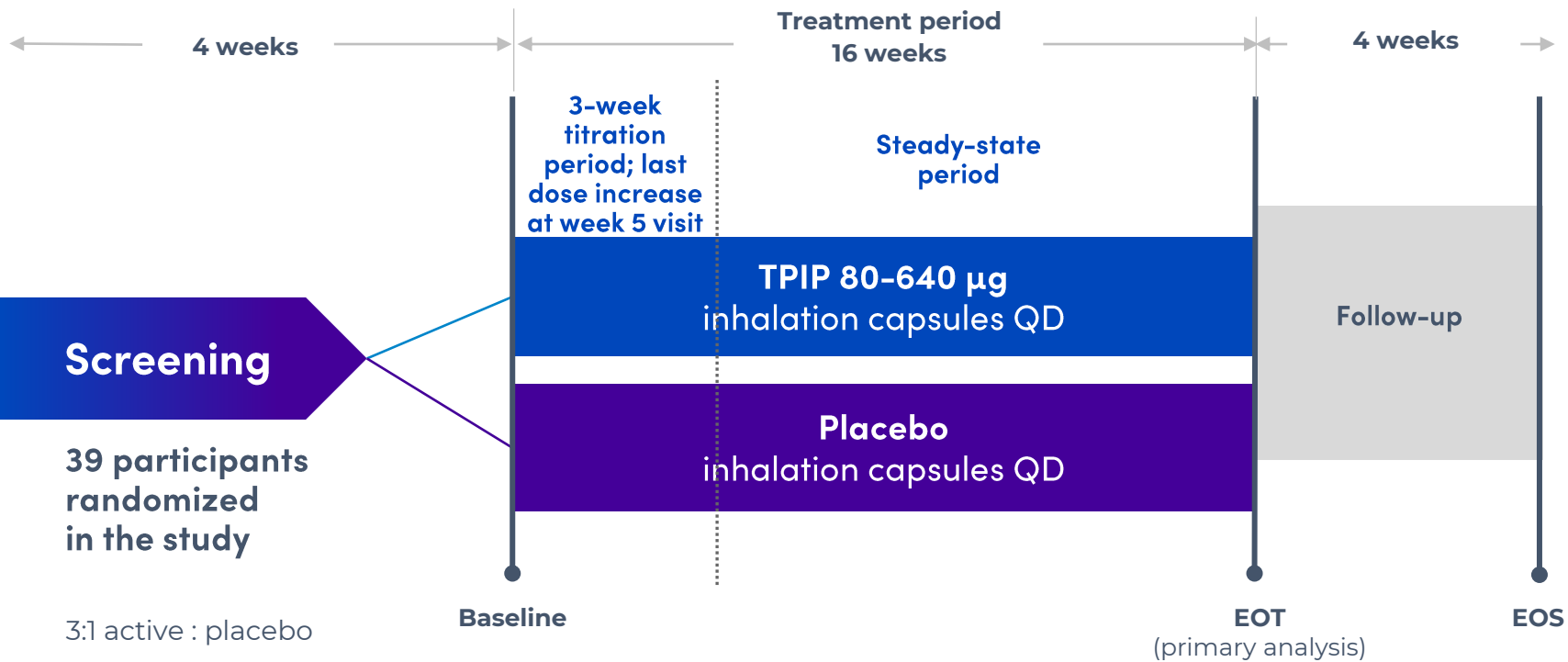
SUBJECT DISPOSITION, TEAEs

Lower TEAE
Frequency with Titration
and Mostly Mild

	225µg (6)	112.5-225 µg (6)	Placebo (4)	Total (15)
Completed (%)	5 (83.3)	6 (100)	4 (100)	15 (93.8)
TEAEs (%)	6 (100.0)	4 (66.7)	2 (50.0)	12 (75.0)
Moderate TEAEs (%)	3 (50.0)	0 (0.0)	0 (0.0)	3 (18.8)
Prostanoid-Related AEs				
Headache (%)	4 (66.7)	2 (33.3)	0 (0.0)	6 (37.5)
Nausea (%)	3 (50.0)	1 (16.7)	0 (0.0)	4 (25.0)
Dizziness (%)	2 (33.3)	1 (16.7)	0 (0.0)	3 (18.8)
Syncope (%)	1 (16.7)*	0 (0.0)	0 (0.0)	1 (6.3)
Diarrhea (%)	1 (16.7)	0 (0.0)	0 (0.0)	1 (6.3)
Abdominal Pain (%)	1 (16.7)	0 (0.0)	0 (0.0)	1 (6.3)
Hypotension (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory AEs				
Cough (%)	6 (100.0)	1 (16.7)	2 (50.0)	9 (56.3)
Throat Irritation (%)	1 (16.7)*	0 (0.0)	0 (0.0)	1 (6.3)
Chest Discomfort (%)	1 (16.7) 1 (16.7)*	2 (33.3)	0 (0.0)	4 (25.0)

* Moderate TEAEs: 225 µg – 1 subject with chest discomfort (subject discontinued day 2), 1 subject with throat irritation (day 2-7), 1 subject with syncope (day 1)
Includes all AEs that occurred in more than two subjects, as well as others of interest

TPIP Phase 2 in PH-ILD



Primary Endpoint

- Safety and tolerability
- Oxygenation

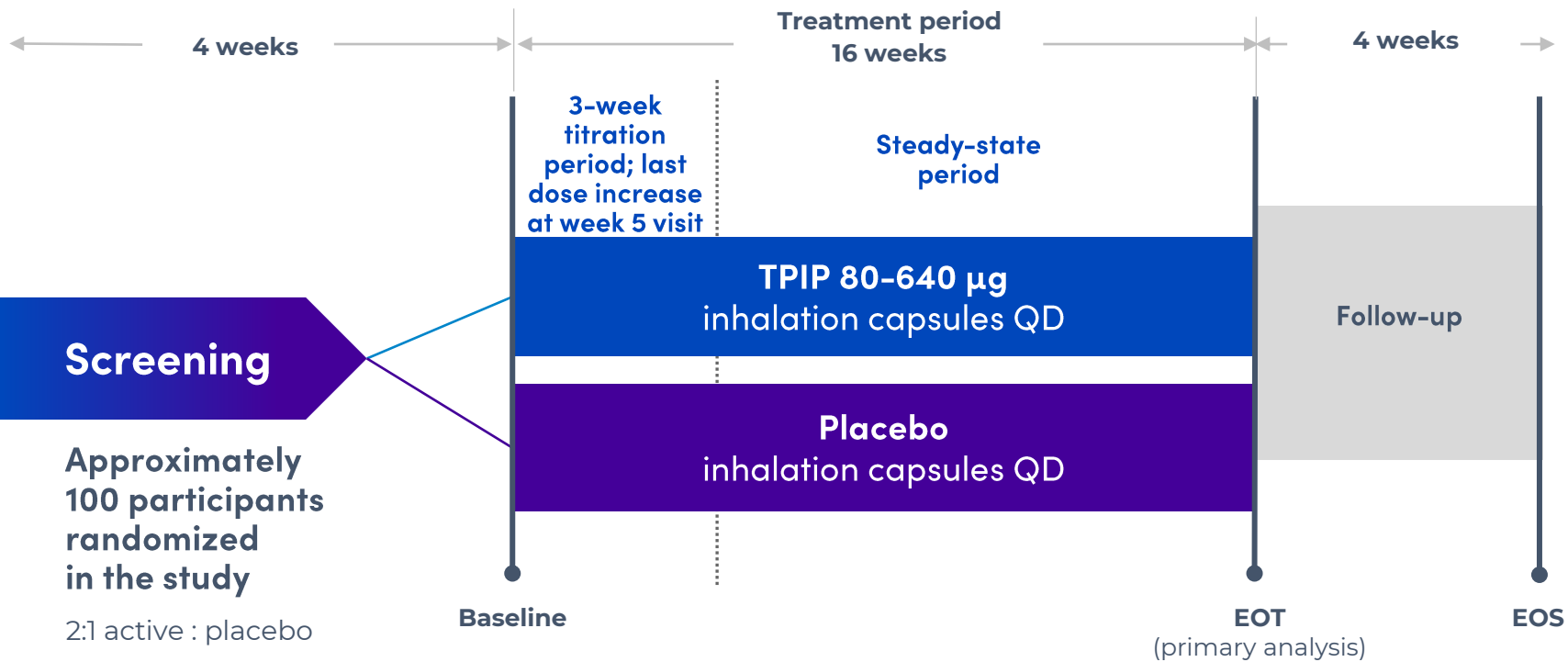
Secondary Endpoint

PK

Exploratory Efficacy Endpoints

- Improvement in exercise capacity (6MWD)
- Improvement in biomarkers of cardiac stress (NT-proBNP)
- Improvement in lung function and pulmonary vascular volume (FRI)
- Improvements in Quality of Life (CAMPOR questionnaire)

TPIP Phase 2b in PAH



Primary Endpoint

Change from baseline in pulmonary vascular resistance (PVR) at week 16

Secondary Exploratory Efficacy Endpoints

- Change from baseline in exercise capacity (6MWD)
- Change from baseline in WHO Functional class
- Change from baseline in Quality of Life (CAMPHOR questionnaire)
- Change from baseline in biomarkers of cardiac stress (NT-proBNP)