

# Bellerophon Therapeutics

Company Presentation | June 2022

# Forward Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make due to a number of important factors, including risks and uncertainties relating to: INOpulse® not proving to be an effective treatment for COVID-19 or approved for marketing by the FDA, the timing and outcomes of our ongoing and expected clinical trials for our product candidates; our ability to successfully develop, commercialize and market any of our product candidates; our ability to obtain, maintain and enforce intellectual property rights; competition; our reliance on third parties; our ability to obtain necessary financing; and those risk factors discussed in the “Risk Factors” section and elsewhere in our most recent Form 10-K and other periodic filings we make with the SEC.

All forward-looking statements contained in this presentation reflect our current views with respect to future events. We assume no obligation, except as required by applicable law, to update any forward-looking statements publicly, or to update the reasons why actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

# Bellerophon Therapeutics (BLPH)

**Late-stage  
biotherapeutics  
company developing  
inhaled nitric oxide  
(iNO) therapies to  
address significant  
unmet need in serious  
cardiopulmonary  
disorders**

- **INOpulse® inhaled nitric oxide (iNO) for chronic use**
  - Targeted, pulsatile NO delivered via proprietary, portable, user-friendly device
  - Inhalational delivery to well ventilated areas of the lung overcomes drawbacks of systemic vasodilators
  - Positive results from multiple Phase 2 studies support mechanism of action
- **Broad market opportunity in multiple cardiopulmonary disorders**
  - Fibrotic interstitial lung disease (fILD) represents a broad underserved population >200K patients
  - Potential \$1Bn+ markets in follow-on indications of pulmonary hypertension (PH) associated with sarcoidosis & chronic obstructive pulmonary disease (COPD)
  - IP protection up to 2039 before extensions
- **Simplified de-risked regulatory pathway**
  - NO approved for use in neonates (Ikaria); ability to leverage existing NDA
  - FDA agreement on MVPA primary endpoint in fILD Phase 3 REBUILD trial
- **Highly experienced leadership team and solid financials**
  - Unrestricted cash & equivalents \$20.0 M<sup>1</sup>; no debt<sup>1</sup>; 11.8 million shares outstanding<sup>1,2</sup>

# Highly Experienced Leadership Team with Expertise in Respiratory & Rare Diseases



**Naseem Amin, M.D.**  
Chairman of the Board of  
Directors



**Edwin Parsley, D.O.**  
Acting Chief Medical  
Officer



**Peter Fernandes**  
Principal Executive Officer;  
Chief Regulatory, Safety &  
Quality Officer



**Parag Shah, Ph.D.**  
VP, Business Operations



**Nicholas Laccona**  
Principal Financial &  
Accounting Officer



**Martin Dekker**  
VP, Device Engineering  
& Manufacturing



# Addressing Unmet Needs in Multiple Cardiopulmonary Diseases

## INOpulse development pipeline



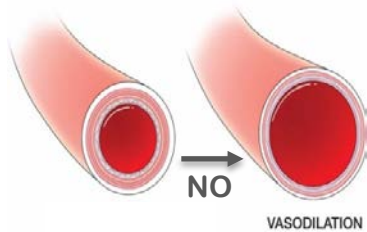
Indication	Phase 1	Phase 2	Phase 3	Current Status
<b>fILD</b> Fibrotic Interstitial Lung Disease at risk of Pulmonary Hypertension				<b>REBUILD trial recruiting</b> Underpinned by positive Phase 2 acute hemodynamic trial (2020) & Phase 2 chronic trial (2019)
<b>PH-SARC</b> Pulmonary Hypertension associated with Sarcoidosis				<b>Acute hemodynamic study completed</b> Positive study results reported end-2021 Phase 2 chronic use trial to be designed
<b>PH-COPD</b> Pulmonary Hypertension associated with COPD				<b>Phase 2b ready</b> Multiple phase 2 studies completed Phase 2b trial design finalized



# Nitric Oxide is a well-established vasodilator being developed for ambulatory setting

## Portable Delivery System Allows Chronic iNO Therapy

### Nitric Oxide



“Molecule of the Year” 1992<sup>1</sup>

Nobel Prize for discovering  
its signaling role<sup>2</sup>

### Hospital based acute therapy



- Approved for use in 1999 for persistent pulmonary hypertension in neonates
- Continuous flow iNO delivery system for acute administration
- Commercially established for 20+ years

### Ambulatory chronic therapy

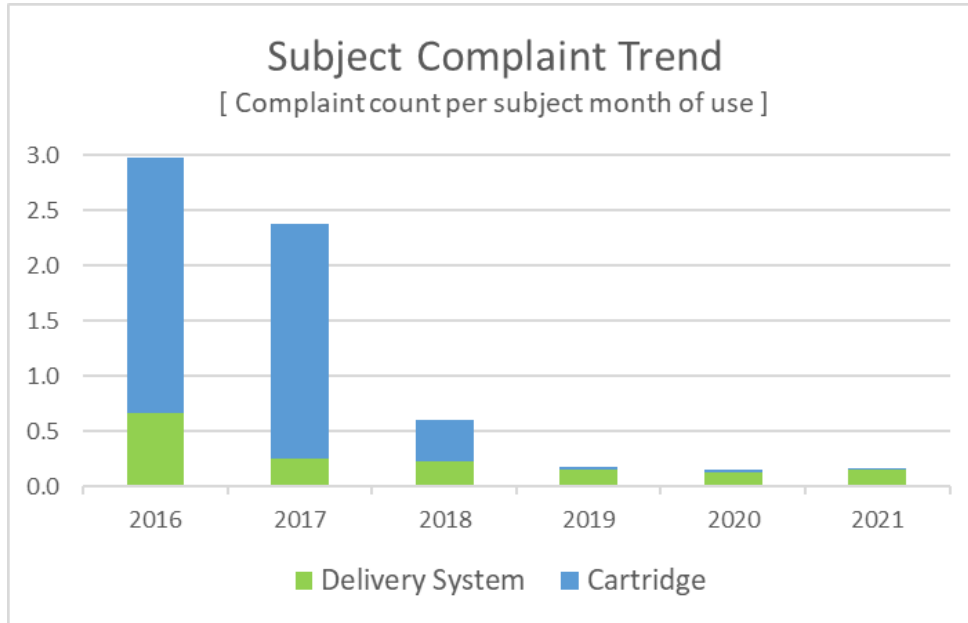
**INO**pulse®



- Portable pulsatile iNO delivery system for use in chronic in-home setting
- 376 patients treated to date in PH trials; average duration of ~10 months each
- Additional 368 patients treated as part of COVID-19 related clinical trial
- Cumulative subject exposure 300+ years; longest subject treatment 8+ years<sup>3</sup>

# INOpulse Delivery System performance in clinical trial setting

Significant quality improvements achieved following introduction in 2016



**Delivery System data represents both the INOpulse Device and Cannula**

**REBUILD patients receive:**

- Two INOpulse Devices upon enrollment
- One INOpulse Cannula for every two weeks of use
- One re-fillable INOpulse Cartridge per day of use

**95% improvement achieved in 2021 compared to 2016 across the INOpulse Device, Cannula and Cartridge**

**Active continuous improvement process ongoing; additional trend reduction expected during course of the REBUILD trial**

# Preventing Ventilation/Perfusion Mismatch is Critical in PH

## Baseline

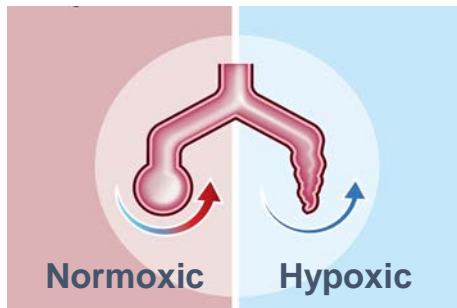
Significant lung disease results in alveolar hypoxia



Triggers protective hypoxic vasoconstriction response



Prevents systemic oxygen desaturation but increases pulmonary pressure resulting in PH

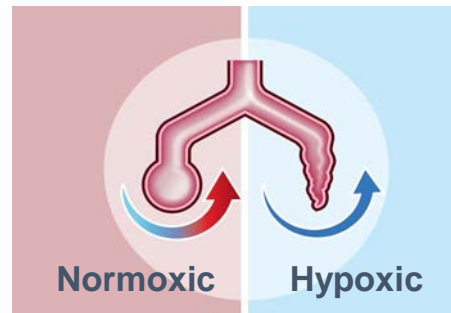


## Systemic therapies

Generalized vasodilation

Reverses protective hypoxic vasoconstriction response

Results in ventilation / perfusion (V/Q) mismatch and worsened systemic oxygenation



## INOpulse®

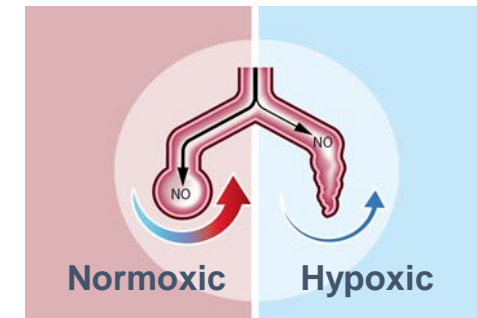
Targeted vasodilation of only well ventilated alveoli



Synergistic with hypoxic vasoconstriction response



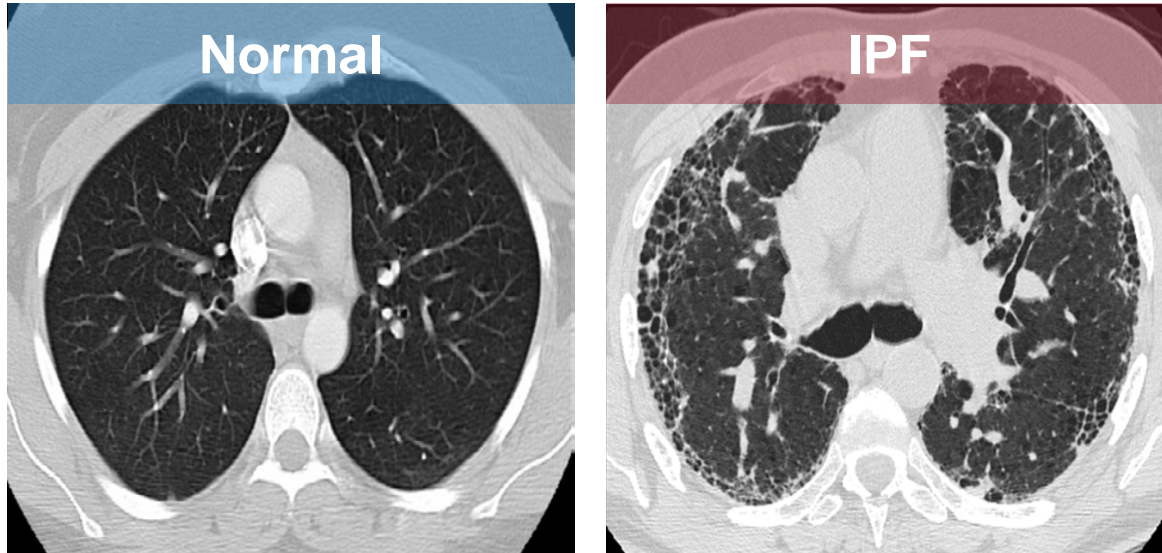
Prevents V/Q mismatch, improves systemic oxygenation, improves PH





# Fibrotic Interstitial Lung Disease (fILD)

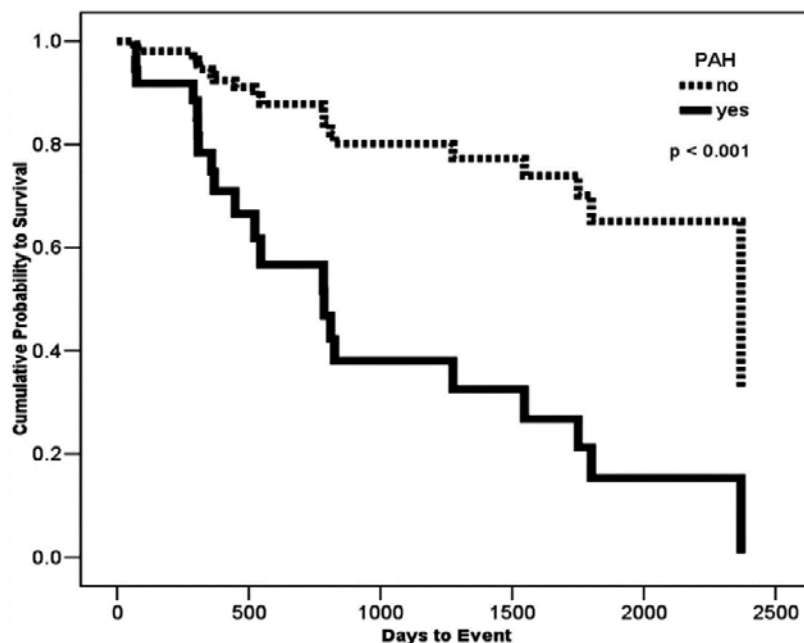
A broad category of diffuse lung diseases with significant unmet need



- Characterized by variable amounts of inflammation and fibrosis of lung air sacs
- Idiopathic Pulmonary Fibrosis (IPF) is the most commonly diagnosed and most serious fILD
- Patients often require supplemental oxygen (O<sub>2</sub>) to maintain O<sub>2</sub> saturation
- Severely impaired quality of life and limitations on activities of daily living
- Prognosis and survival significantly worse for patients with associated pulmonary hypertension (PH)

# Pulmonary Hypertension (PH) associated with fILD Significantly Reduces Survival

## Pulmonary Hypertension as Predictor of Survival in IPF



~40%

of IPF patients exhibit PH symptoms at rest

3x

increase in risk of death with PH-IPF vs. IPF alone

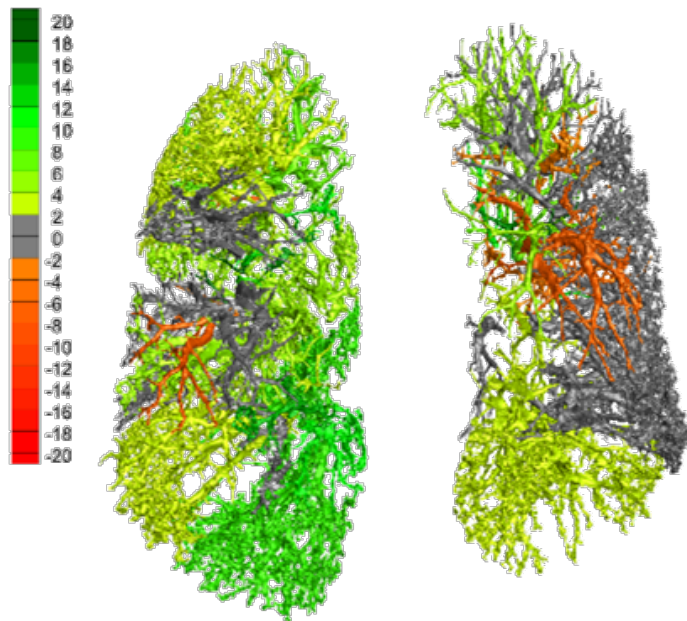
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approved therapies to improve physical function or quality of life<sup>†</sup>

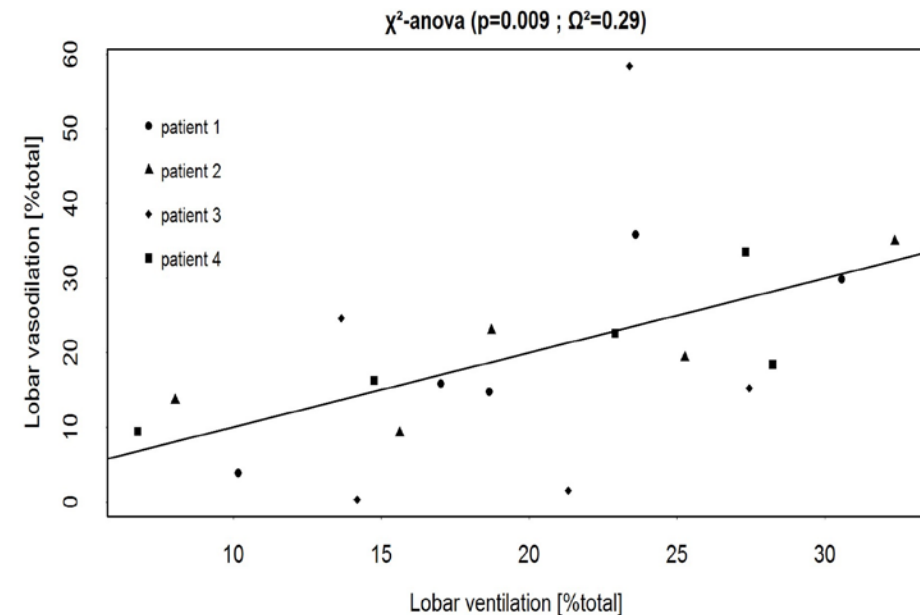
# INOpulse Demonstrates Targeted Vasodilation in fILD Supporting the Mechanism of Action

Acute Phase 2 Data Showed Immediate Benefit of INOpulse on Vasodilation and Ventilation/Perfusion Matching

Targeted vasodilation to better ventilated areas of lung



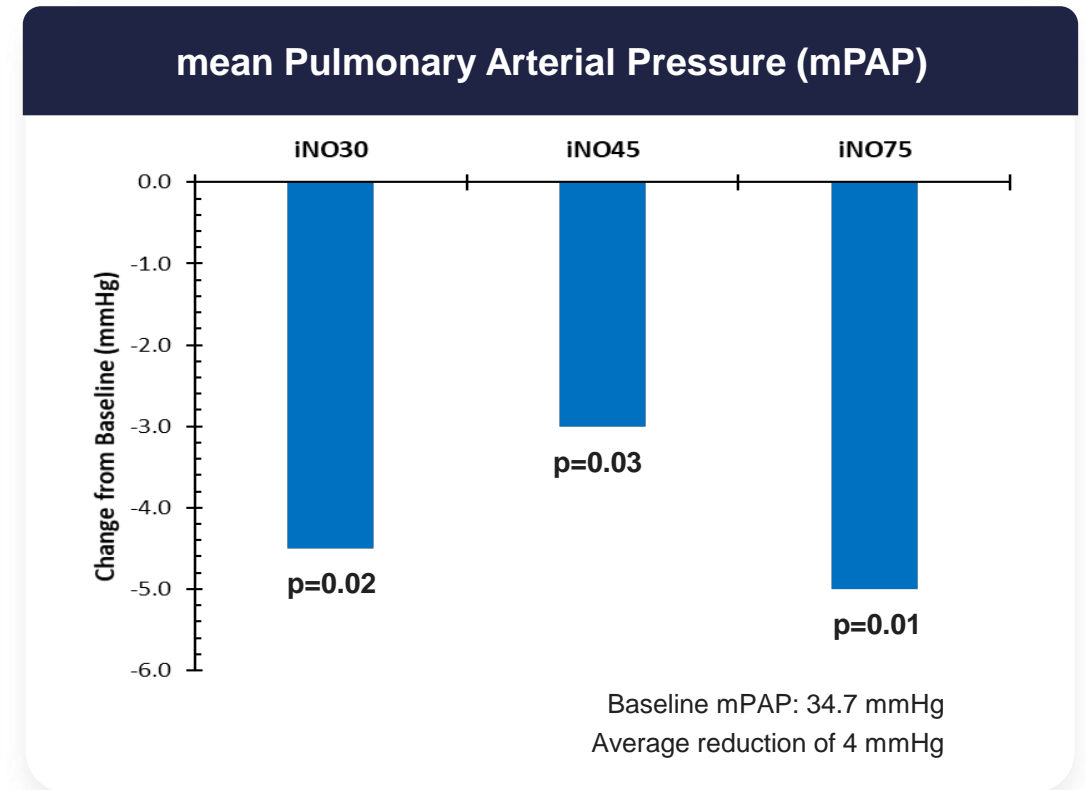
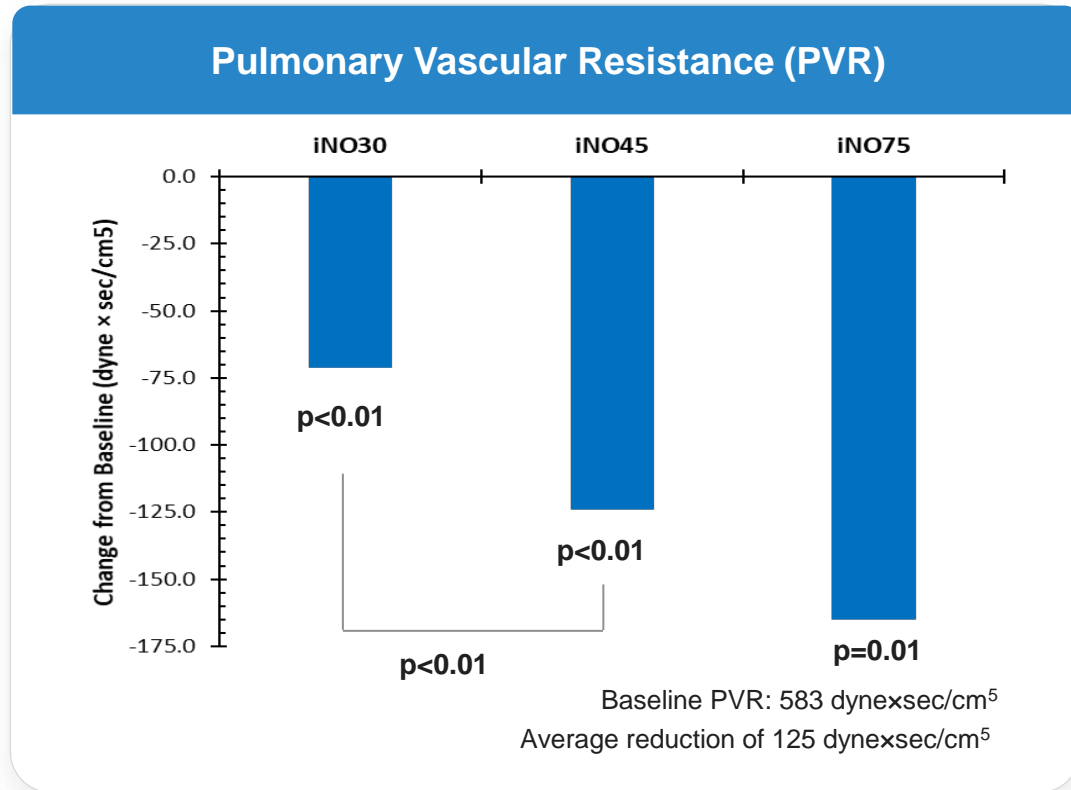
Significant correlation between ventilation/vasodilation matching



# Acute Hemodynamic Benefit in fILD Supports Continuing iNO45 in Phase 2b/3

Clinically and statistically meaningful cardiopulmonary improvement on iNO30 with statistically significant benefit in PVR on dose escalation to iNO45

- Pulmonary hemodynamics measured via right heart catheterization at baseline and following each sequential iNO dose



Bar graphs are median values at each assessment for all available study participants; p-value based on Wilcoxon Rank Test (no correction for multiplicity); Oxygen saturation remained stable and iNO was well-tolerated with no safety concerns across doses; Data based on 9 fILD study participants

# Phase 2 Development in fILD used to Select Primary Endpoint

Exploratory trial designed to identify optimal endpoints and dose for Phase 3 trial

PHASE 2 Chronic study	Cohort 1: n=41 iNO30 vs placebo (1:1) 2-month blinded treatment	Complete	Cohort 1 study participants continue in open label extension (OLE)
	Cohort 2: n=44 iNO45 vs placebo (2:1) 4-month blinded treatment	Complete	Cohort 2 study participants continue in open label extension (OLE)

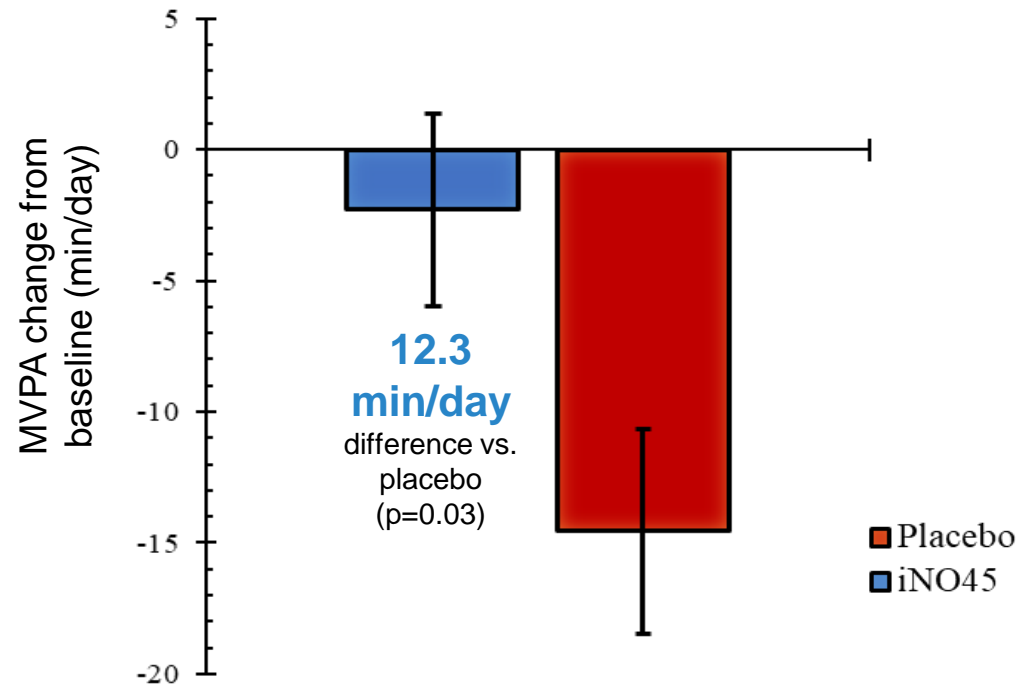
- Trial assessed multiple exploratory endpoints including actigraphy (continuous monitoring of daily physical activity) and patient reported outcomes
- Both cohorts supported use of MVPA (moderate to vigorous physical activity) assessed by actigraphy as the optimal endpoint to progress into Phase 3
- FDA acceptance of the overall study design and MVPA as the primary endpoint for the Phase 3 registration study, with the validation of the MVPA endpoint by establishing meaningful changes in PROs

fILD diagnosed in accordance with accepted guidelines and confirmed by high resolution CT (HRCT) scan; Forced vital capacity (FVC) of  $\geq 40\%$  predicted in the 6 months prior to screening; Needing supplemental oxygen defined as desaturation to  $\leq 88\%$  at rest or with exertion

## Phase 2 data supports use of MVPA measurement as primary endpoint for Phase 3 trial

Target patient population has a median survival of 1.5 to 2 years and typically struggle to perform basic activities such as walking up stairs, showering, housework<sup>†</sup>

Moderate to vigorous physical activity (MVPA; min/day)  
maintained on iNO45 while placebo patients deteriorate



### 14.6 min/day decline in MVPA on placebo; 2.3 min/day decline in MVPA on iNO45 at month 4

- 12.3 min/day (~21%) difference in time spent in MVPA as compared to placebo
- 10-20% change in actigraphy parameters estimated to be clinically relevant in diseased populations (fILD, COPD, heart failure)<sup>‡</sup>

### Similar trend seen in overall activity

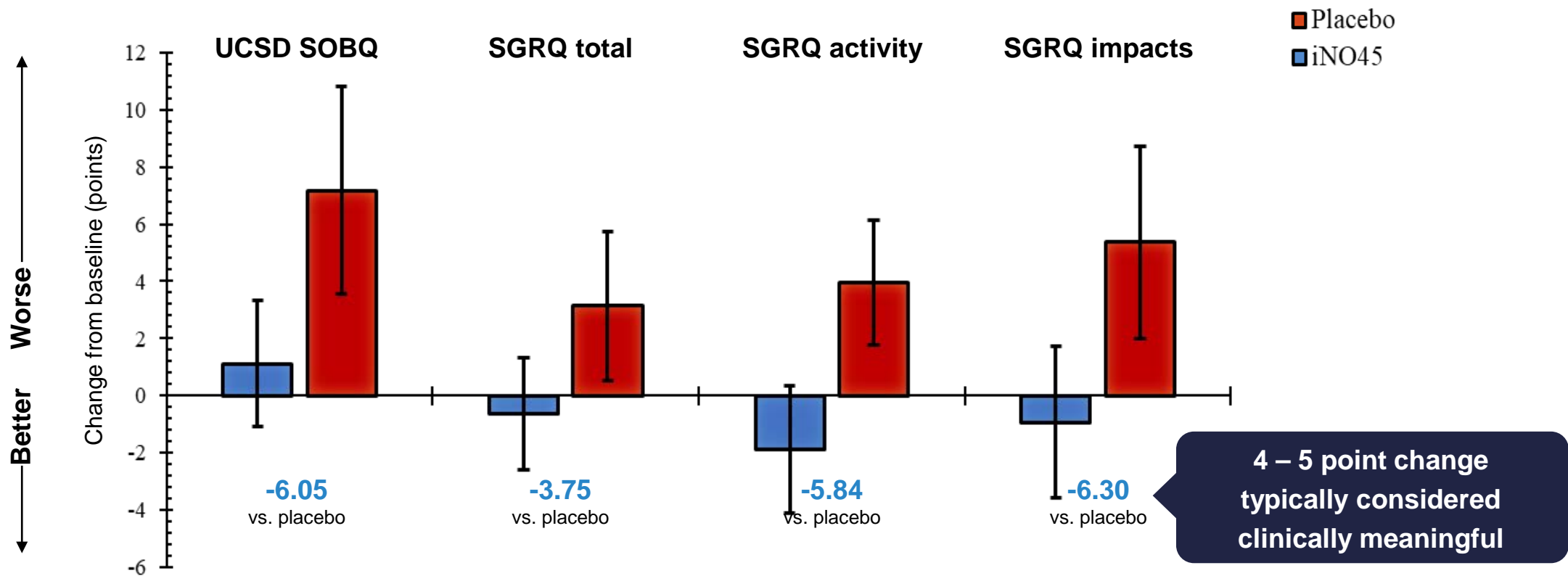
- iNO45 group remained stable
- ~6% placebo adjusted difference (89.4 counts/min)

MMRM analysis based on change from Month 1 to Month 4; data points and error bars = LS mean and standard error; p-value not adjusted for multiplicity



# MVPA Results Mirrored Closely by Patient Reported Outcomes

Outcomes measured by UCSD Shortness Of Breath Questionnaire (SOBQ) and St. George's Respiratory Questionnaire (SGRQ) remained stable on iNO45 vs. deterioration on placebo



MMRM analysis based on change from Baseline to Month 4; data points and error bars = LS mean and standard error

# Phase 2 Safety Summary

## INOpulse was well-tolerated in Cohort 1 and Cohort 2

- Incidence of SAEs was low in both active and placebo groups and all reported as unrelated to study drug
- AEs were balanced and generally non-serious with no observable trends

	Cohort 1 (8 weeks)		Cohort 2 (16 weeks)	
	iNO 30 n=23	Placebo n=18	iNO 45 n=30	Placebo n=14
Patients with Adverse Events	19 (82.6%)	15 (83.3%)	26 (86.7%)	9 (64.3%)
Patients with Serious Adverse Events	2 (8.7%)	2 (11.1%)	3 (10.0%)	3 (21.4%)
Total Serious Adverse Events Reported	3 (0.13/patient)	4 (0.22/patient)	4 (0.14/patient)	7 (0.5/patient)
Deaths	1 (4.3%)	0	0	0

# Phase 2 fILD Key Takeaways

Data supported move to Phase 3 with MVPA as a primary endpoint

## Observed meaningful effects on key activity levels and patient recorded outcomes (PRO)

- INOpulse (iNO30 and iNO45) group maintain activity levels while placebo group deteriorates across activity parameters
- iNO45 group maintain PRO scores (UCSD & SGRQ) while placebo group deteriorates consistent with change in activity levels
- Physical activity levels maintained during OLE; patients switching from placebo to active demonstrated reversal in decline

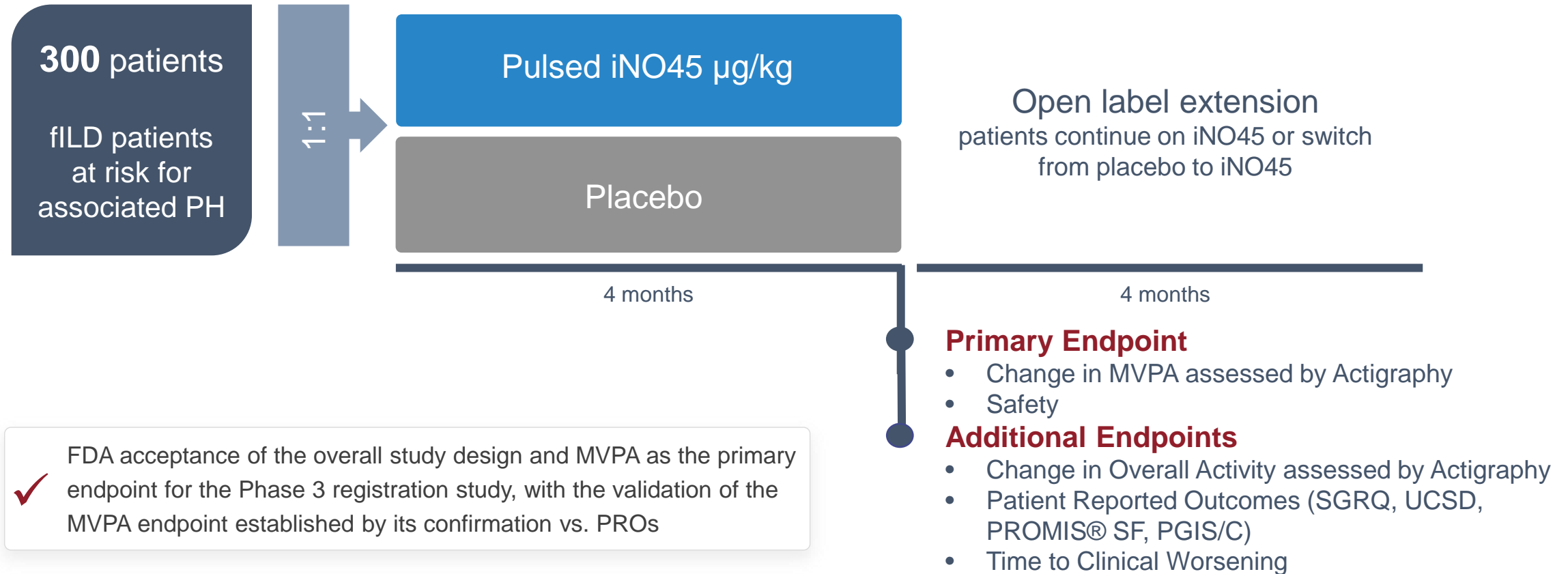
## Generally well-tolerated with no serious adverse events considered related to INOpulse

**INOpulse®**

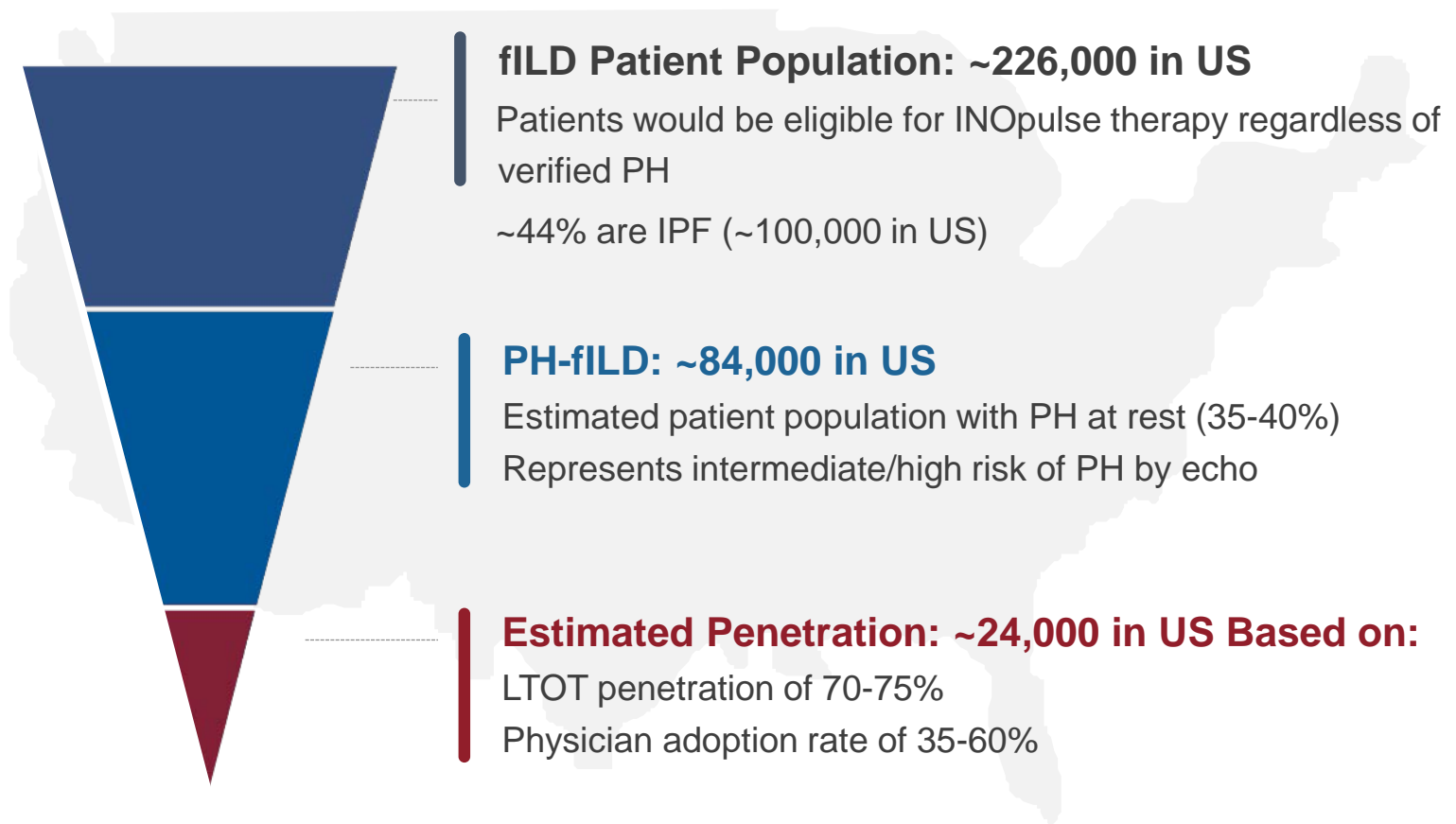
**Advanced into  
Phase 3 REBUILD  
study in fILD**

# Pivotal Phase 3 Trial in fILD

FDA agreement on study design with MVPA as the primary endpoint



# fILD Represents a Significant Market Opportunity in the US and Beyond



Pricing assessment supported by current IPF and PAH therapies (\$100-200k/year)

# INOpulse Could Address Multiple Large Market Opportunities

	Significant Unmet Need		Large Potential Market	
<b>fILD</b> (fibrotic interstitial lung disease at risk of pulmonary hypertension)	fILD with PH reduces 1-year survival from 28% to 5.5% <sup>5</sup>	<b>1</b> approved therapy; no approved therapy to improve physical function or quality of life	226,000 fILD in the US; 30-40% with associated PH <sup>4</sup>	<b>\$2B+</b> market opportunity
<b>PH-SARC</b> (sarcoidosis associated with pulmonary hypertension)	SARC with PH reduces 5-year survival from 96% to 59% <sup>1</sup>	<b>0</b> approved therapies	200,000 Sarc prevalence in the US; up to 30% with associated PH <sup>2</sup>	<b>\$1B+</b> market opportunity
<b>PH-COPD</b> (COPD associated with pulmonary hypertension)	COPD with PH reduces 5-year survival from 63% to 37% <sup>3</sup>	<b>0</b> approved therapies	12.7 M diagnosed COPD in the U.S; ~27% with associated PH <sup>4</sup>	<b>Multi-billion \$</b> market opportunity



# Beyond fILD: Positive top-line Phase 2 data in PH-Sarcoidosis

Dose-escalation study designed to verify acute hemodynamic effect of INOpulse

**All 8 patients demonstrated decreases in mPAP and PVR across the doses of INOpulse utilized in the study**

- iNO45 dose median decrease of 20% (-54% to +22%) in PVR, compared to a median baseline PVR of 329 dynes/cm<sup>2</sup>
- iNO125 dose (7 out of 8 patients) median decrease of 29% (-43% to -5%) in PVR p=0.02 vs. baseline and prior dose)
- mPAP decreased by a median of 6-10% across the doses of iNO30 to iNO125, compared to median baseline of 37.2 mmHg

**Generally well-tolerated**

- No treatment-emergent adverse events or serious adverse events

**Acute hemodynamic data supports progressing to a chronic dosing Phase 2b study**

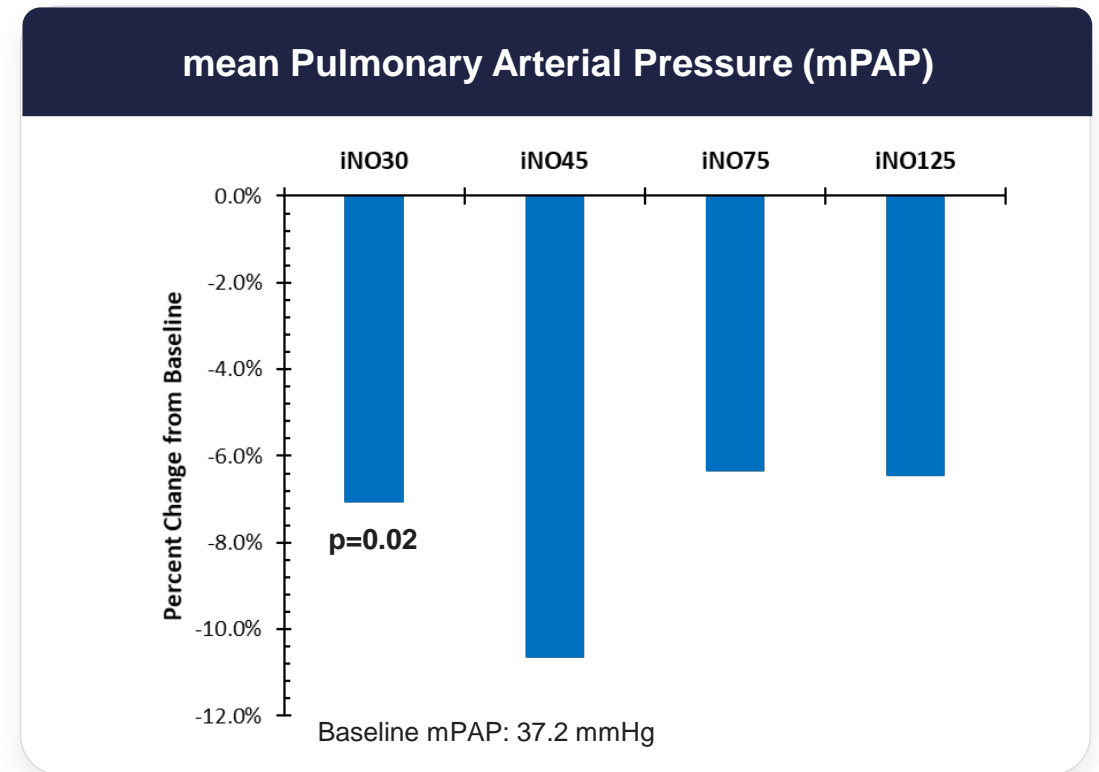
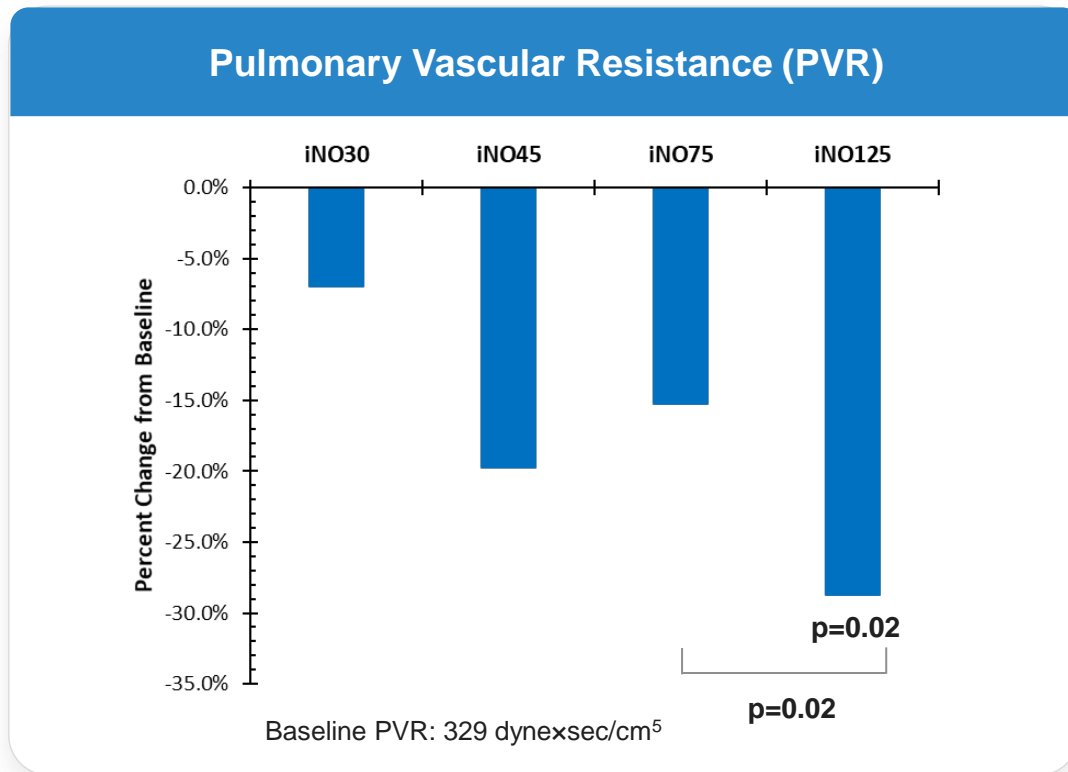
✓ **20%+**  
reduction in PVR  
which is typically  
considered clinically  
meaningful

**Next steps:**  
design multi-dose Phase 2b  
trial in chronic use in  
consultation with Scientific  
Advisors and FDA

mPAP – mean pulmonary arterial pressure; PVR – pulmonary vascular resistance; p-value based on Wilcoxon Rank Test (no correction for multiplicity); range represents max and min values for each condition; data based on 8 PH-Sarc patients; 7 of 8 patients escalated to dose of iNO125

# INOpulse Demonstrates Acute Hemodynamic Improvement in PH-Sarc

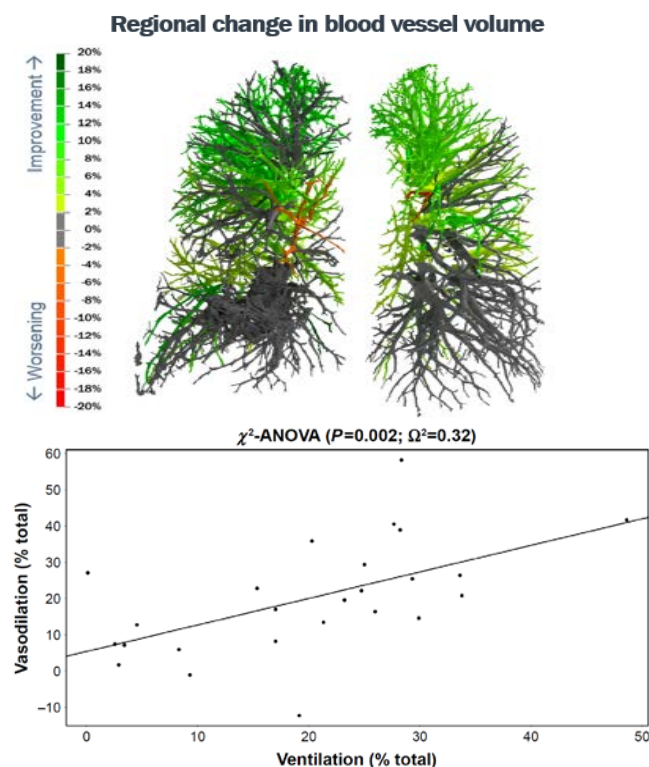
- Pulmonary hemodynamics measured via right heart catheterization at baseline and following each sequential iNO dose
- Clinically meaningful reduction in PVR on iNO45 with potentially increased benefit at highest dose of iNO125
- No treatment-emergent adverse events (TEAEs) or serious adverse events (TESAEs)



Baseline values are median of the group; bar graphs are median values at each assessment for all available study participants; p-value based on Wilcoxon Rank Test between baseline and each dose and between dose and prior dose (no correction for multiplicity); Data based on 8 PH-Sarc patients; 7 of 8 patients escalated to dose of iNO125

# Beyond fILD: INOpulse Provides Targeted Delivery and Improves Hemodynamics and Exercise Capacity in PH-COPD Patients

Delivery to well ventilated pulmonary vessels and ventilation/vasodilation matching



Patients completing 4 weeks of chronic treatment on iNO30 demonstrated:

- Statistically significant increase in 6MWD at 2 weeks and 4 weeks (+50.7m) as compared to baseline
- Statistically and clinically significant decrease in sPAP at 4 weeks (-12.0 mmHg; 19.9% reduction)
- sPAP increased to near baseline upon stopping treatment with iNO
- The iNO therapy was well tolerated with no related safety concerns

Primary concepts for Phase 2b trial design in agreement with FDA

# Compelling Investment Opportunity in Late Stage Biotherapeutics Company with Multiple High Value Indications

## Clinically validated approach

- NO is a proven, well-established vasodilator approved for acute use in persistent pulmonary hypertension in neonates
- Being developed for chronic administration to address multiple significant unmet and underserved needs



## Clear development pathway

- Phase 2a completed establishing V/Q matching and acute hemodynamics
- Phase 3 initiated for lead program in fILD; PH-Sarc and PH-COPD are Phase 2b ready
- Simplified, de-risked approval pathway with ability to leverage Ikaria's existing NDA



## Large market opportunities

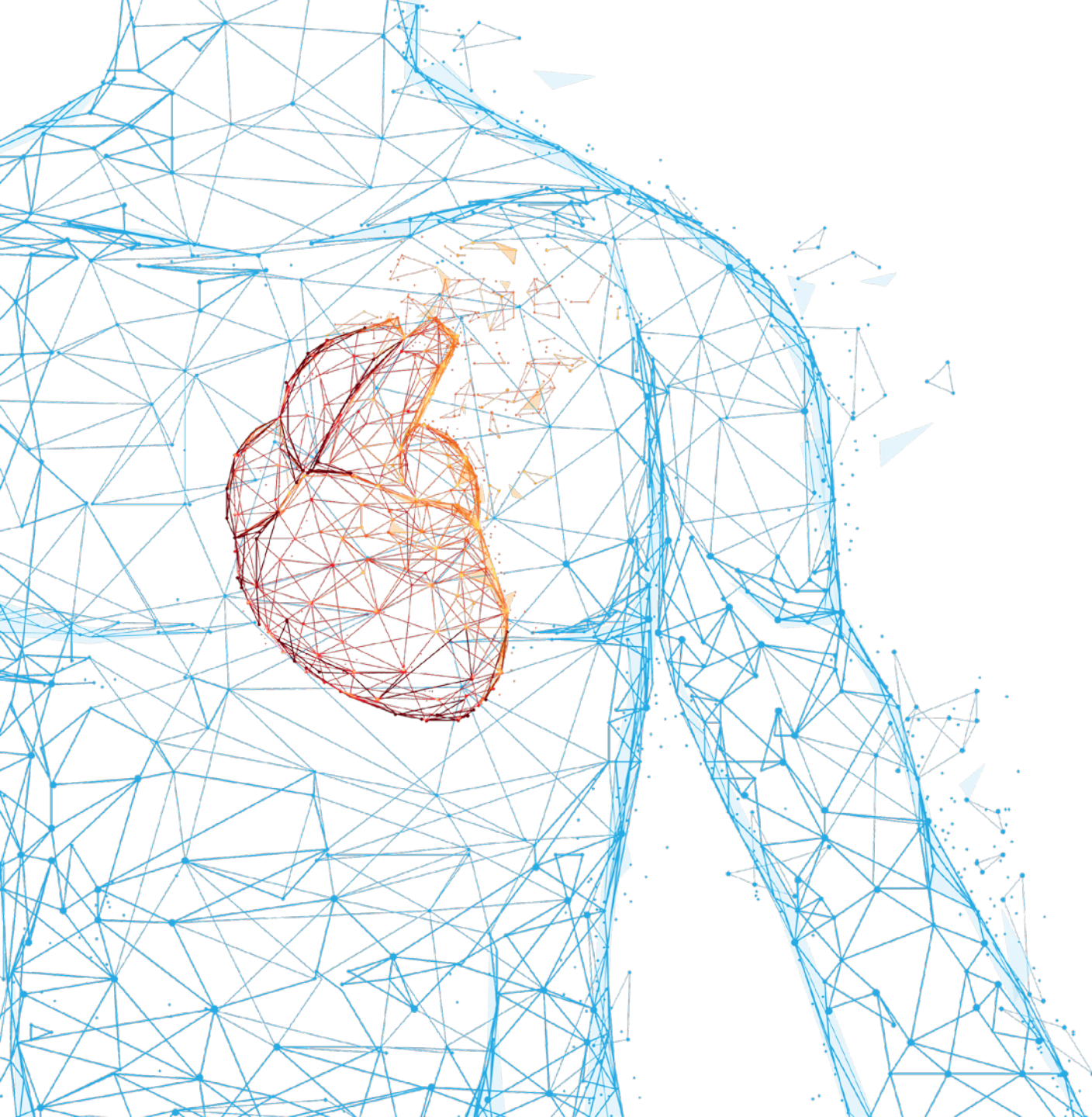
- Targeting \$2Bn+ market in fILD
- Potential \$1Bn+ markets in follow-on indications of PH-Sarc and PH-COPD
- IP protection through 2039



## Corporate profile

- Highly experienced team with expertise in rare and respiratory disease
- Unrestricted cash & equivalents of \$20.0 M<sup>1</sup>, no debt





# Investor Contacts

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