# Corporate Presentation

January 2022

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# Forward-Looking Statements Disclaimer

Statements contained in this presentation and oral statements made regarding the subject of this presentation regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements are subject to risks and uncertainties, and actual results may differ materially from those expressed or implied by such forward-looking statements. Such forward-looking statements include, but are not limited to, statements regarding our business plans and objectives, including future plans or expectations for our product candidates, clinical trials of our product candidates, and expectations regarding our uses and sufficiency of capital; and other statements containing the words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “would,” “could,” “continue” and similar expressions, although not all forward-looking statements contain these identifying words. Risks that contribute to the uncertain nature of the forward-looking statements include: uncertainties regarding the success, cost, and timing of the our product candidate development activities and clinical trials; uncertainties as to the potential impact to our clinical trials and operations of the COVID-19 pandemic; the risk that results from a clinical trial may not be predictive of the results of other future clinical trials; potential regulatory developments in the United States and foreign countries; uncertainties inherent in estimating future expenses, capital requirements and other financial results; risks with respect to our ability to fund our operations on a continuing basis; as well as the other risks and uncertainties set forth in our Quarterly Report on Form 10-Q for the period ended September 30, 2021, filed with the Securities and Exchange Commission and in subsequent filings with the Securities and Exchange Commission. All forward-looking statements contained in this presentation speak only as of the date of this presentation. We undertake no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. We believe that these third-party sources and estimates are reliable but have not independently verified them. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions. The industry in which we operate is subject to a high degree of uncertainty and risk due to a variety of important factors that could cause results to differ materially from those expressed in the estimates made by third parties and by us.

# Executive Summary

| | |
|---|---|
| Differentiated MOA | Only oral dual acting MOA in clinical development that works both peripherally and centrally to rebalance the kappa and mu receptors, both of which are important in mediating pruritus and cough |
| Strong Pruritus Data | Statistically significant pruritus reduction in uremic pruritus Ph2b/3 trial<br>Prurigo nodularis (PN) Ph2a WI-NRS reduction vs. placebo<br>Prurigo nodularis Ph2a open-label extension demonstrated disease improvement[1] |
| Near Term Data for Lead Indications | Near-term data expected in large attractive markets with broad expansion opportunities<br>Pruritus in PN Ph2b/3 and chronic cough in idiopathic pulmonary fibrosis (IPF) Ph2a topline data expected in 1H 2022 |
| Experienced Management | Experienced management team with several successful drug approvals in relevant indications |
| Strong IP | 18 issued US and foreign patents with terms expiring from 2026 to 2032 and additional applications with terms, if issued, expiring from 2032 to 2041 |

[1]Prurigo nodularis Ph2a open-label extension demonstrated disease improvement in patients on HADUVIO ≥6 months

# HADUVIO™ (nalbuphine ER) Advancing Two Lead Clinical Programs with Expected Readouts 1H 2022

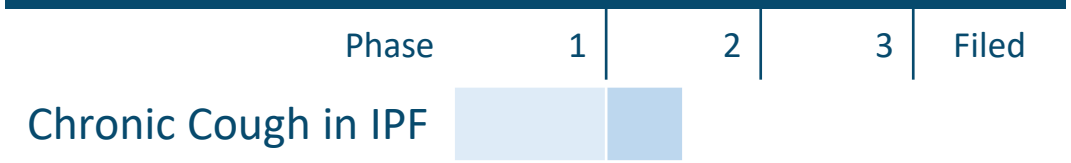
PRISM
Pruritus Relief through Itch-Scratch Modulation

## Pruritus Associated with Prurigo Nodularis[1]

- Enrollment to end January 31, 2022
- Data expected in 1H 2022
- FDA Fast Track designation granted for moderate to severe pruritus in PN

CANAL

## Chronic Cough in Idiopathic Pulmonary Fibrosis




- Phase 2 proof-of-concept trial n=44
- Planned interim statistical update expected 1Q 2022
- Data expected in 1H 2022

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HADUVIO™ (nalbuphine ER) is an investigational drug

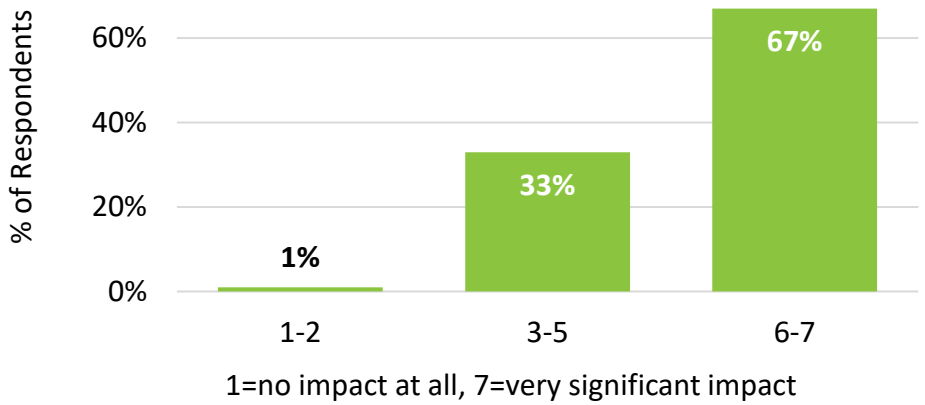
[1] Our prurigo nodularis program consists of our ongoing Phase 2b/3 clinical trial and an additional Phase 3 clinical trial that we plan to conduct.

# Attractive Categories for Lead Indications

## Pruritus Associated with Prurigo Nodularis

- ✓ No approved therapies
- ✓ No oral option available
- ✓ High unmet need
- ✓ PN is a serious, potentially debilitating, chronic skin condition[1,2]

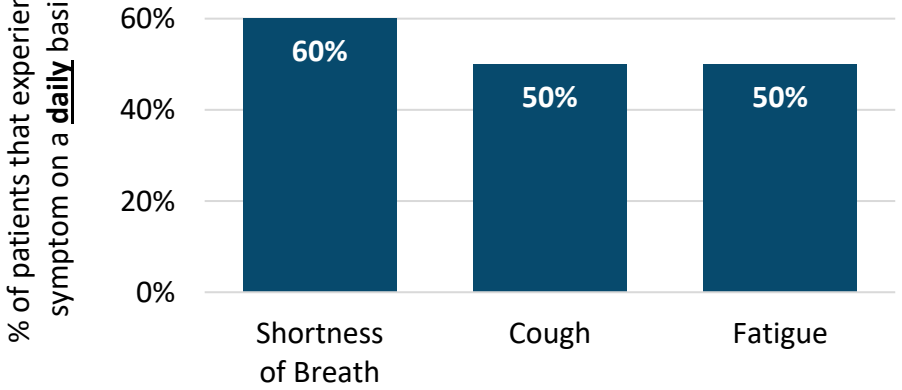
### Dermatologist View on PN Impact on QoL[3] (N=126)




## Chronic Cough in Idiopathic Pulmonary Fibrosis

- ✓ No approved therapies
- ✓ No oral option available
- ✓ High unmet need
- ✓ IPF is a life-threatening, debilitating disease[4]

### Most Bothersome Daily IPF Symptom[4]

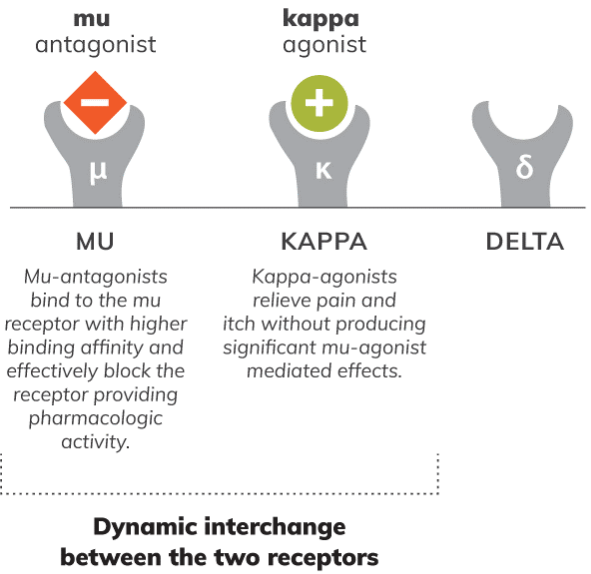


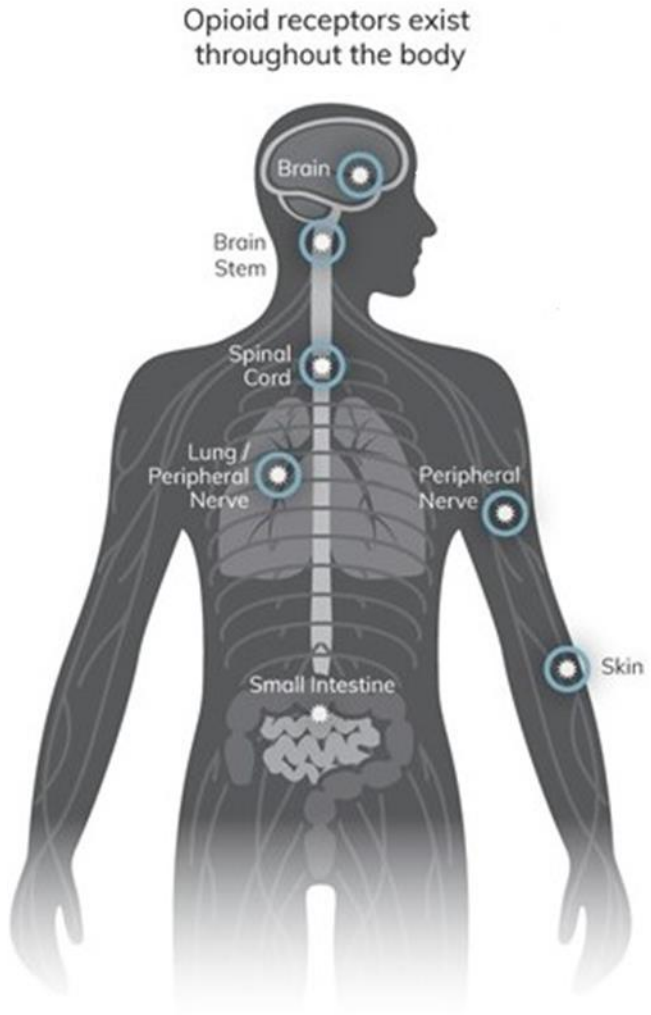

[1]Iking A JEADV 2013 [2]Vaidya DC & Schwartz RA Acta Derm Croat 2008 [3]Trevi data on file [4]Voice of the Patient – IPF Patient-focused Drug Development Initiative, 2015

# Broad Applications for Mechanism of Action of HADUVIO™

## Haduvio™ targets the endogenous opioid system to treat serious neurologically mediated conditions

**Haduvio™** has a dual mechanism of action that affects both mu and kappa opioid receptors:




**Chronic Pruritus**
- Reward parts of brain
- Spinal cord
- Skin
- Peripheral skin nerves

Both mu antagonists and kappa agonists have shown pharmacological activity in reducing pruritus

**Chronic Cough**
- Brain stem
- Lung
- Peripheral lung nerves

Opioid receptors are believed to play an important role in the modulation of respiration and cough

**Levodopa Induced Dyskinesia (LID)**
- Thalamus/basal ganglia

Pharmacologic intervention of both mu and kappa receptors has potential to impact the generation of LID

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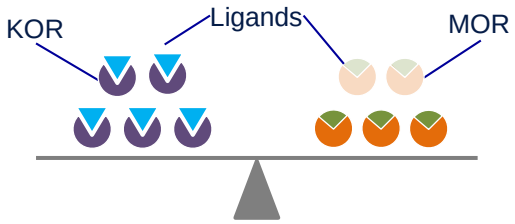
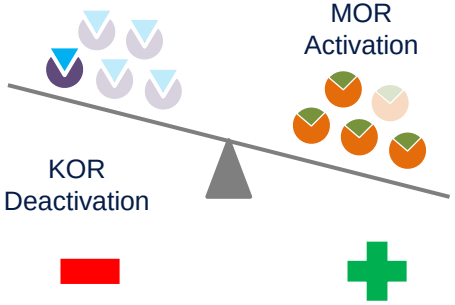
# HADUVIO™ Acts by Rebalancing Kappa (KOR) and Mu (MOR) Pathways to Regulate Itch and Cough

## Normal State




## Imbalanced State Pruritic or Cough

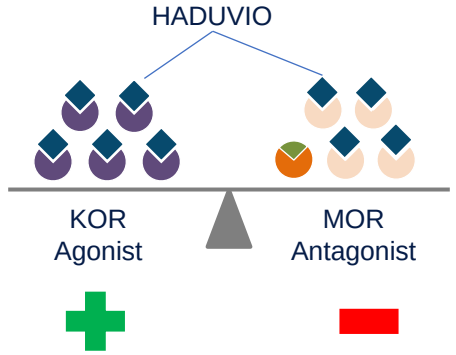
Too little KOR activation and/or too much MOR activation




**Induction of Itch/Cough**

## HADUVIO Rebalancing

Dual action as both a KOR agonist and a MOR antagonist



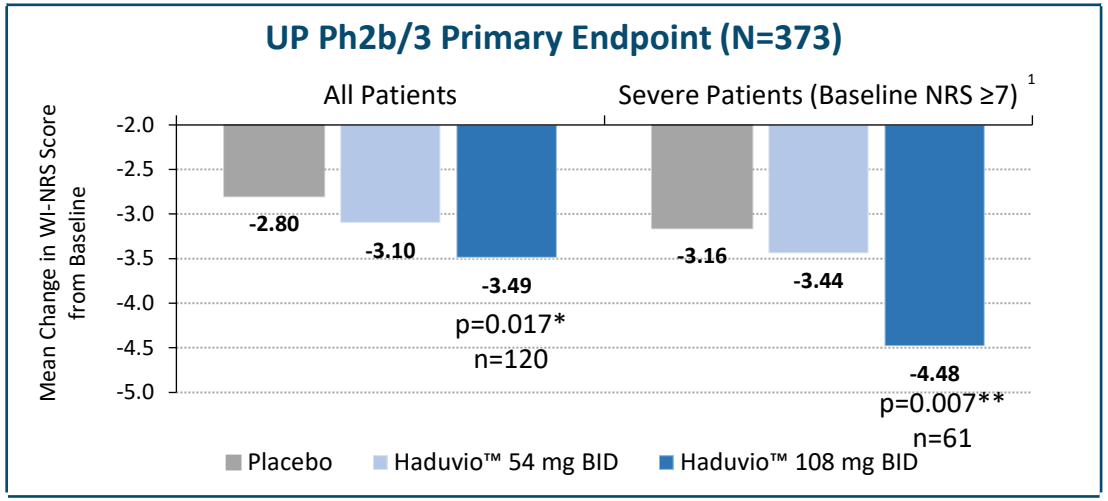

**Suppression of Itch/Cough**

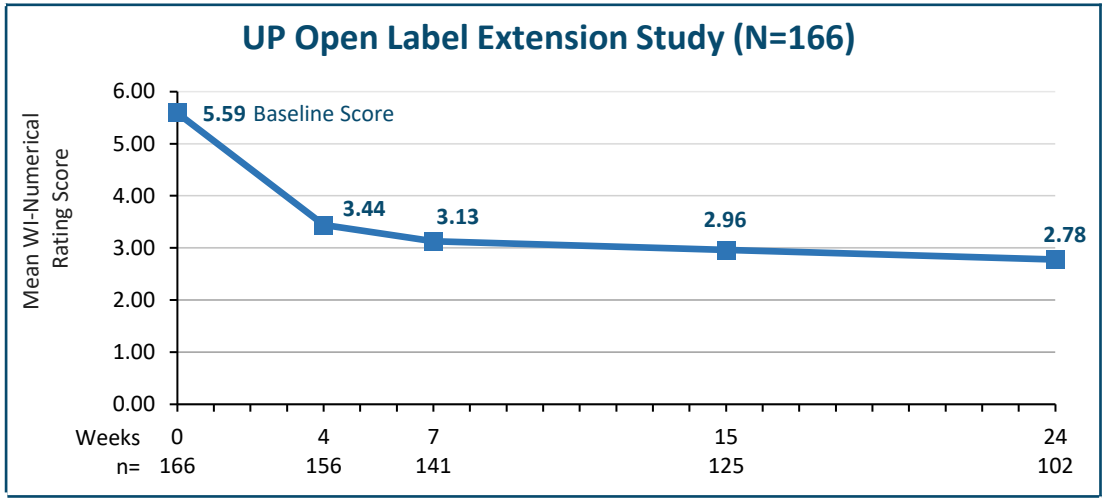
Proposed mechanism of action of HADUVIO
KOR, ĸ-opioid receptor; MOR, μ-opioid receptor
Bigliardi PL Bigliardi-Qi M *Itch Basic Mechanisms and Therapy* 2004, Komiya E, et al. In *J Mol Sci.* 2020, Ko MCH Naughton NN Anesthesiology 2000

# HADUVIO™ Showed Durable Results in Itch Across Multiple Studies and Endpoints

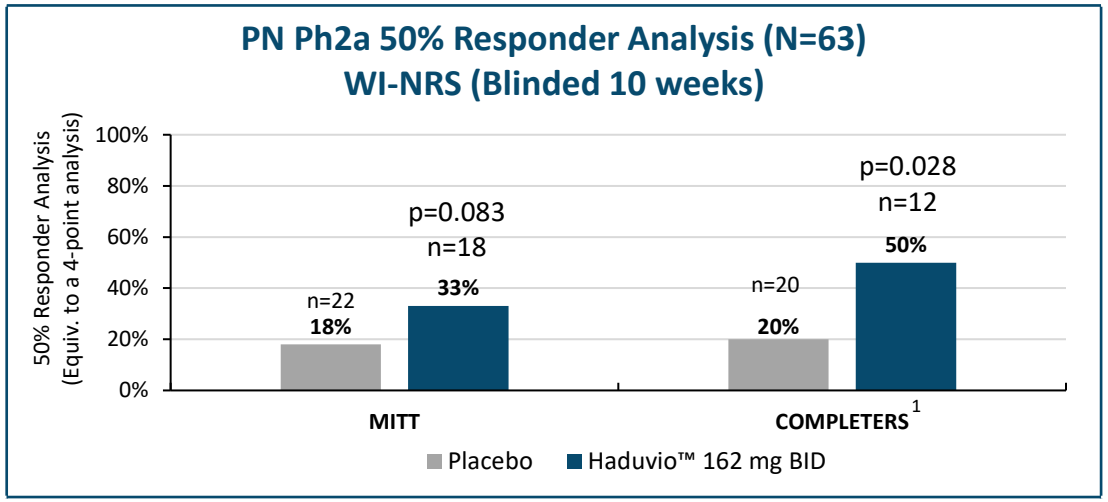
## Over 400 subjects studied with moderate to severe pruritus

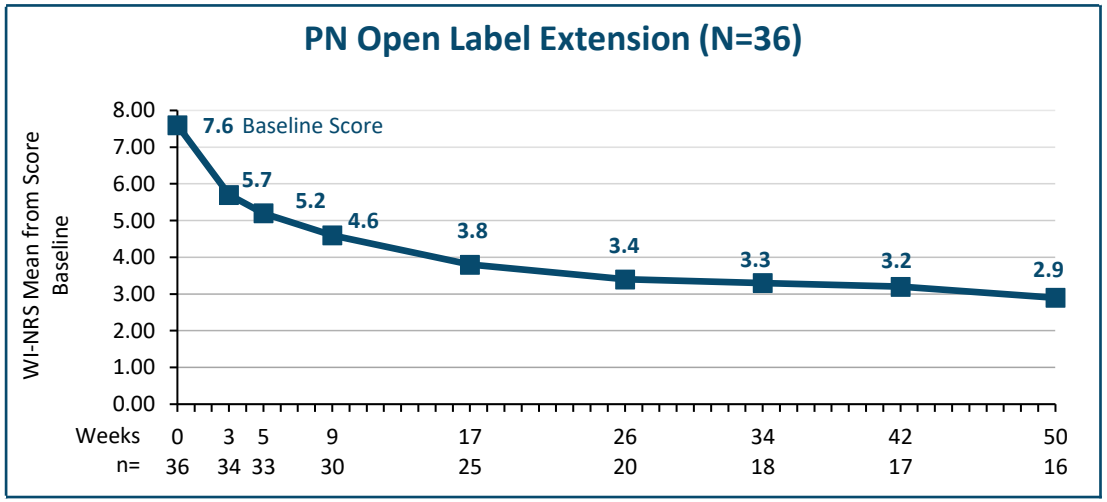
### Uremic Pruritus (UP)




### Prurigo Nodularis (PN)




*All p-values compare treatment group to placebo. Only the UP data was powered for statistical significance.

[1] Post-hoc analysis

# Chronic Pruritus in Prurigo Nodularis

PRISM

Pruritus Relief through Itch-Scratch Modulation

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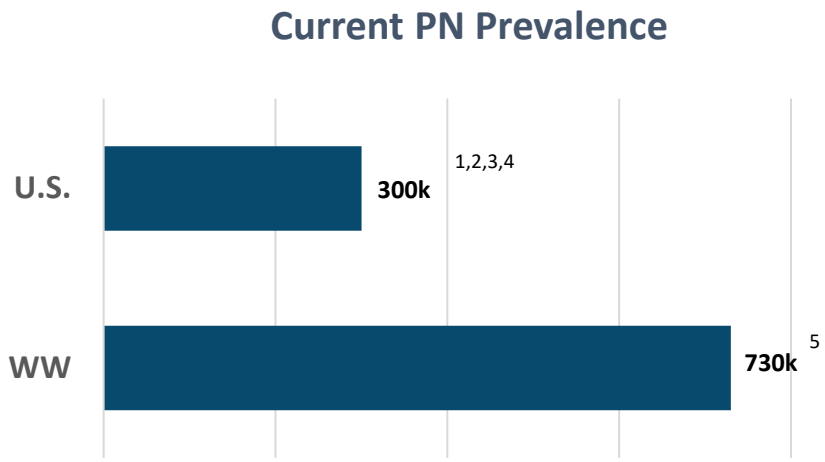
# Opportunity to be the First Oral Therapy Approved in Pruritus Associated with Prurigo Nodularis

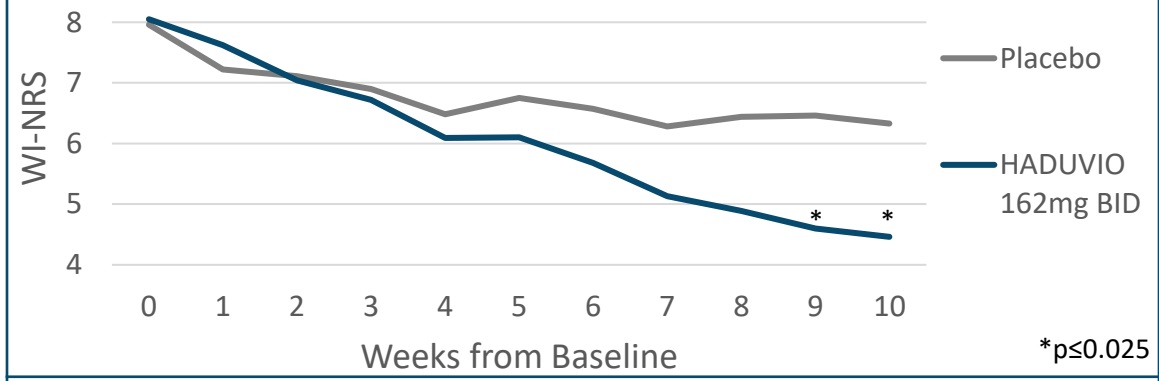


- Current off-label treatments for itch lack efficacy and/or have an unfavorable AE profile
  - We believe 40-50% of patients are uncontrolled on off-label therapies
- Oral therapy enables opportunity to be used in earlier lines of therapy
- Many underlying etiologies of itch, but initial scratching may create an itch-scratch cycle resulting from central and/or peripheral nervous tissue changes[6,7,8,9]

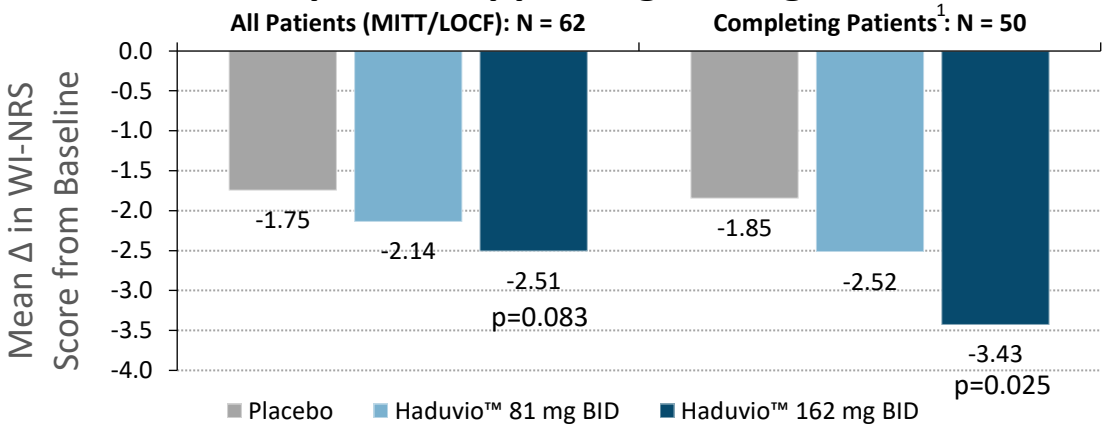
[1]Huang AH JID 2020 [2]Stander S JAAD 2020 [3]Iking A JEADV 2013 [4]Pereira M JEADV 2018 [5]Prurigo Nodularis - Market Insights, Epidemiology and Market Forecast [6]Eigelshoven CME Derm 2009 [7]Vaidya DC & Schwartz RA Acta Derm Croat 2008 [8]Lee MR, Shumack S Aus J Derm 2005 [9]Iking A JEADV 2013

# Results from Ph2a Prurigo Nodularis Trial and Open Label Extension (OLE)

## Continued Separation of WI-NRS Over Time

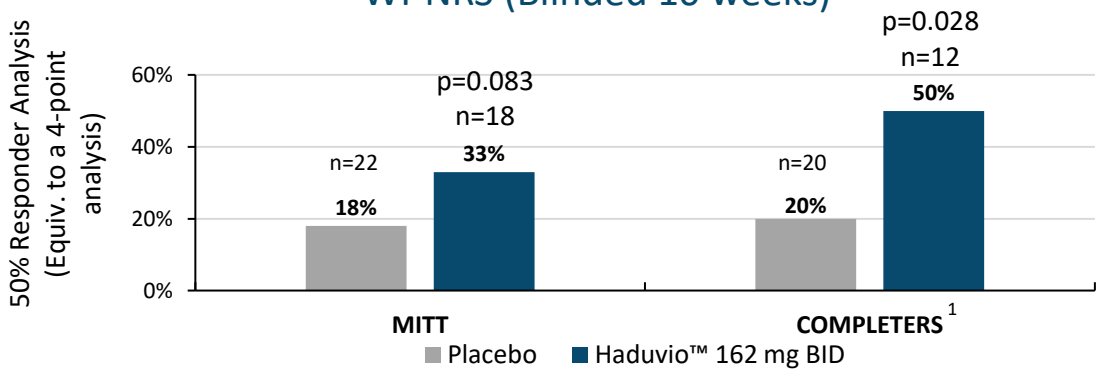



## Dose Response Supporting 162mg Selection†



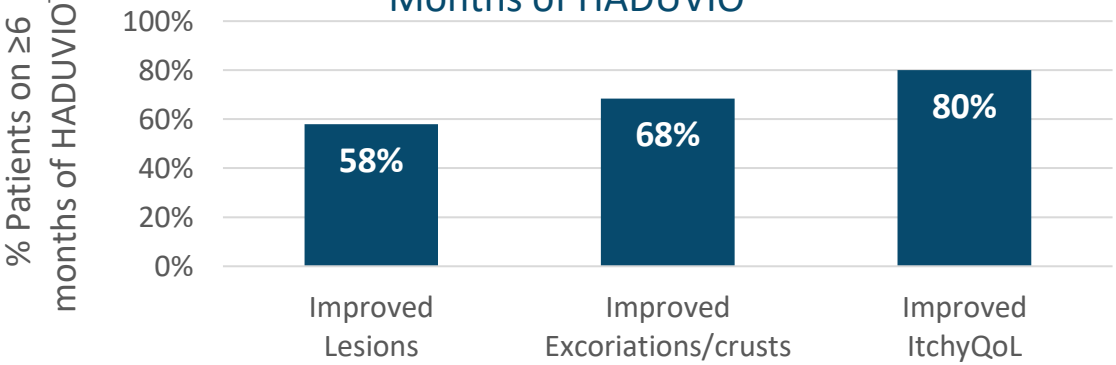

## Drug Separation vs. PBO

PN Ph2a 50% Responder Analysis (N=63)
WI-NRS (Blinded 10 weeks)




## (OLE) HADUVIO™ Showed Disease Improvements

Percent of Patients Achieving Outcomes on ≥6 Months of HADUVIO™

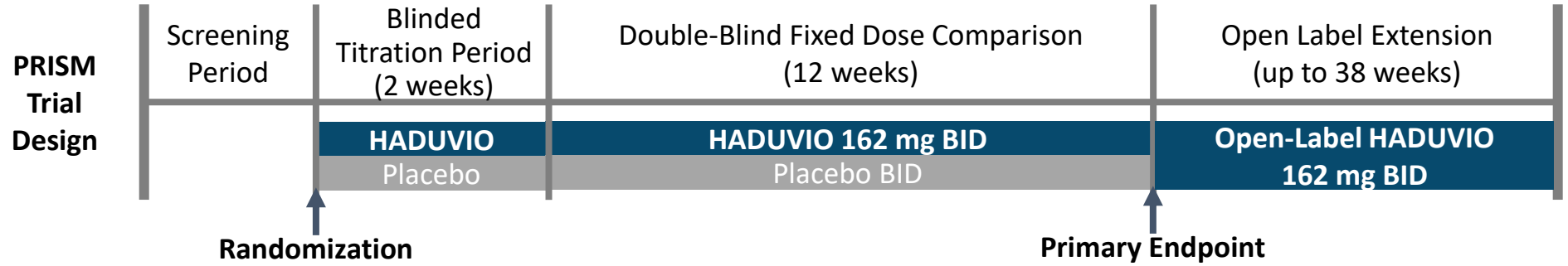



†All p-values compare treatment group to placebo. Only the primary endpoint [30% responder analysis] was powered for statistical significance.
[1]Post-hoc analysis on completers. Consists of the patients who completed the 10-week course of treatment.
DOI: 10.1111/jdv.17816

# Phase 2b/3 PRISM Trial Design (N=360)

## Top-Line Data Expected 1H 2022

| Optimizations from Ph2a to Ph2b/3 PRISM Trial | | |
|---|---|---|
| **Increased Powering** | **Enriched Population** | **Increased Duration** |
| 63 patients (Ph2a) → 360 patients (Ph2b/3) | Focusing on severe population<br>WI-NRS ≥5 (Ph2a) → WI-NRS ≥7 (Ph2b/3) | 10 weeks (Ph2a) → 14 weeks (Ph2b/3) |




**Trial Status:**
- 60+ Sites
- Enrollment ends January 31, 2022

**Inclusion Criteria:**
- Worst-Itch Numerical Rating Scale (WI-NRS) Score ≥7
- 10+ pruriginous nodules
- PN present on at least 2 separate body parts

**Primary Efficacy Endpoint (responder analysis):**
- % WI-NRS Responders for NAL-ER versus PBO
- Responder = 4-point reduction from baseline at Wk 14

**Key Secondary Endpoints (change from baseline):**
- QoL (ItchyQoL)
- Skin lesions
- Sleep disturbances

**Open Label Extension:**
- ~90% of subjects who reached Wk 14 have continued into the open label extension
- Long-term safety
- Durability of effect
- Lesion healing

# Patient Images from PRISM

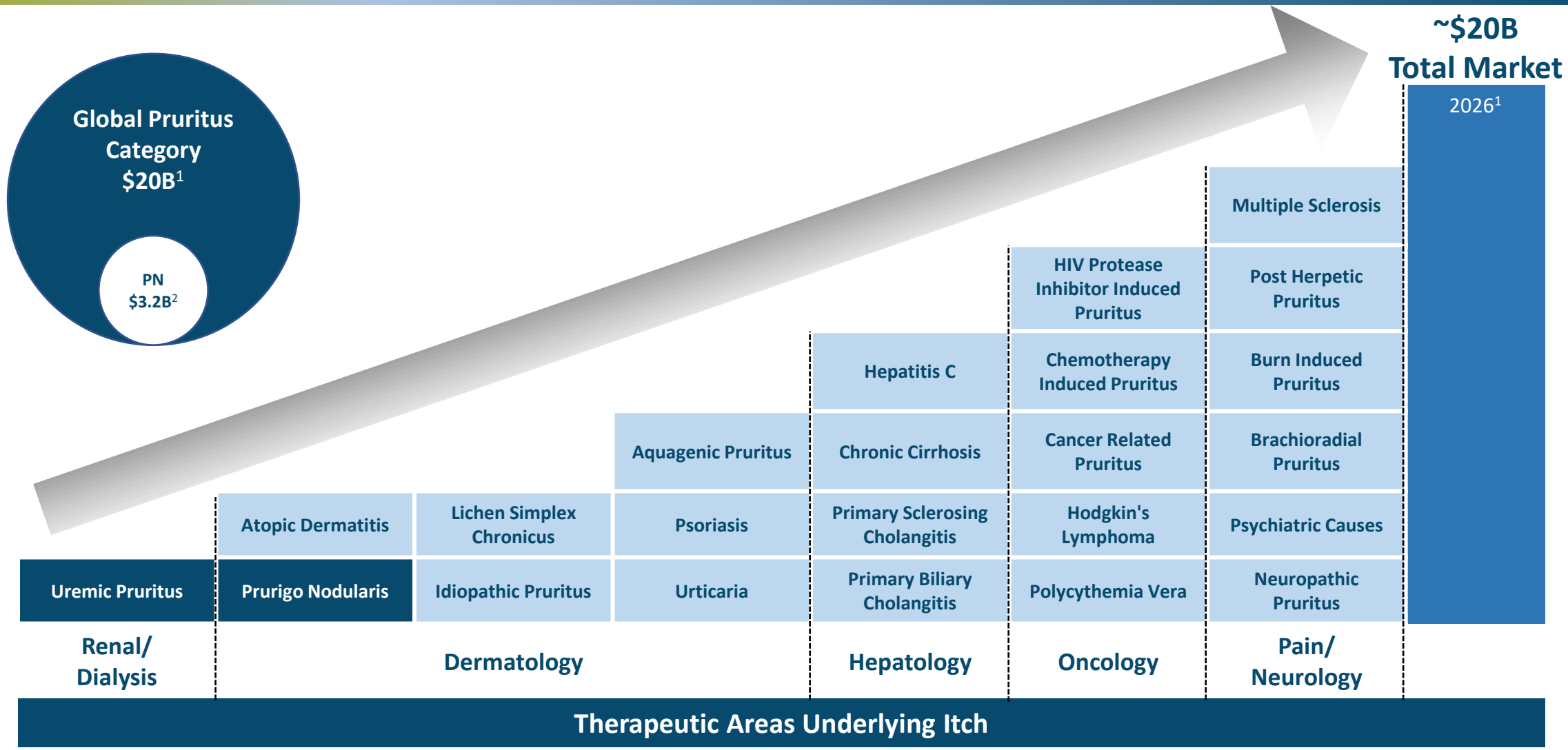
HADUVIO 162mg BID or Placebo → HADUVIO 162mg BID

| Baseline | Week 14 | Week 52 |
|---|---|---|
| | | |

| Baseline | Week 14 | Week 28 |
|---|---|---|
| | | |

The images provided are from two separate patients.

# Potential Market Opportunity Across a Broad Array of Chronic Pruritic Conditions




[1]2026 est. OG Analysis Global Pruritus Therapeutics Market [2]2031 est. DelveInsight Prurigo Nodularis Market Insight, Epidemiology, and Market Forecast May 2020

# Chronic Cough in Idiopathic Pulmonary Fibrosis

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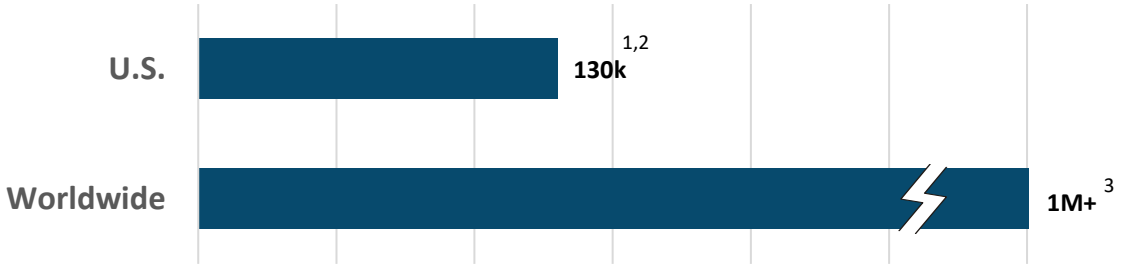
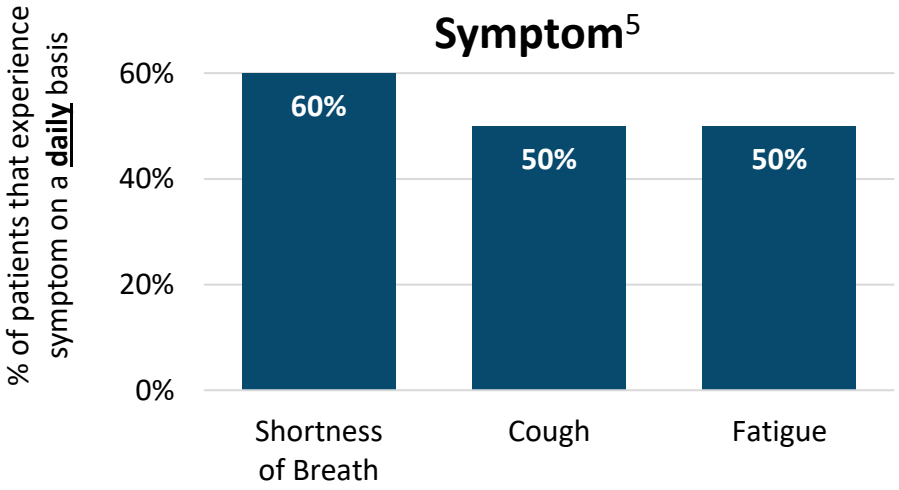
# Opportunity to be First in Class for Chronic Cough in Idiopathic Pulmonary Fibrosis

## Current IPF Prevalence



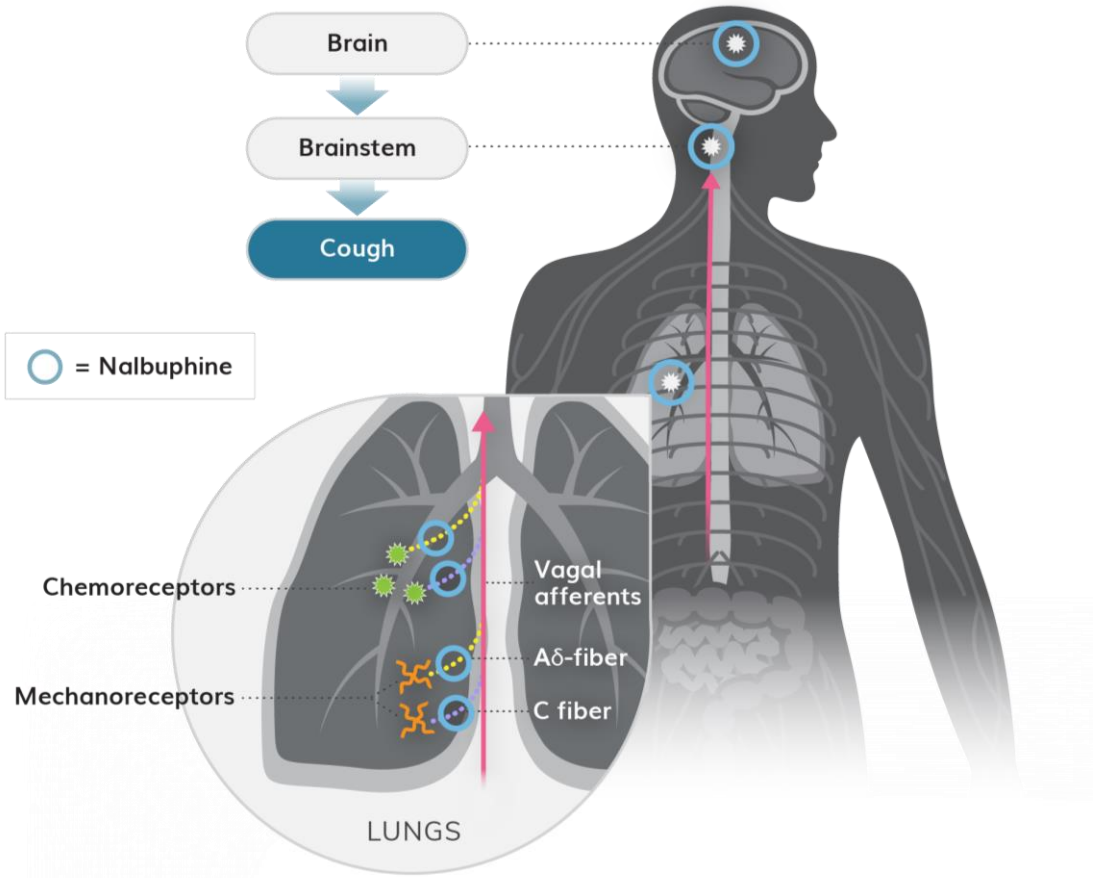

- 70% to 85% of IPF patients are reported to suffer from chronic cough[4]
- Cough is one of the most bothersome symptoms of IPF[5]
  - ≥75% of IPF patients report cough as being one of their most significant symptoms
- Current IPF therapies (anti-fibrotics), which have not been shown to reverse disease progression, are not labeled to reduce cough frequency/severity

## Most Bothersome Daily IPF Symptom[5]




[1]Raghu G et al. Eur Resp J 2016 [2]Raghu G et al. Am J Resp Care Med 2006 [3]Nalsnyk L et al. Eur Resp Rev 2012 [4]Ryerson CJ et al. Respirology 2011 [5]Voice of the Patient – IPF Patient-focused Drug Development Initiative, 2015

# Nalbuphine ER has the Potential to Work at Multiple Pathways in IPF Chronic Cough




Mu, kappa and delta receptors are found in the respiratory regions of the brain stem, lung and peripheral lung nerves

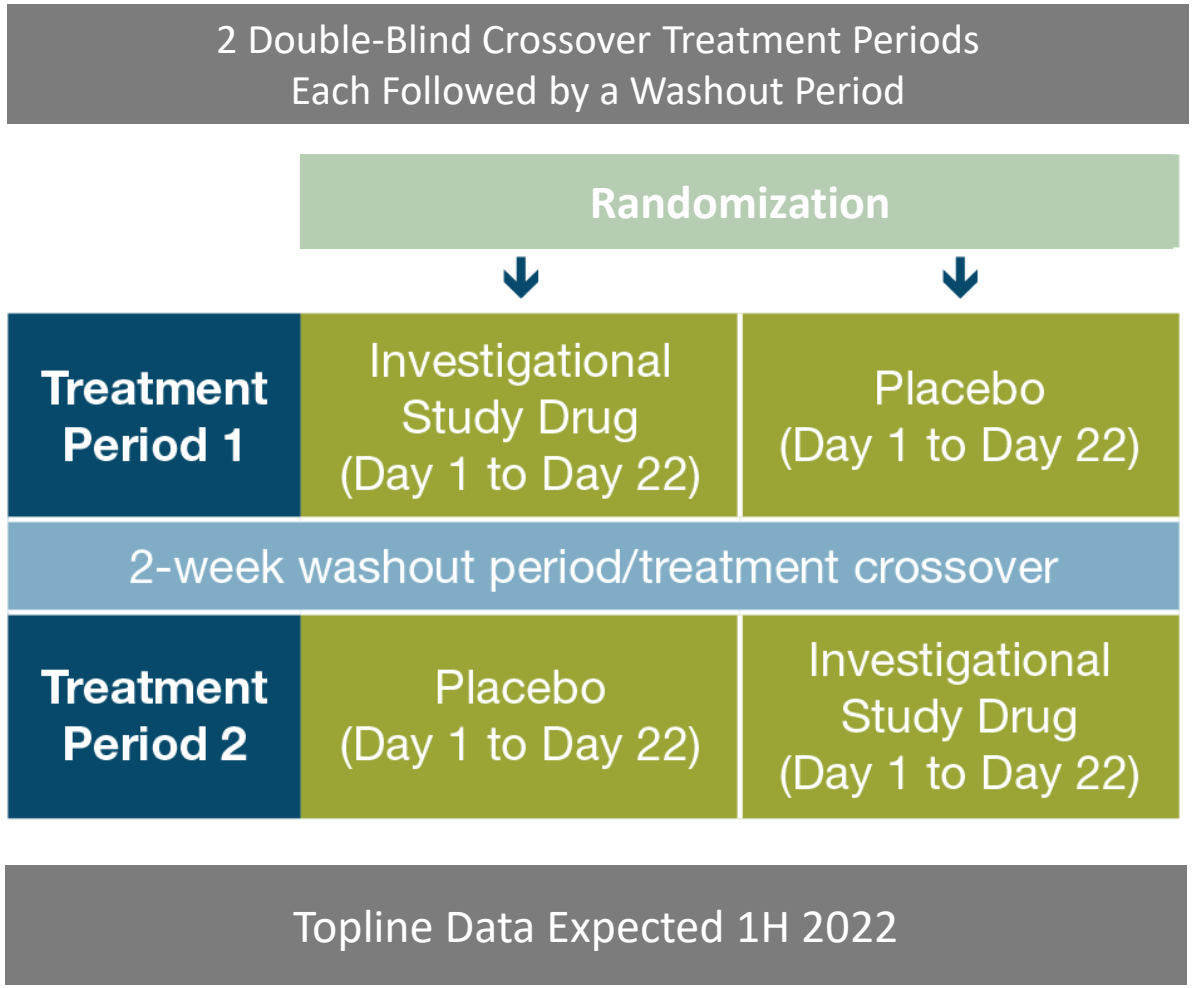
Endogenous opioids are believed to play an important role in modulating respiration[1]

Nalbuphine prevented sufentanil-induced cough during anesthesia induction[2]

Graphic: Vigeland CL et al, Respiratory Medicine 2017
[1]Lally PM Respir Physiol Neurobiol 2008 [2]Wang J et al. Therapeutics and Clinical Risk Management 2020

# Chronic Cough in IPF Recruiting in the UK

## Phase 2a Trial (Enroll 60 patients with 44 Completers)




Planned interim statistical update expected 1Q 2022

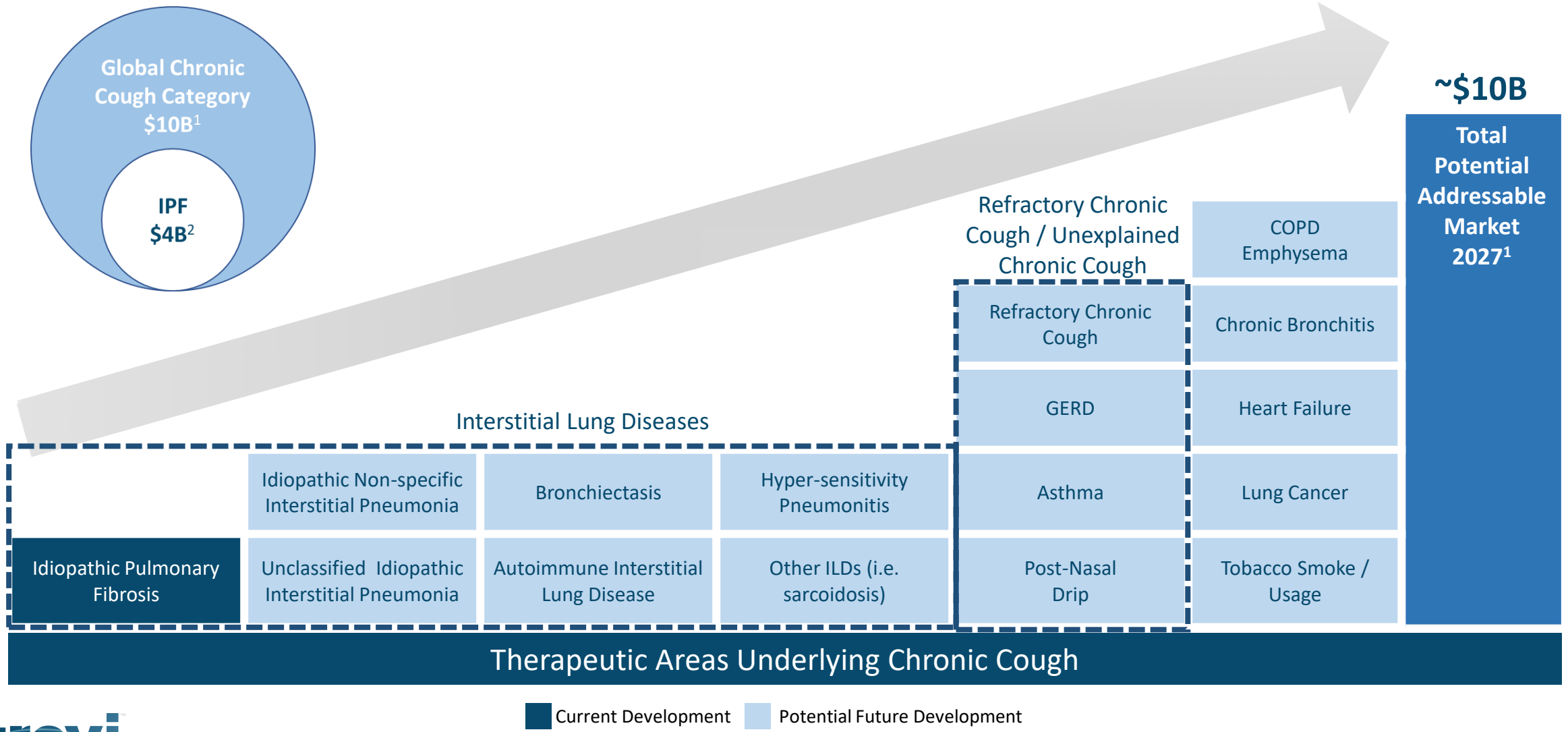
Primary endpoint

- Mean percent change in daytime cough frequency from baseline as measured by a digital cough monitor between the nalbuphine ER and placebo treatments

Secondary endpoints measured at various time points:

- Cough
- Fatigue
- Dyspnea

# Potential Market Opportunity Across a Broad Array of Chronic Cough Conditions




[1]2027 est. The Insight Partners Jun 2020 [2]2028 est. VPA Research Idiopathic Pulmonary Fibrosis Report Feb 2021

# Upcoming Milestones 2022—Key Data readouts in 1H

| Date | Milestone |
|---|---|
| Jan 31, 2022 | PRISM (Pruritus in PN Phase 2b/3) Enrollment Ends |
| 1Q 2022 | CANAL (Cough in IPF Phase 2) Interim Statistical Update Results |
| 1H 2022 | CANAL Topline Data |
| 1H 2022 | PRISM Topline Data |

# Trevi Value Proposition

| | |
|---|---|
| Rebalancing the Itch/Cough Pathway | Dual acting MOA in clinical development that works both peripherally and centrally to rebalance the kappa and mu receptors, both of which are important in mediating pruritus and cough |
| Existing Safety and Efficacy Data | Statistically significant pruritus reduction in uremic pruritus Ph2b/3 trial<br>Prurigo nodularis Ph2a WI-NRS reduction vs. placebo<br>Prurigo nodularis Ph2a open-label extension demonstrated disease improvement[1] |
| Broad Potential Use Across Therapeutics Areas | Ability to utilize Nalbuphine ER across a variety of Therapeutic Areas that experience itch and cough |
| Near Term Data for Lead Indications | Near term data in large attractive markets with broad expansion opportunities<br>Pruritus in PN Ph2b/3 and cough in IPF Ph2a topline data 1H 2022 |

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[1]Prurigo nodularis Ph2a open-label extension demonstrated disease improvement in patients on Nalbuphine ER ≥6 months

# Thank You