# Investor Presentation

July 2021

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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 March 31, 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 Ph2a WI-NRS reduction vs. placebo<br>Prurigo nodularis Ph2a open-label extension demonstrated disease improvement |
| Near Term Data for Lead Indications | Near term data in large attractive markets with broad expansion opportunities<br>Prurigo nodularis Ph2b/3 and IPF Ph2a topline data 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 |

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

# Experienced Leadership with Strong Financial Backing

## Management Team

**Jennifer Good**
President & Chief Executive Officer

**Thomas Sciascia, M.D.**
Chief Medical Officer

**William Forbes, Pharm.D.**
Chief Development Officer

**Farrell Simon, Pharm.D.**
VP, Head of U.S. Marketing

## Board of Directors

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*Rhythm Pharmaceuticals*

**Ed Mathers**
*New Enterprise Associates, Inc*

**Jennifer Good**
*Trevi Therapeutics*

**Dominick Colangelo**
*Vericel Corporation*

**Michael Heffernan**
*Collegium Pharmaceutical, Inc.*

**James Cassella, Ph.D.**
*Concert Pharmaceuticals*

**Anne VanLent**
*AMV Advisors*

## Shareholders (as of April 19, 2021)

NEA®

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OMEGA FUNDS

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**Insider held**

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# HADUVIO™ (nalbuphine ER) Overview

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

## Lead Indications

*Pruritus Associated with Prurigo Nodularis (PN) - PRISM*

- 730k patients WW, 300k in U.S. with no current approved therapies
- Only oral compound in clinical development in $3B PN category[1]
- Shown reductions in pruritus in moderate to severe itch patients (Ph2a)

*Chronic Cough in Idiopathic Pulmonary Fibrosis (IPF) - CANAL*

- 1M+ patients WW, 130k in U.S. with no current approved therapies
- Most advanced oral compound in clinical development for cough in $4B IPF category[2]

## Broad Pipeline Potential in Each Indication

- Potential for broad application in $20B pruritus and $10B chronic cough categories[3,4]

## Anticipated Milestones

PRISM
Pruritus Relief through Itch-Scratch Modulation

PRISM Ph2b/3 PN trial enrollment completion (2H 2021) and topline data (1H 2022)

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CANAL Ph2a IPF trial topline data (1H 2022)

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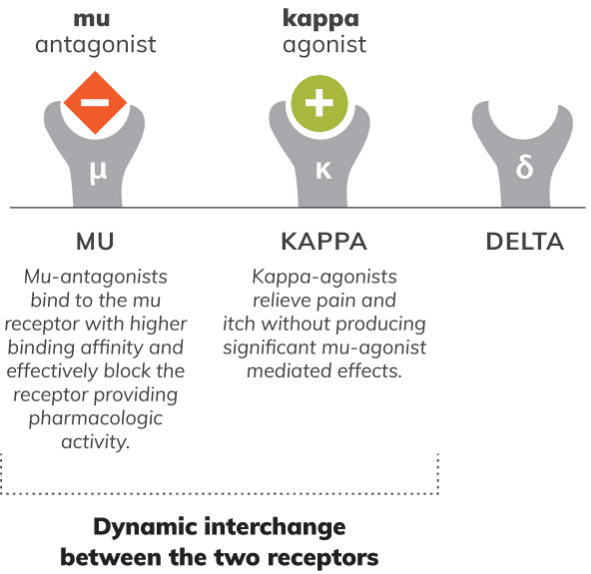
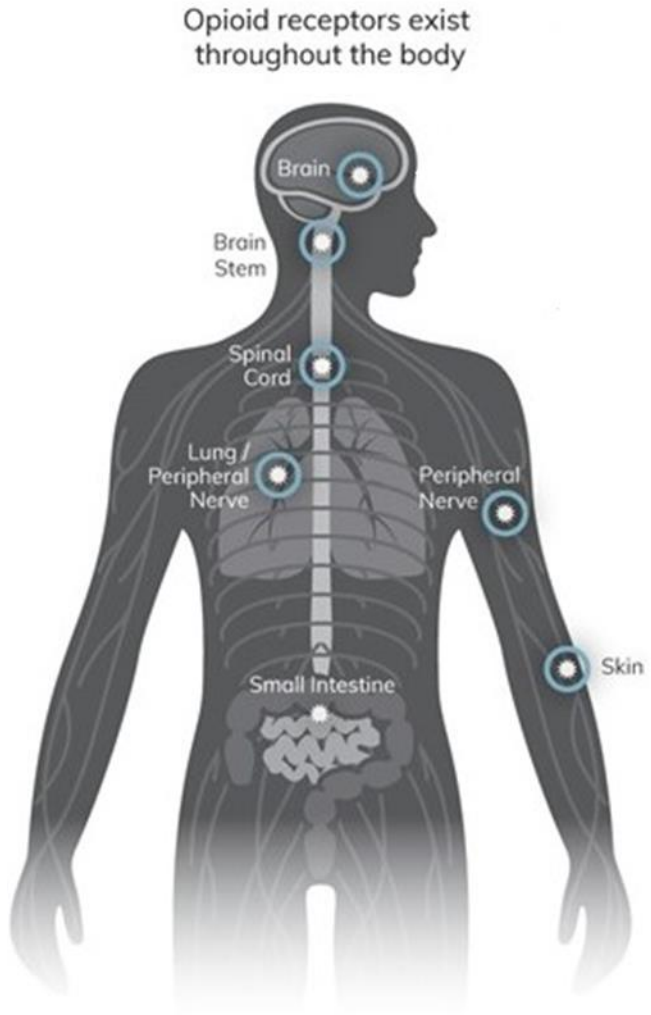
HADUVIO™ (nalbuphine ER) is an investigational drug
[1]2031 est. Prurigo Nodularis Market Report May 2020 [2]2028 est. Research Idiopathic Pulmonary Fibrosis Report Feb 2021 [3]2026 est. Global Pruritus Therapeutics Market Prurigo [4]2027 est. The Insight Partners Jun 2020

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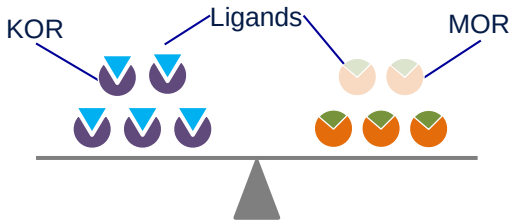
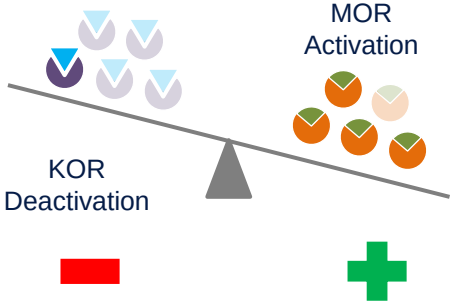
# HADUVIO™ Acts by Rebalancing Kappa (KOR) and Mu (MOR) Pathways to Regulate Itch and Cough

## Normal State




## Imbalanced State Pruritic or Cough

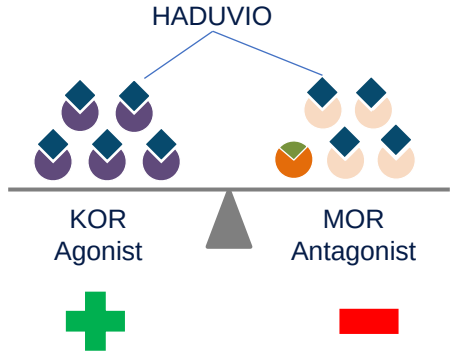
Too little KOR activation and/or too much MOR activation




**Induction of Itch/Cough**

## HADUVIO Rebalancing

Dual action as both a KOR agonist and a MOR antagonist



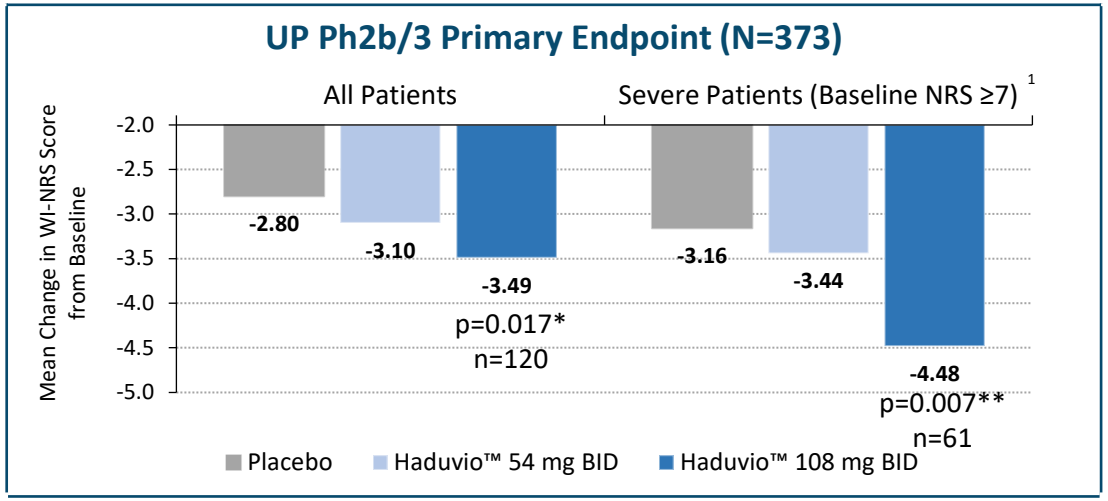

**Suppression of Itch/Cough**

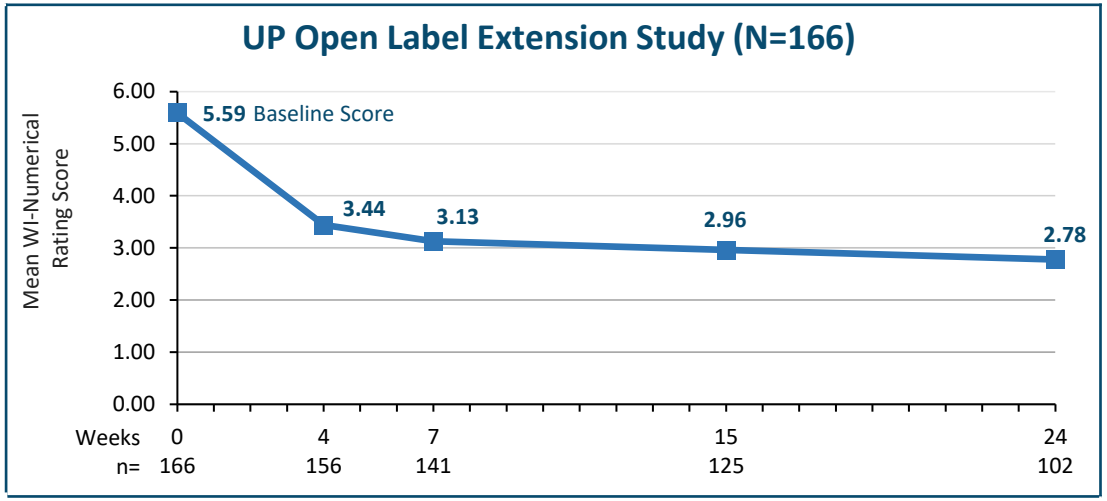
Proposed mechanism of action of HADUVIO
KOR, ƙ-opioid receptor; MOR, μ-opioid receptor
Bigliardi PL Bigliardi-Qi M *Itch Basic Mechanisms and Therapy* 2004, Komiya E, et al. In *J Mol Sci.* 2020, Ko MCH Naughton NN Anesthesiology 2000

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

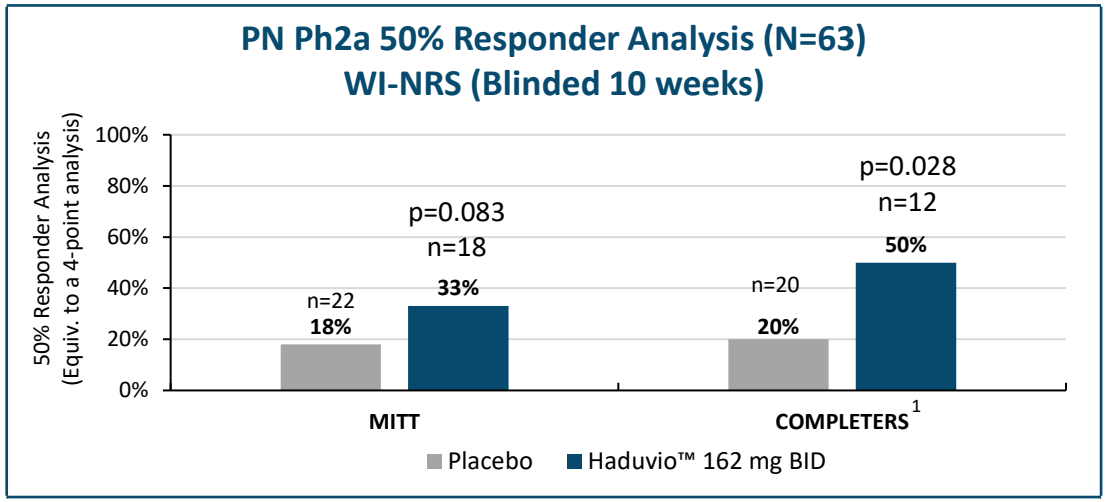
## Over 400 subjects studied with moderate to severe pruritus

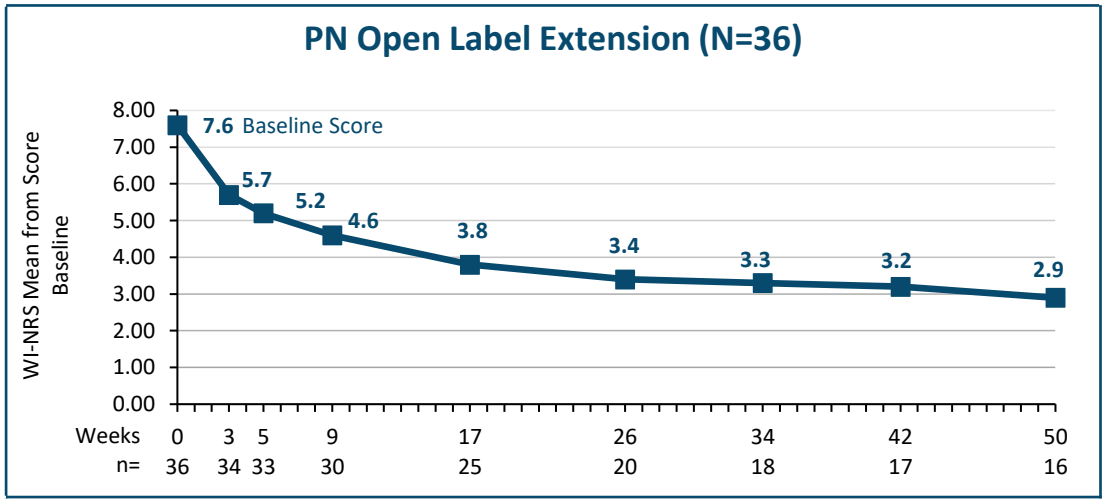
### Uremic Pruritus (UP)




### Prurigo Nodularis (PN)




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

[1] Post-hoc analysis

# HADUVIO™ is Advancing Two Lead Clinical Programs with Near-Term Readouts

## Substantial Unmet Needs with No Approved Therapies

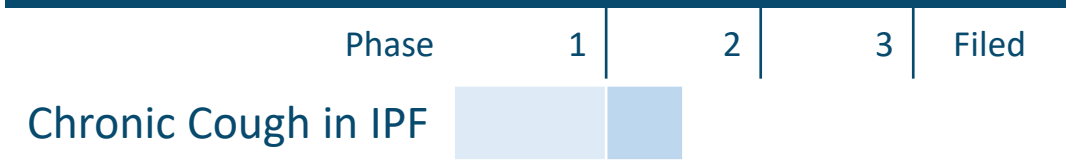
PRISM
Pruritus Relief through Itch-Scratch Modulation

### Pruritus Associated with Prurigo Nodularis[1]

- ~80% enrolled as of July 2021
- Enrollment completion expected – 2H 2021
- FDA Fast Track designation granted for moderate to severe pruritus in PN
- Data expected in 1H 2022

CANAL

### Chronic Cough in Idiopathic Pulmonary Fibrosis




- UK reopened after covid restrictions and sites are screening and enrolling
- Data expected in 1H 2022

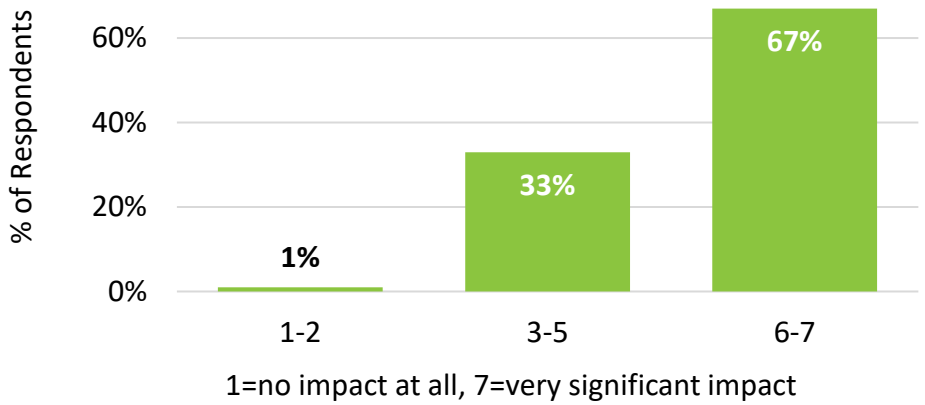
[1] Our prurigo nodularis program consists of our ongoing Phase 2b/3 clinical trial and an additional Phase 3 clinical trial that we plan to conduct.

# 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]

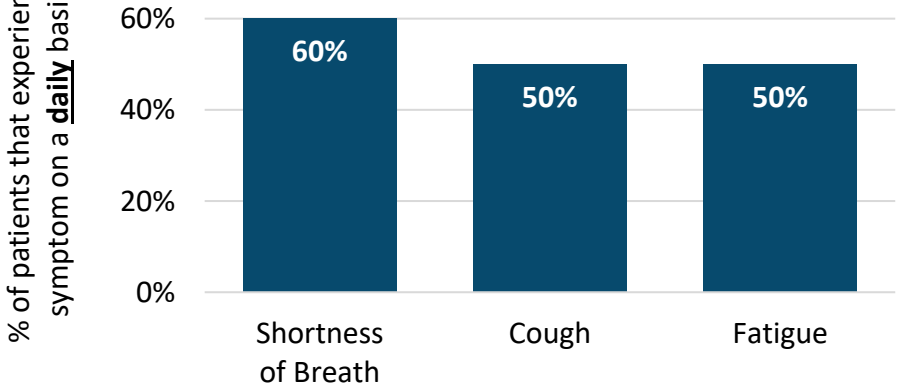
### Dermatologist View on PN Impact on QoL[3] (N=126)




## Chronic Cough in Idiopathic Pulmonary Fibrosis

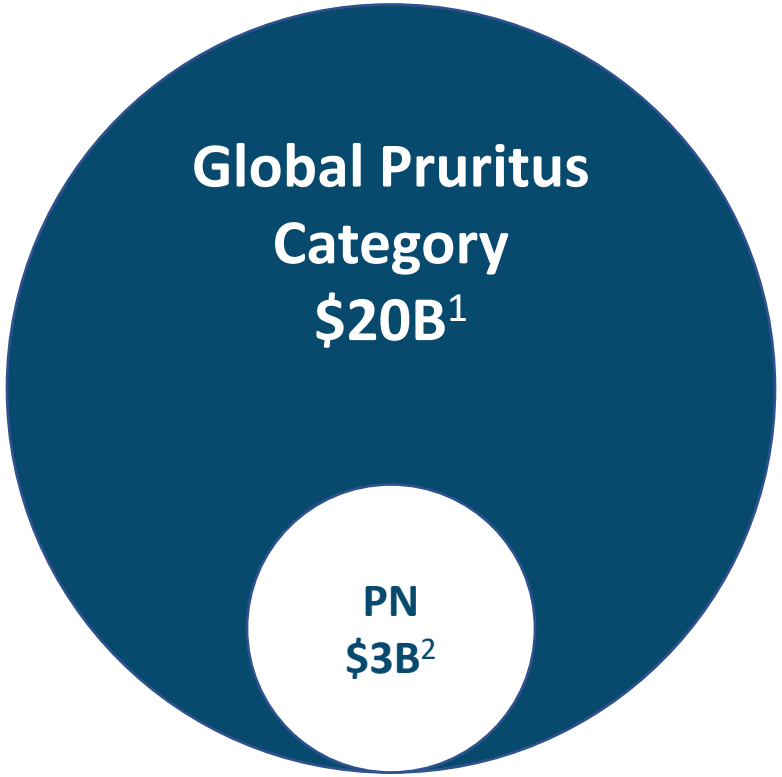
- ✓ No approved therapies
- ✓ No oral option available
- ✓ High unmet need
- ✓ IPF is a life-threatening, debilitating disease[4]

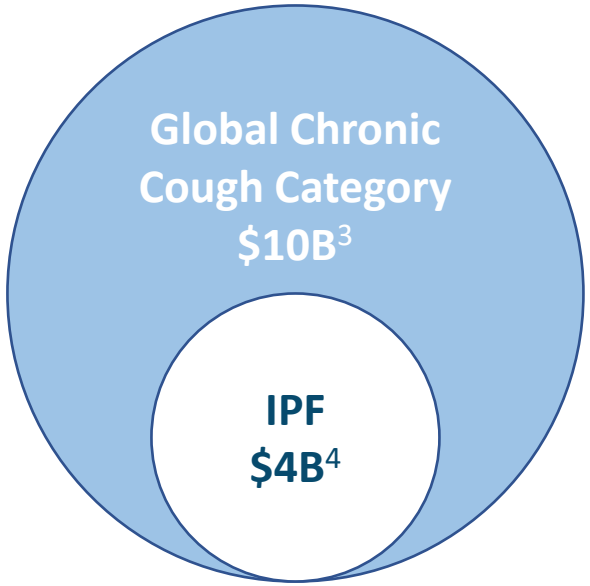
### Most Bothersome Daily IPF Symptom[4]




[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

# HADUVIO™ Global Potential in Categories Totaling $30B




**Prurigo Nodularis (PN)**
300,000 U.S. patients
730,000 patients Globally

**Idiopathic Pulmonary Fibrosis (IPF)**
130,000 U.S. patients
1M+ patients Globally

[1]2026 est. OG Analysis Global Pruritus Therapeutics Market [2]2031 est. DelveInsight Prurigo Nodularis Market Insight, Epidemiology, and Market Forecast May 2020 [3]2027 est. The Insight Partners Jun 2020 [4]2028 est. VPA Research Idiopathic Pulmonary Fibrosis Report Feb 2021

# Chronic Pruritus in Prurigo Nodularis

PRISM

Pruritus Relief through Itch-Scratch Modulation

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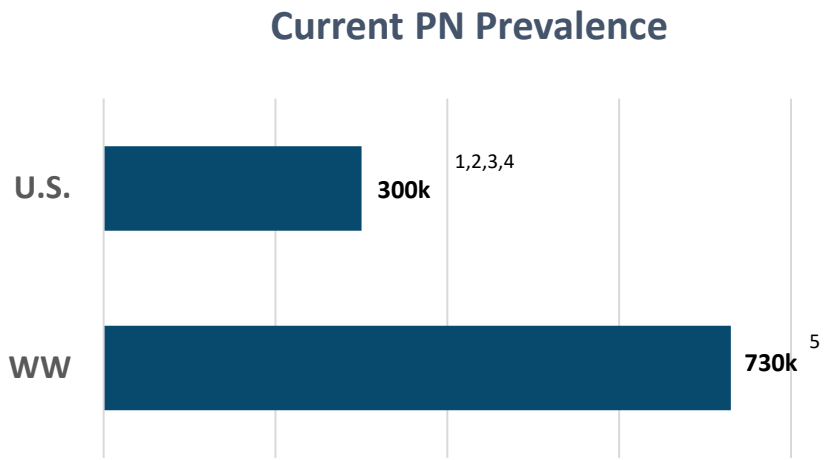
# Opportunity to be the First and Only Oral Therapy Approved in Pruritus Associated with Prurigo Nodularis

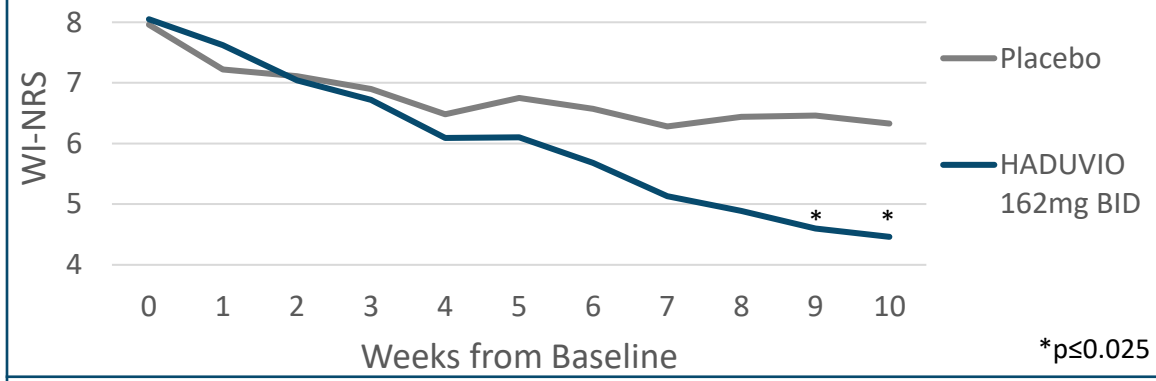


- Current off-label treatments for itch lack efficacy and/or have an unfavorable AE profile
  - 40-50% of patients are uncontrolled on off-label therapies
- Oral therapy enables opportunity to be used in earlier lines of therapy
- Many underlying etiologies of itch, but initial scratching may create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

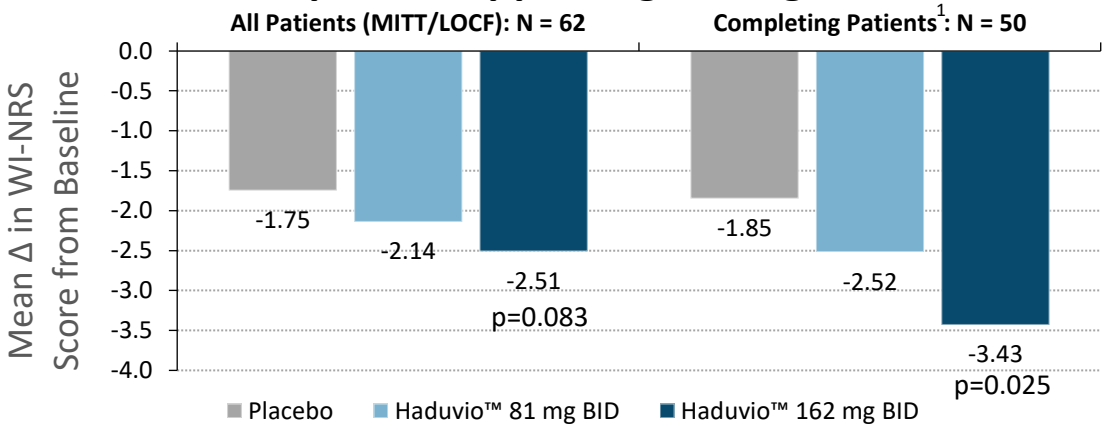
[1]Huang AH JID 2020 [2]Stander S JAAD 2020 [3]Iking A JEADV 2013 [4]Pereira M JEADV 2018 [5]Prurigo Nodularis - Market Insights, Epidemiology and Market Forecast [6]Eigelshoven CME Derm 2009 [7]Vaidya DC & Schwartz RA Acta Derm Croat 2008 [8]Lee MR, Shumack S Aus J Derm 2005 [9]Iking A JEADV 2013

# Results from Ph2 Prurigo Nodularis Trial and Open Label Extension (OLE)

## Continued Separation of WI-NRS Over Time

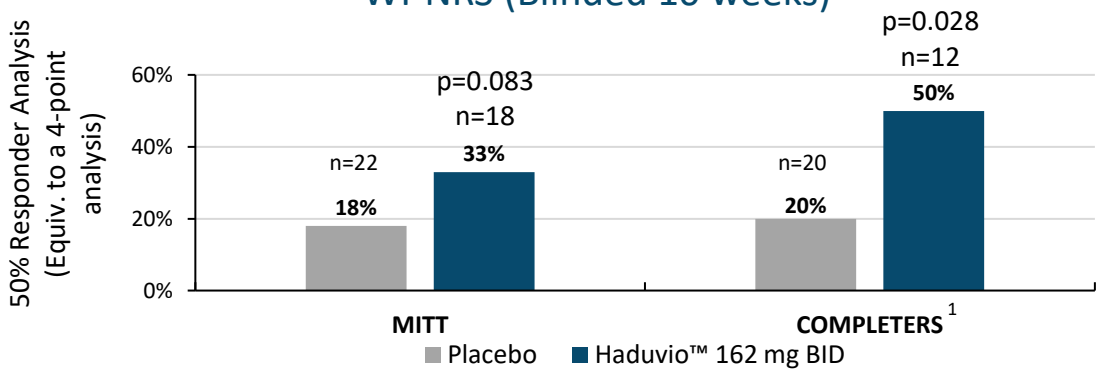



## Dose Response Supporting 162mg Selection†



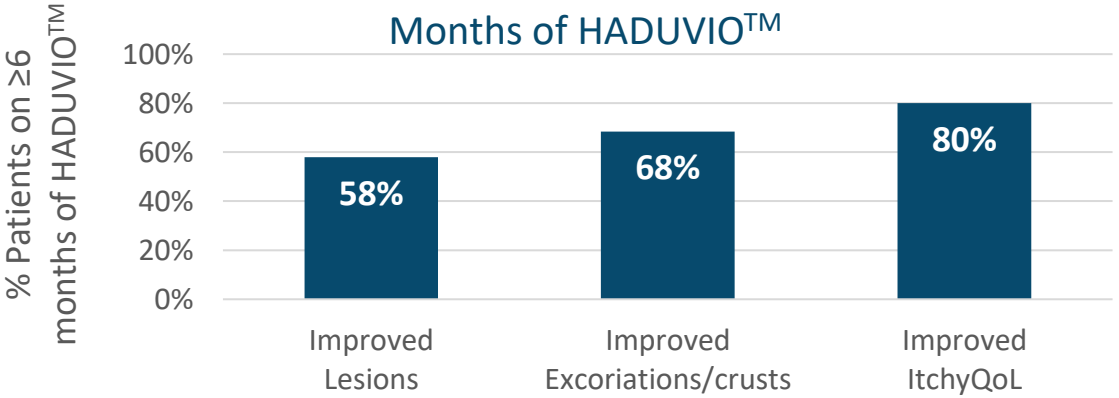

## Drug Separation vs. PBO

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™

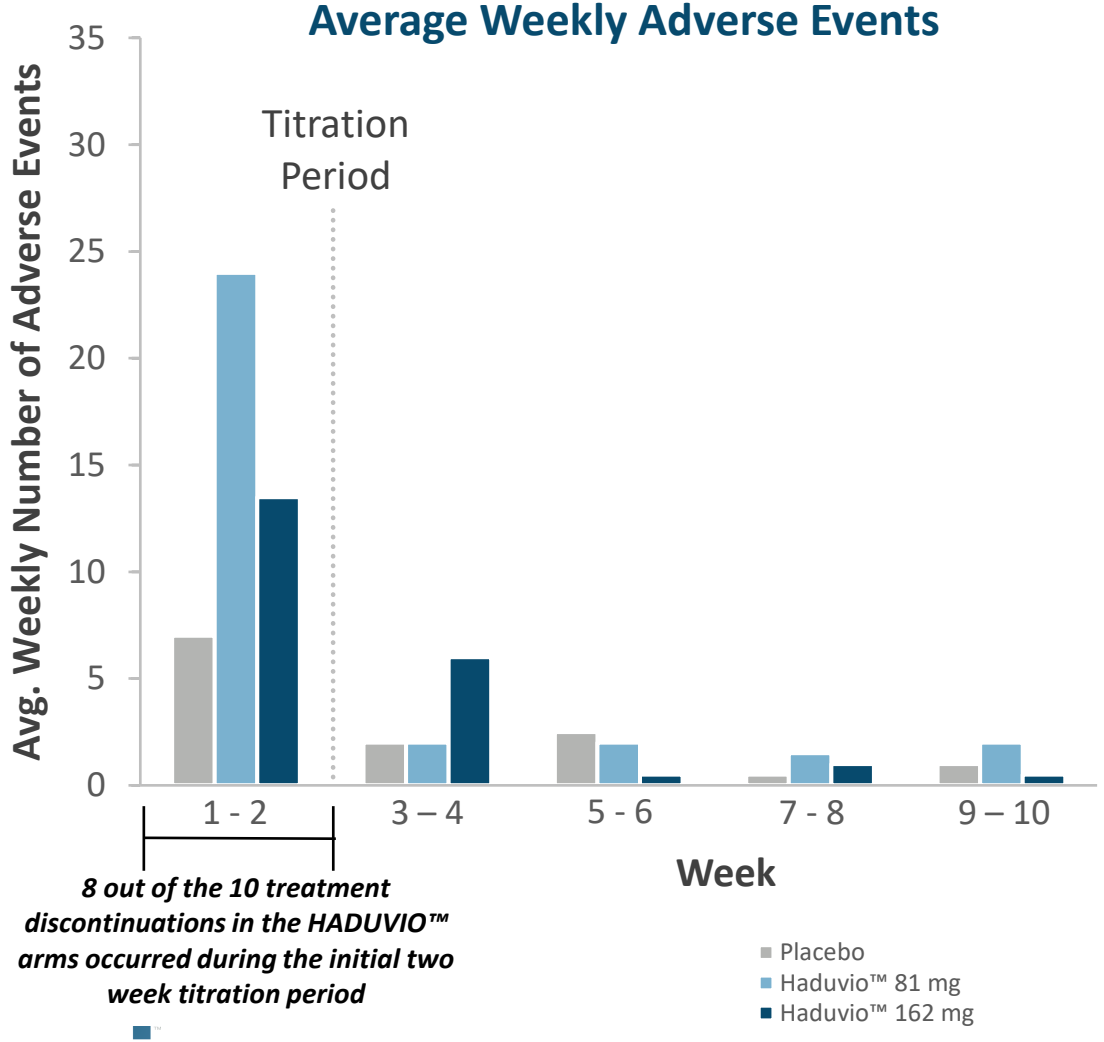



†All p-values compare treatment group to placebo. Only the primary endpoint [30% responder analysis] was powered for statistical significance.
[1]Post-hoc analysis on completers. Consists of the patients who completed the 10-week course of treatment.

# Prurigo Nodularis Phase 2 Trial Adverse Events (AEs) by Week (mITT population)

## Number of AEs approximates placebo post the titration period

### Average Weekly Adverse Events




***8 out of the 10 treatment discontinuations in the HADUVIO™ arms occurred during the initial two week titration period***

### Adverse Events by Dose and Grade[1]

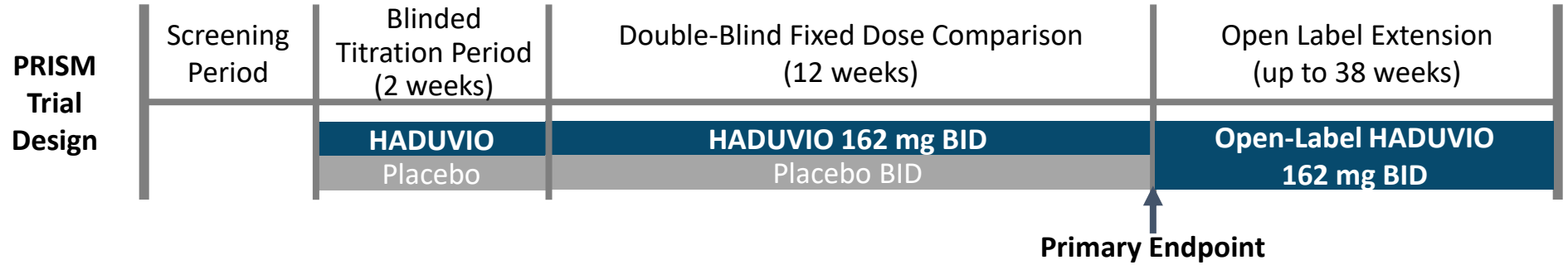
| | Placebo (N=22) | | HADUVIO™ ER 81 mg (N=22) | | | HADUVIO™ ER 162 mg (N=18) | |
|---|---|---|---|---|---|---|---|
| **GRADE** | **1** | **2** | **1** | **2** | **3** | **1** | **2** |
| Dizziness | 1 (5%) | - | 3 (14%) | 2 (9%) | - | 5 (28%) | 2 (11%) |
| Nausea | 1 (5%) | - | 2 (9%) | 2 (9%) | - | 3 (17%) | 4 (22%) |
| Headaches | 1 (5%) | 1 (5%) | 2 (9%) | 4 (18%) | - | 2 (11%) | 3 (17%) |
| Fatigue | - | - | 3 (14%) | 1 (5%) | 1 (5%) | 2 (11%) | - |

[1] One subject may have multiple AEs or an AE continuing across multiple doses.

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

## Trial to Complete Enrollment in 2H 2021

| Optimizations from Ph2 to Ph2b/3 PRISM Trial | | |
|---|---|---|
| Increased Powering | Enriched Population | Increased Duration |
| 63 patients (Ph2) → 360 patients (Ph2b/3) | Focusing on severe population<br>WI-NRS ≥5 (Ph2) → WI-NRS ≥7 (Ph2b/3) | 10 weeks (Ph2) → 14 weeks (Ph2b/3) |




**Trial Status:**
- 60+ Sites
- ~80% enrolled as of July 2021

**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:**
- >95% of subjects who reach Wk 14 have continued into the open label extension
- Long-term safety
- Durability of effect
- Lesion healing

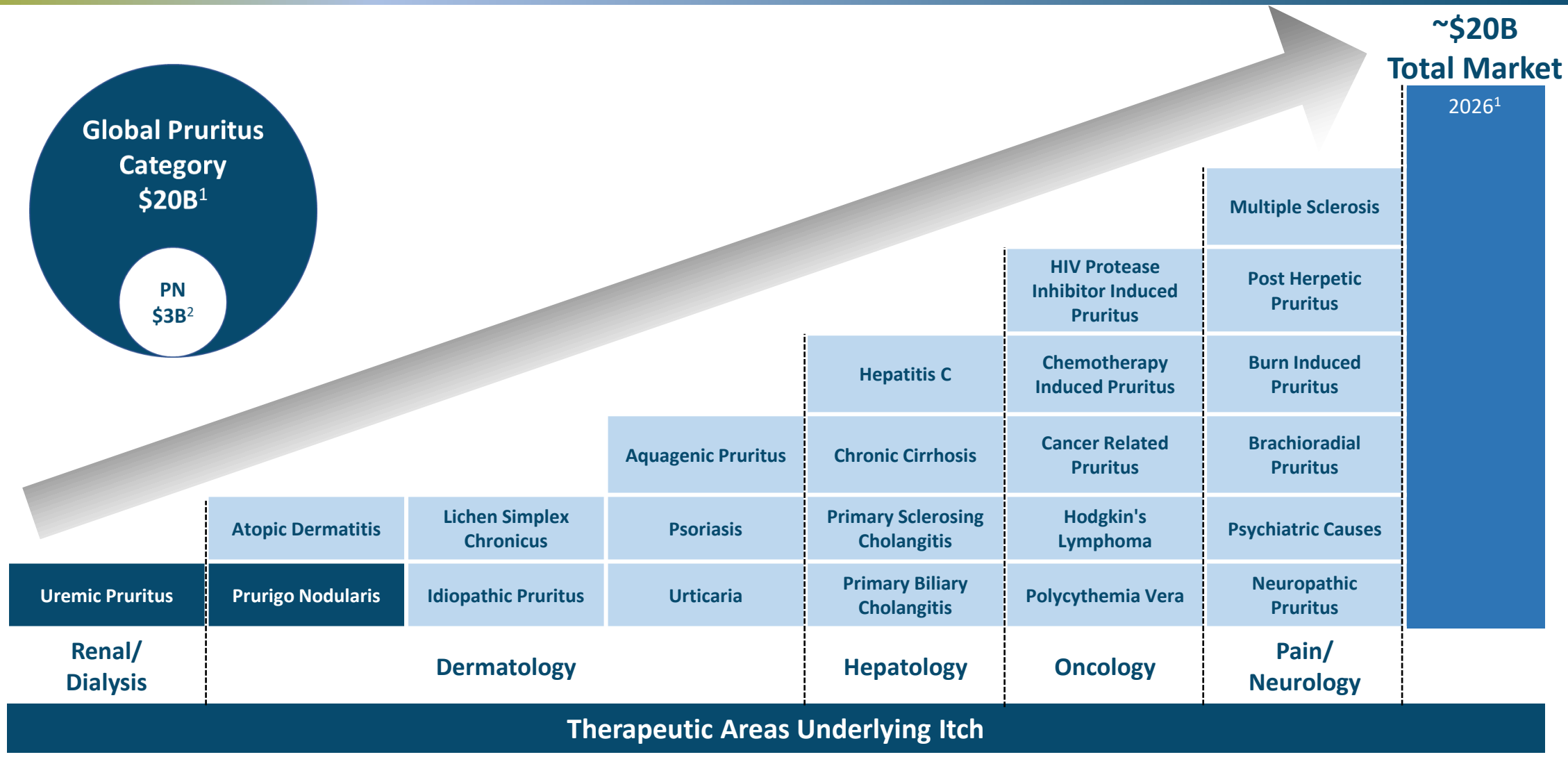
# Patient Images from PRISM

HADUVIO 162mg BID or Placebo | HADUVIO 162mg BID

Baseline | Week 14 | Week 52

Baseline | Week 14 | Week 28

# 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

# Expansion Strategy in Pruritus

**Prurigo Nodularis**

Establish pruritus efficacy and safety in highest baseline worst itch condition

**Complete Uremic Pruritus Development**

Showed positive efficacy and safety data in Ph2b/3 trial

- High severity of underlying itch

**Additional Derm Indication**

Move earlier in the course of the disease where severe chronic itch is present:

- High severity of pruritus
- Chronic condition with high unmet need
- Neurologically mediated condition

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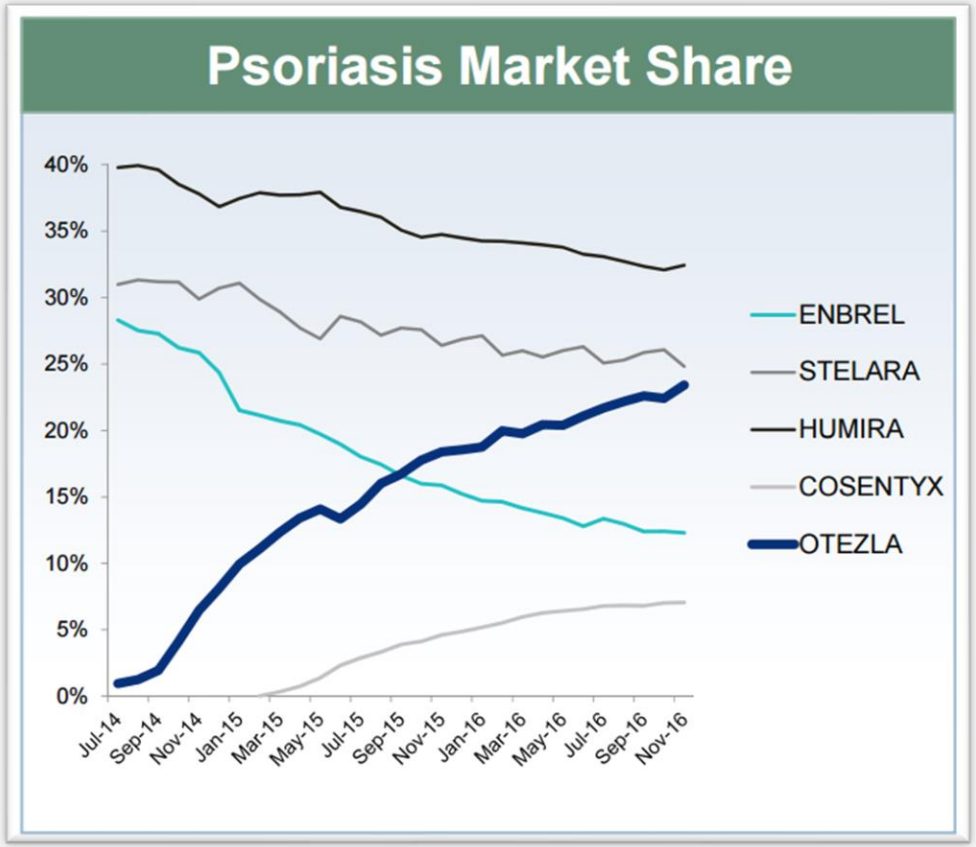
# Otezla Shows the Potential for a Safe and Effective Oral Option




- Otezla launched in 2014 in moderate-severe plaque psoriasis
- Both Otezla and HADUVIO are oral therapies and require titration to maintenance dose with twice a day dosing
- Despite an established biologic market, Otezla captured +25% share of advanced therapies and achieved ~$1B in U.S. revenues (in 2016)
- Otezla, given insurer access, is used as an option prior to biologics because of its RoA, but specifically because of its safety profile which requires no lab monitoring, making it a preferred oral therapy over methotrexate
- A ***high efficacy oral could represent an attractive option*** for patients looking to avoid escalating treatment to an injectable therapy

# Chronic Cough in Idiopathic Pulmonary Fibrosis

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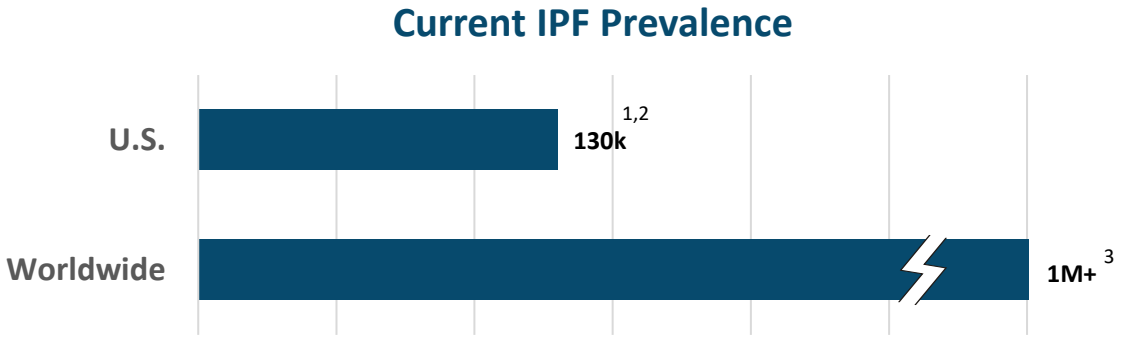
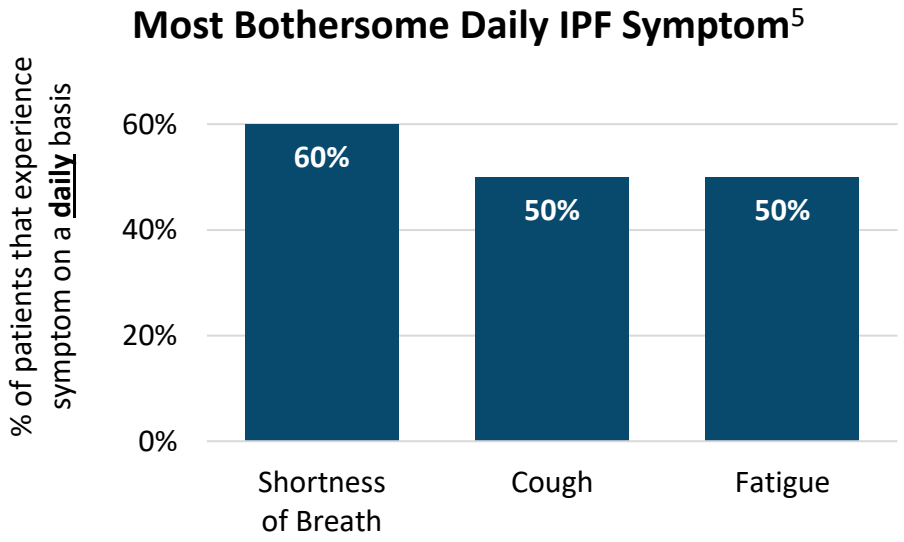
# Opportunity to be First in Class for Chronic Cough in Idiopathic Pulmonary Fibrosis

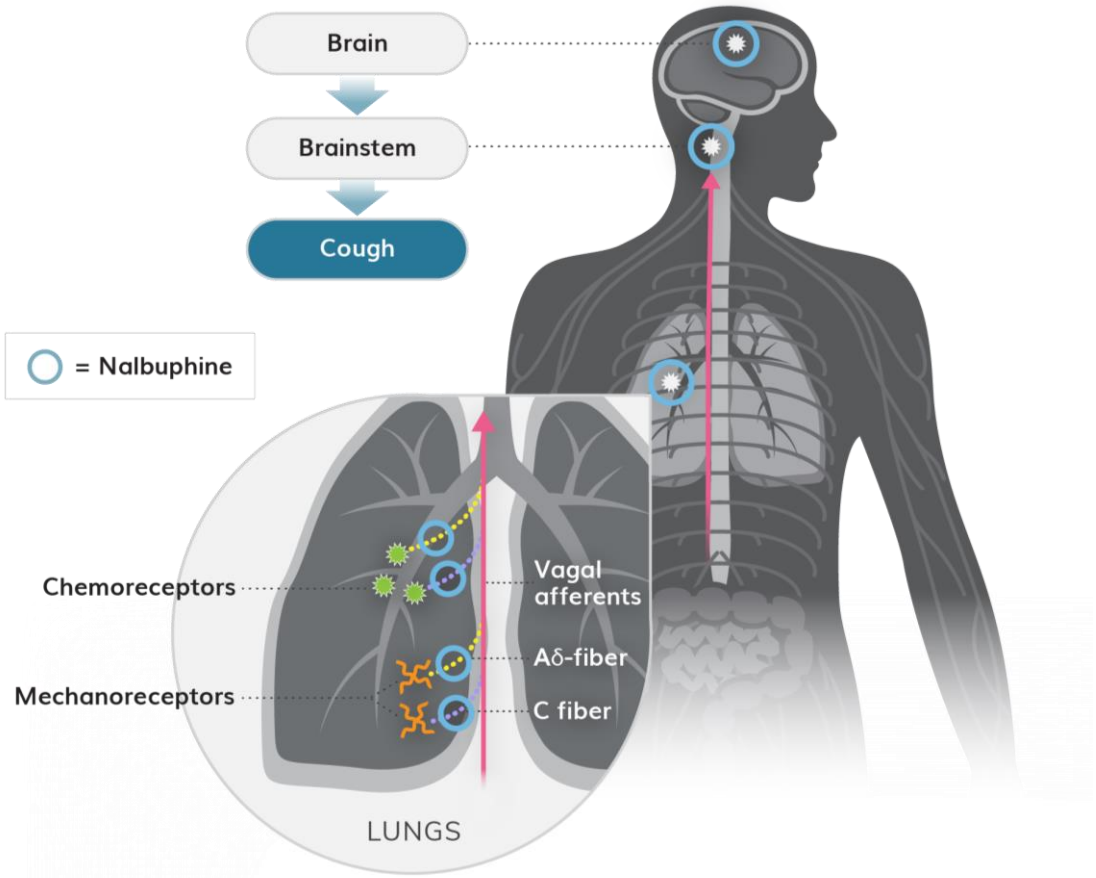



- 70% to 85% of IPF patients are reported to suffer from chronic cough[4]
- Cough is one of the most bothersome symptoms of IPF[5]
  - ≥75% of IPF patients report cough as being one of their most significant symptoms
- Current IPF therapies (anti-fibrotics), which have not been shown to reverse disease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




[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

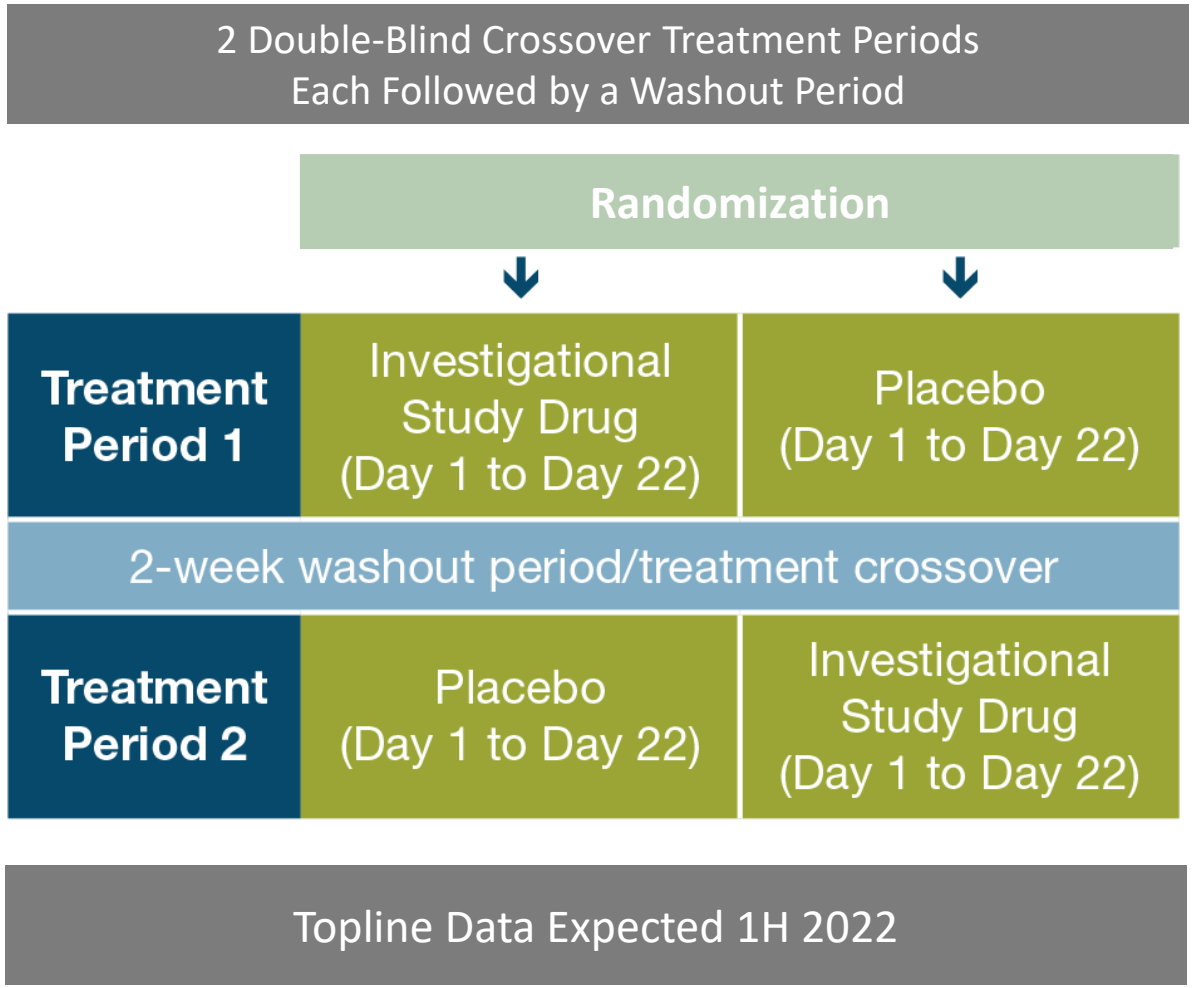
Endogenous opioids are believed to play an important role in modulating respiration[1]

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)




Patient screening activity has resumed at multiple sites in the UK

- Working to re-open all remaining sites
- Shelter in place restrictions lifted at the end of March

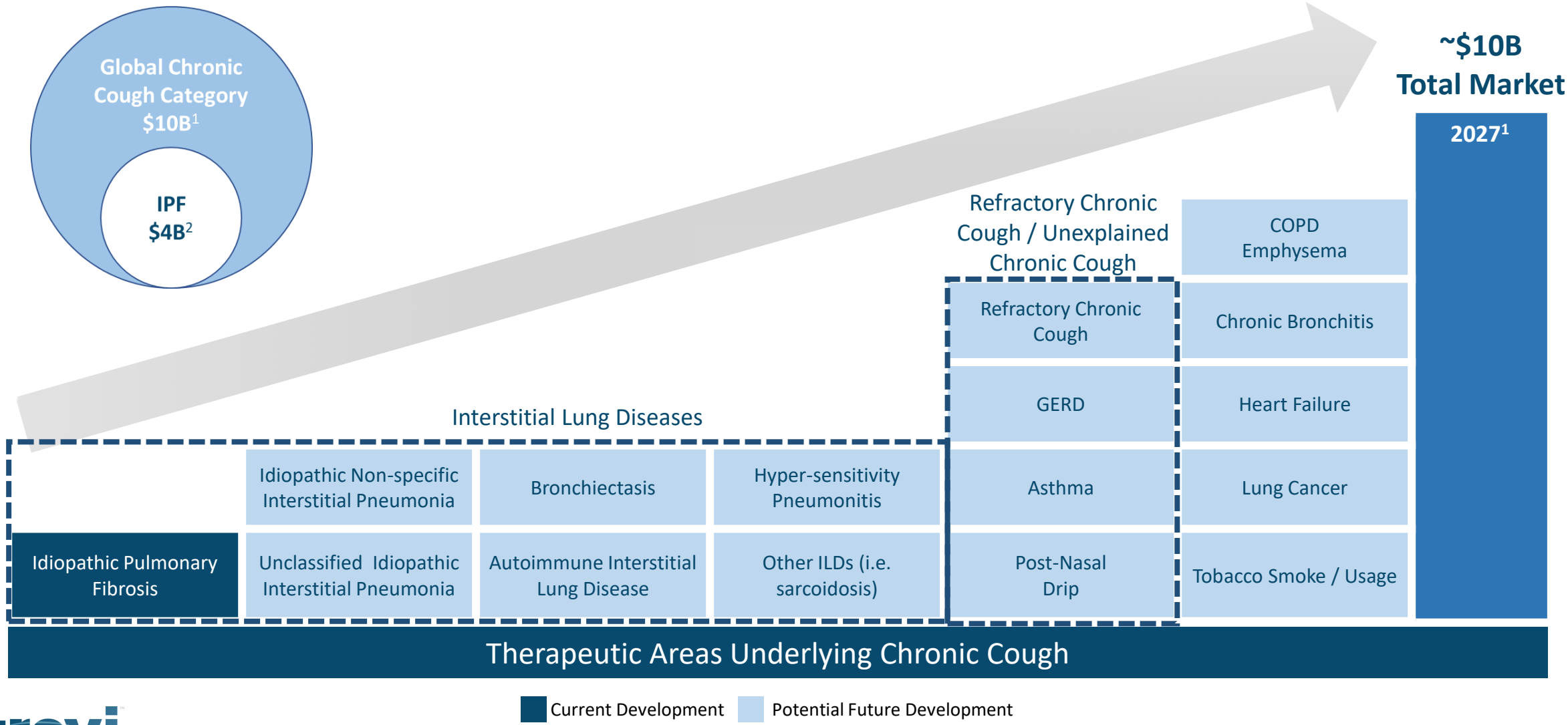
Primary endpoint

- 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

# 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

# Expansion Strategy in Chronic Cough

**Idiopathic Pulmonary Fibrosis**

Establish cough efficacy and safety in worst chronic cough condition

**Interstitial Lung Diseases**

Expand to other progressing, fibrotic interstitial lung diseases

- High cough severity
- Non-productive cough
- Similar etiology to chronic cough in IPF

**Refractory Chronic Cough/ Unexplained Chronic Cough**

Potential to expand into other neurologically mediated cough conditions

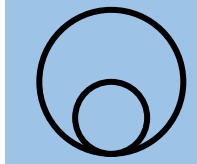
- High cough severity
- High unmet need where alternatives to P2X3 are needed

trevi THERAPEUTICS

# Investment Highlights

## Attractive Markets with Established MOA

- $3B+ est. PN global category in ***$20B pruritus market*** [1,2]
- $4B est. IPF global category in ***$10B chronic cough market*** [3,4]
- Lead Indications have no approved therapies
- ***Only oral dual acting kappa-agonist and mu-antagonist in clinical development***
- ***Rebalances opioid system*** to potentially regulate itch and chronic cough
- Works through ***both the peripheral and central*** nervous systems



## Near-term Data with Expansion Potential

- PRISM: Ph2b/3 study of pruritus in ***PN enrollment expected to be completed in 2H 2021*** with top-line data 1H2022
- ***Fast Track designation granted*** for moderate to severe pruritus in PN
- CANAL: Ph2 study of chronic cough in IPF has ***restarted enrollment*** post-covid, with top-line data expected 1H2022
- Both data readouts represent significant opportunities for the indication and broader access to the categories of chronic pruritus and chronic cough

## Strong IP and Financial Position

- **18 issued US and foreign patents**
- Issued patents with protection expiring from 2026 through 2032
- Additional applications, if issued, expiring from 2032 to 2041
- Cash balance as of 3/31/21 of $41.6 million expected to fund operations into the second quarter of 2022

HADUVIO™ (nalbuphine ER) is an investigational drug

[1]2026 est. Global Pruritus Therapeutics Market Prurigo [2]2031 est. Prurigo Nodularis Market Report May 2020 [3]2027 est. The Insight Partners Jun 2020 [4]2028 est. Research Idiopathic Pulmonary Fibrosis Report Feb 2021

# Thank You