Corporate Presentation

May 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 planned clinical trials; uncertainties on the potential impact to our clinical trials from the ongoing COVID-19 pandemic; uncertainties regarding our ability to execute on our strategy; the risk that preliminary or interim results from a clinical trial will not be indicative of the final results of the trial or that positive results from a clinical trial may not be predictive of the results of future or ongoing 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.

Investment Highlights

Demonstrated Efficacy and Safety	• Efficacy data in over 400 patients with pruritic conditions • Safety data in more than 800 subjects dosed with long-term safety data (6 and 12 months) in pruritic patients
Late-Stage Programs	• Ph2b/3 Pruritus in Prurigo Nodularis (PN) enrollment 2H 2021 • Ph2 Chronic Cough in Idiopathic Pulmonary Fibrosis (IPF)
Attractive Markets	• Lead oral compound in trials for both indications • PN estimated to be $3B+ global category in 2031[1] • IPF estimated to be ~$4B global category in 2028[2]
Indication Expansion Opportunities	• Mechanism enables broad use in chronic pruritic and cough conditions • Mechanism enables broad use in other neurologically mediated conditions
Strong IP	• 18 issued patents with issued protection through at least 2032 and additional applications extending to 2041

[1]Prurigo Nodularis Market Report May 2020 [2]Research Idiopathic Pulmonary Fibrosis Report Feb 2021

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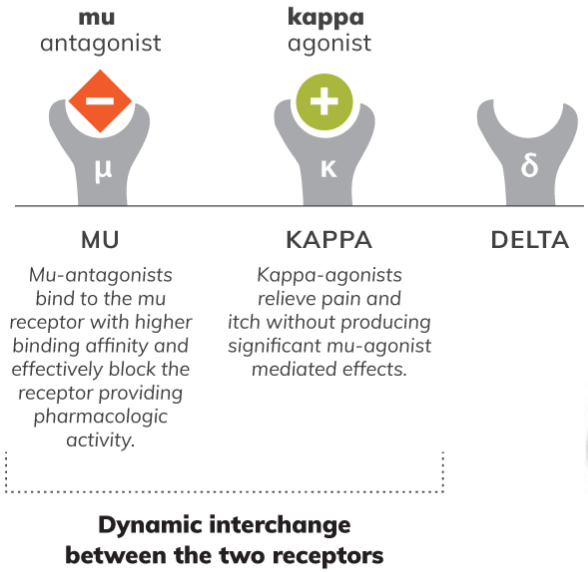
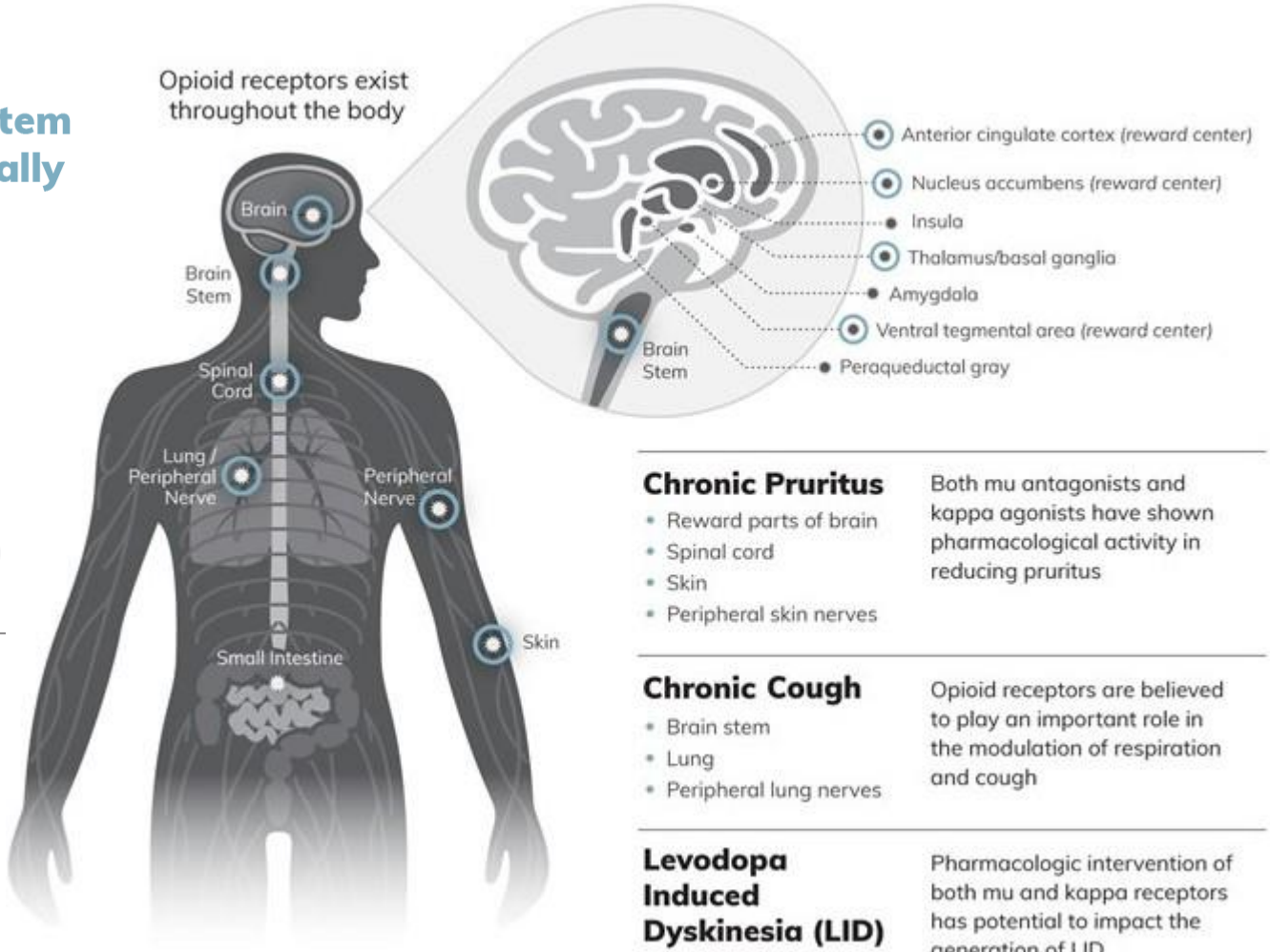
Broad Potential Applications for Mechanism of Action of HADUVIO™

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

Haduvio™ is an investigational therapy

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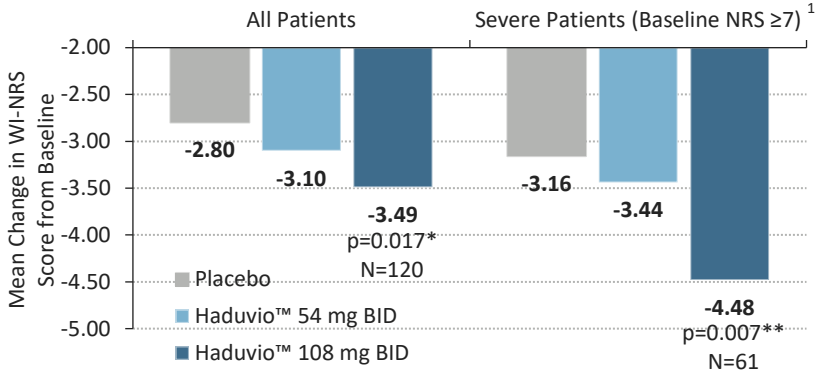
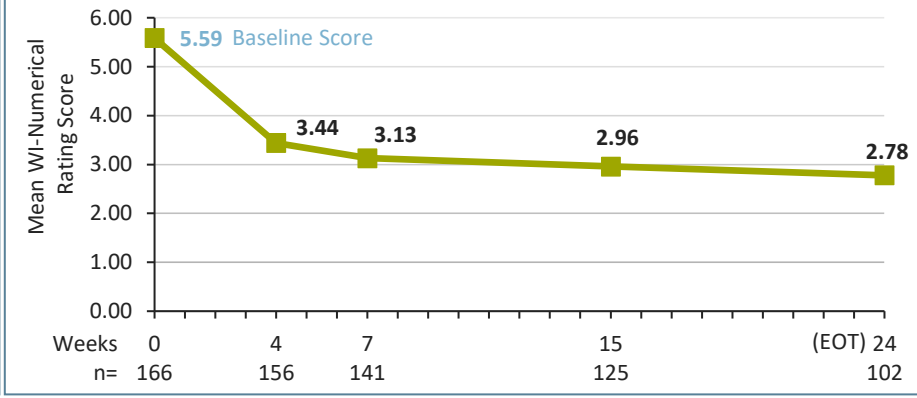
HADUVIO™ Demonstrated Durable Results in Itch Across Multiple Studies and Endpoints

Uremic Pruritus

Uremic Pruritus Phase 2b/3 Primary Endpoint: All Patients and Severe Patients (n=373)

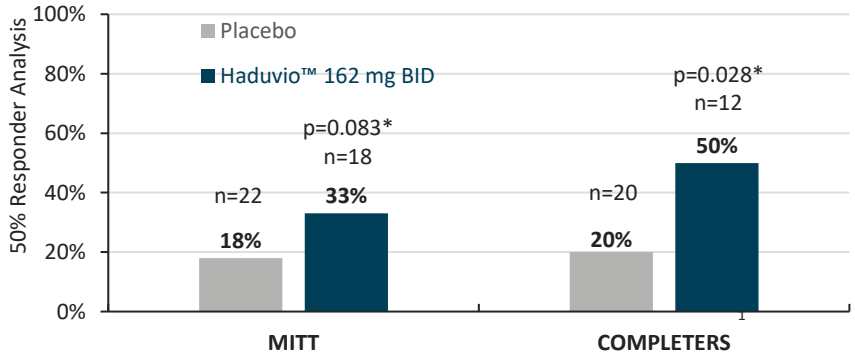


Uremic Pruritus Open Label Extension Study (n=166)

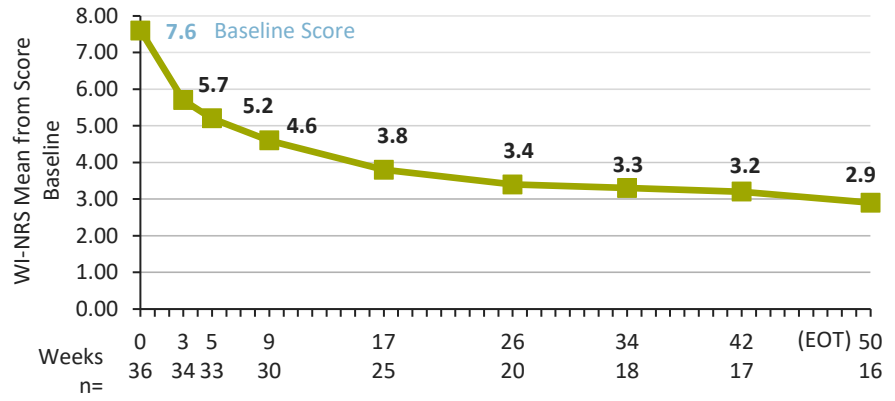


Prurigo Nodularis

50% Responder Analysis (Equiv. to a 4-point Analysis) WI-NRS (Blinded 10 weeks)



PN: Open Label Extension Mean Change in WI-NRS (n=36)



Over 400 subjects studied with moderate to severe pruritus

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

[1] Post-hoc analysis of severe patients.

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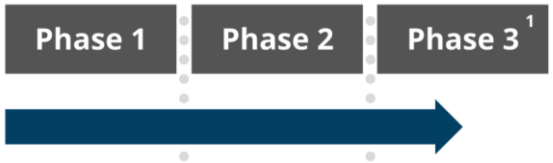
HADUVIO™ is Advancing Two Late-Stage Clinical Programs with Near-Term Readouts

PRISM

Pruritus Relief through Itch-Scratch Modulation

Chronic Pruritus in Patients with Prurigo Nodularis



- More than 70% enrolled
- Enrollment completion expected – 2H 2021
- FDA Fast Track designation granted for moderate to severe pruritus in PN

CANAL

Chronic Cough in Patients with IPF

- Study is open for enrollment in the UK
- UK reopening and screening activity resuming at multiple sites

Substantial Unmet Needs with No Approved Therapies

[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.

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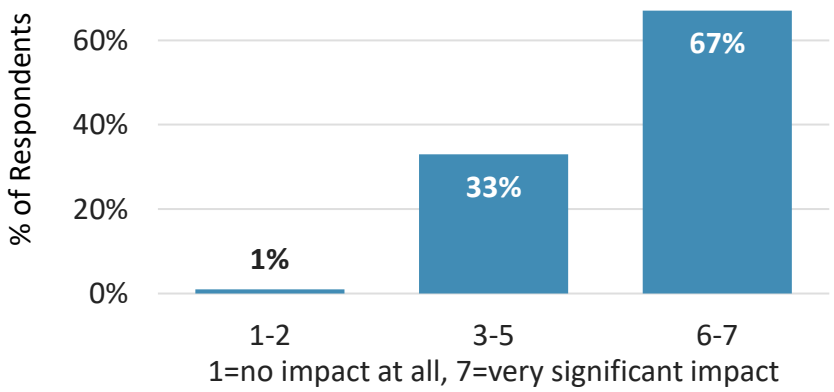
Attractive Categories for Lead Indications

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]

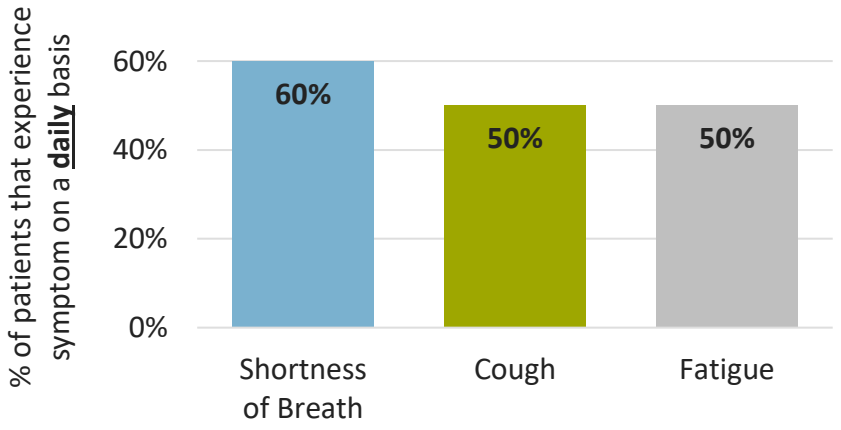
Dermatologist View on PN Impact on QoL[3] (N=126)



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

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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 in Prurigo Nodularis

PN: $3B Global Market in 2031		
US	300,000	Current Prevalence[1,2,3,4,]
	40-50%	Uncontrolled[5]
Ex-US	430,000	Current Prevalence[6]
	40-50%	Uncontrolled[7]

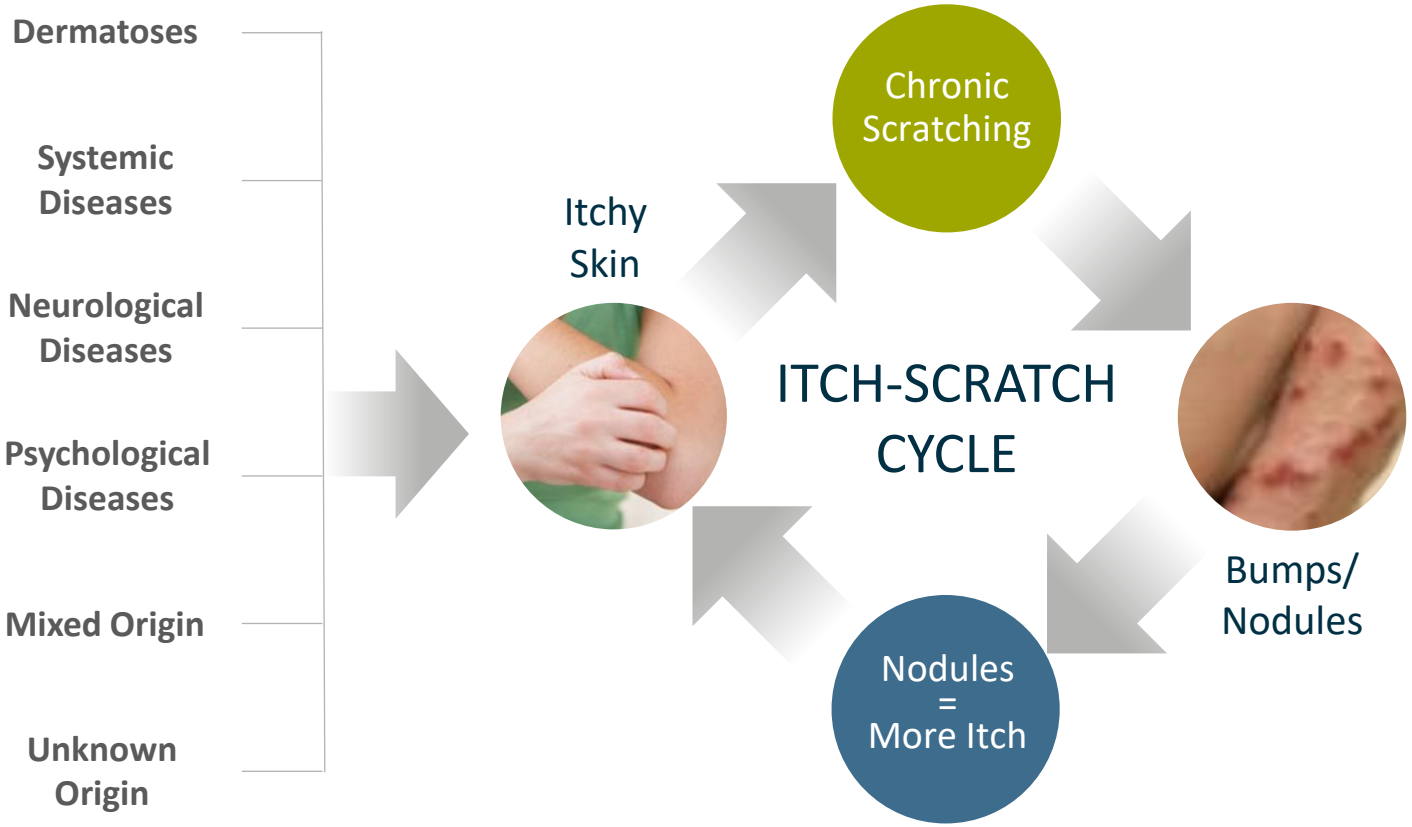
- Current off-label treatments for itch lack efficacy and/or have an unfavorable AE profile
- Oral therapy enables opportunity to be used at different stages of therapy
- Phase 2 results:
  - 58% of patients completing ≥6 months of HADUVIO showed lesion healing
  - QoL (ItchyQoL) improved at every visit throughout 50 weeks of HADUVIO therapy

**Market shares calculated as a percent of the uncontrolled population

[1]Huang AH JID 2020 [2]Stander S JAAD 2020 [3]Iking A JEADV 2013 [4]Pereira M JEADV 2018 [5]Trevi Data on file [6]Prurigo Nodularis - Market Insights, Epidemiology and Market Forecast. [7]Weisshaar E Acta Derm Venereol 2012

Prurigo Nodularis Itch Scratch Cycle

Many underlying etiologies of itch, but initial scratching may create an itch-scratch cycle resulting from central and/or peripheral nervous tissue changes[1,2,3,4]



[1]Eigelshoven CME Derm 2009 [2]Vaidya DC & Schwartz RA Acta Derm Croat 2008 [3]Lee MR, Shumack S Aus J Derm 2005 [4]Iking A JEADV 2013

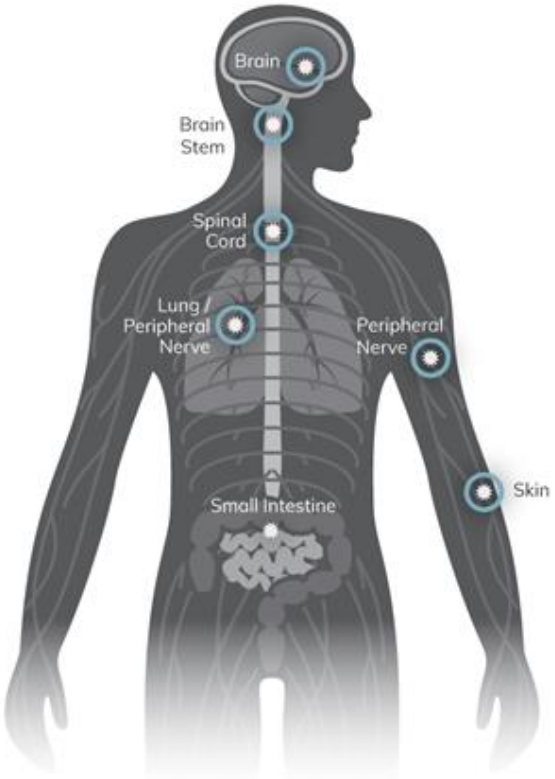
Nalbuphine Impacts the Neuro-Inflammatory Axis with Potential Broad Utility in Pruritus

Neuronal Axis

Central (Brain, Brain Stem, Spinal Cord)
- Central suppression of itch[1]
- Reduction of cough reflex[2]

Peripheral (Peripheral Nerve, Skin, Lung)
- Type C fibers in periphery[3]

Neuronal Sensitization[4]



Inflammatory Axis

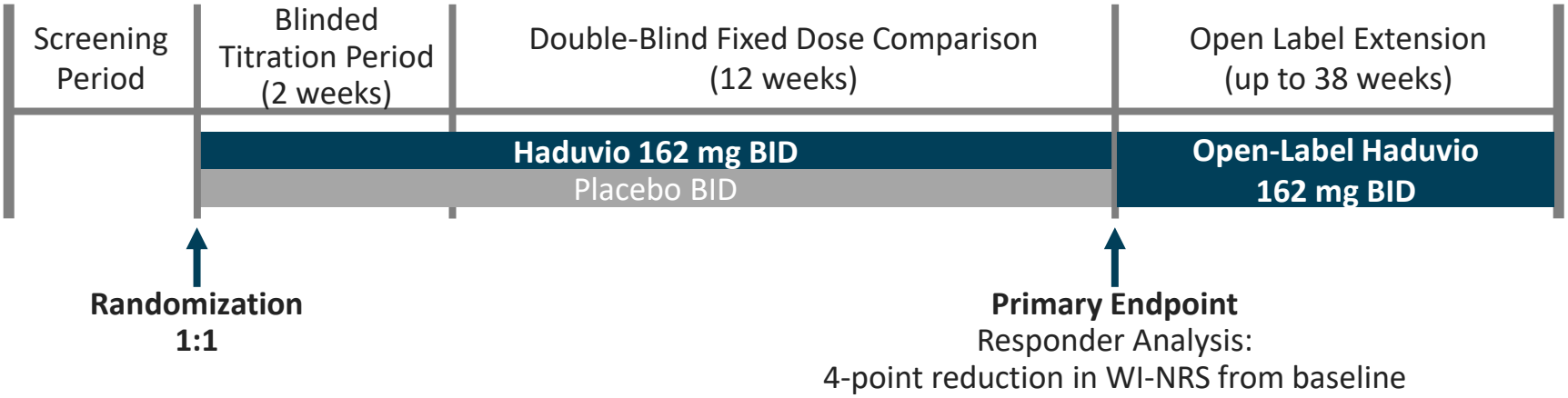
Peripheral (Skin)
- Reduces IL-31[5]
- Pro IL-10[5]
- Reduces Sub P[6]

Peripheral (Lung)[7]
- Reduces TNF-α
- Reduces IL-6
- Reduces IL-10

[1]Schmelz et al. Derm Ther 2005 [2]Wang J et al. Ther Clin Risk Manag [3]Metze et al. JAAD 1999 [4]Hope-Gill BD et al. Am J Resp Crit Care Med 2003 [5]Inan et al. Eur J Pharmacol 2019 [6]Kuraishi et al. 1995, Andoh et al. J Pharmacol Exp Ther 1998 [7]Zhang Y et al. Exper Ther Med 2017

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

Trial to Complete Enrollment in 2H 2021



Trial Status:
- 60+ Sites
- >70% enrolled as of May 2021

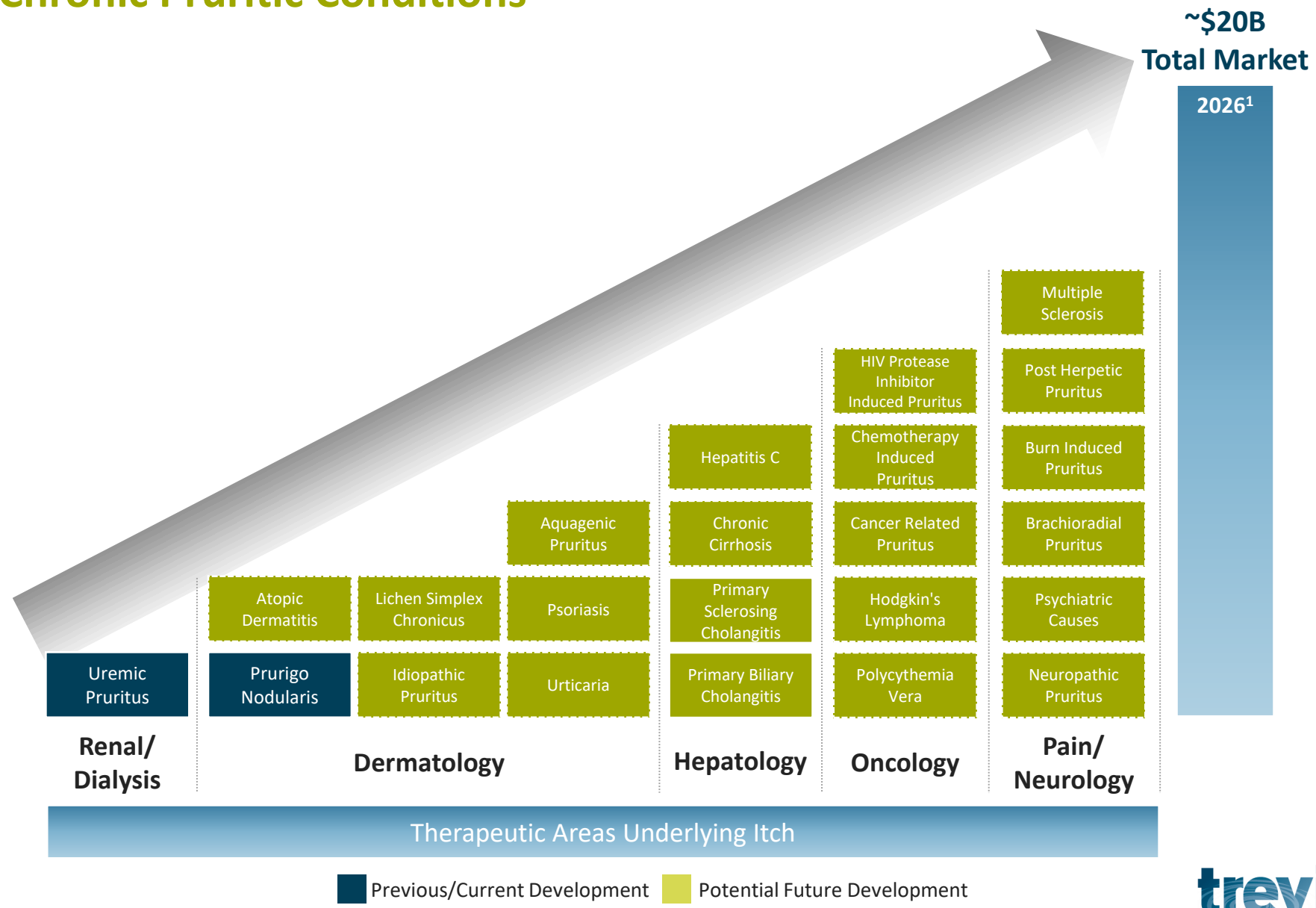
Inclusion Criteria:
- Worst-Itch Numerical Rating Scale (WI-NRS) Score ≥7
- 10+ pruriginous nodules
- PN present on at least 2 separate body parts

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

Market Opportunity of a Broad Array of Chronic Pruritic Conditions



[1]Global Pruritus Therapeutics Market

Chronic Cough in Idiopathic Pulmonary Fibrosis

CANAL

Opportunity to be First in Class for Chronic Cough in Idiopathic Pulmonary Fibrosis (IPF)

IPF: $4B Global Market in 2028

US	101,000	Current Prevalence[4]
	40-50%	Uncontrolled[5]

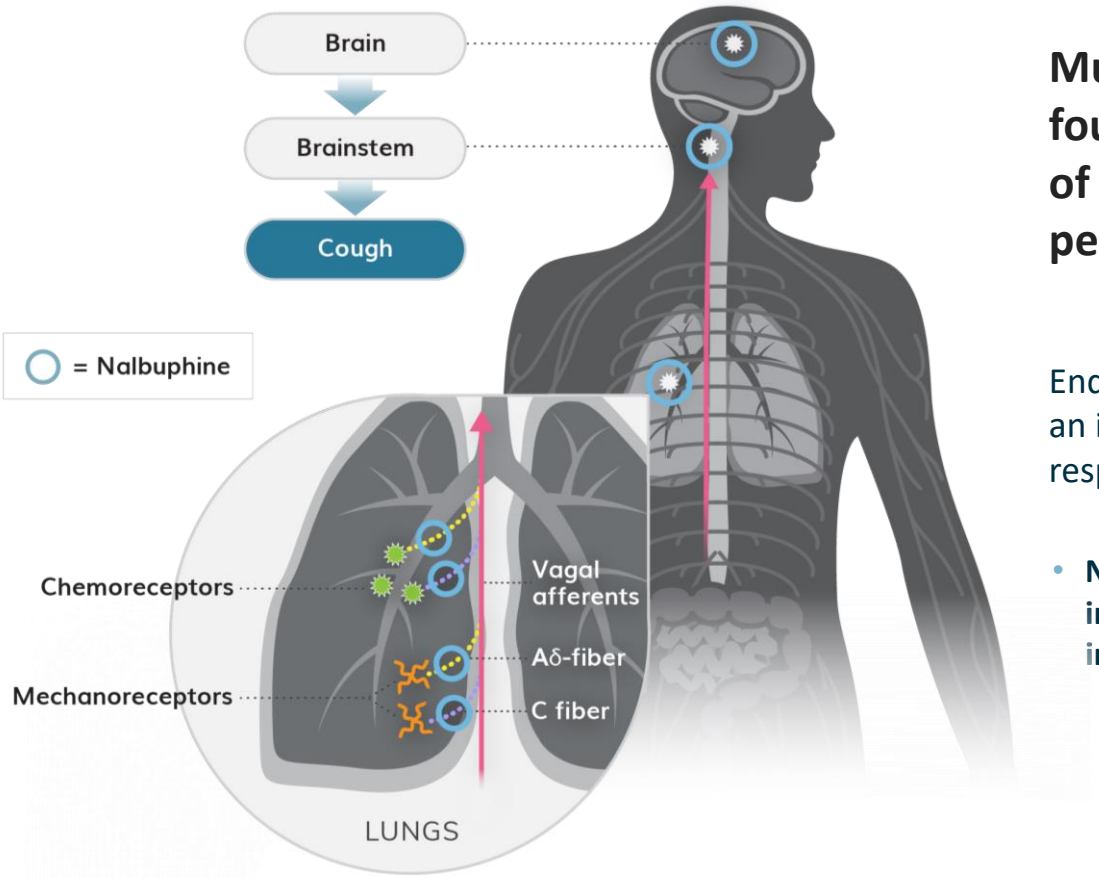
Ex-US	1,000,000+	Current Prevalence[6,7]
	40-50%	Uncontrolled[5]

- 70% to 85% of IPF patients are reported to suffer from chronic cough[1]
- Cough is one of the most bothersome symptoms of IPF[2]
  - ≥75% of IPF patients report cough as being one of their most significant symptoms[2]
- Current IPF therapies have not been shown to reverse disease progression nor labeled to reduce cough frequency/severity

**Market shares calculated as a percent of the uncontrolled population

[1]Ryerson CJ et al. Respirology 2011 [2]Voice of the Patient – IPF Patient-focused Drug Development Initiative, 2015 [3]Wang J et al. Ther Clin Risk Manag. 2020 [4]Martinez FJ Nat Rev Dis Primers 2017 [5]Trevi Data on file [6]Nalysnyk Eur Respir Rev 2012 [7]Meltzer EB ORJD 2008

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



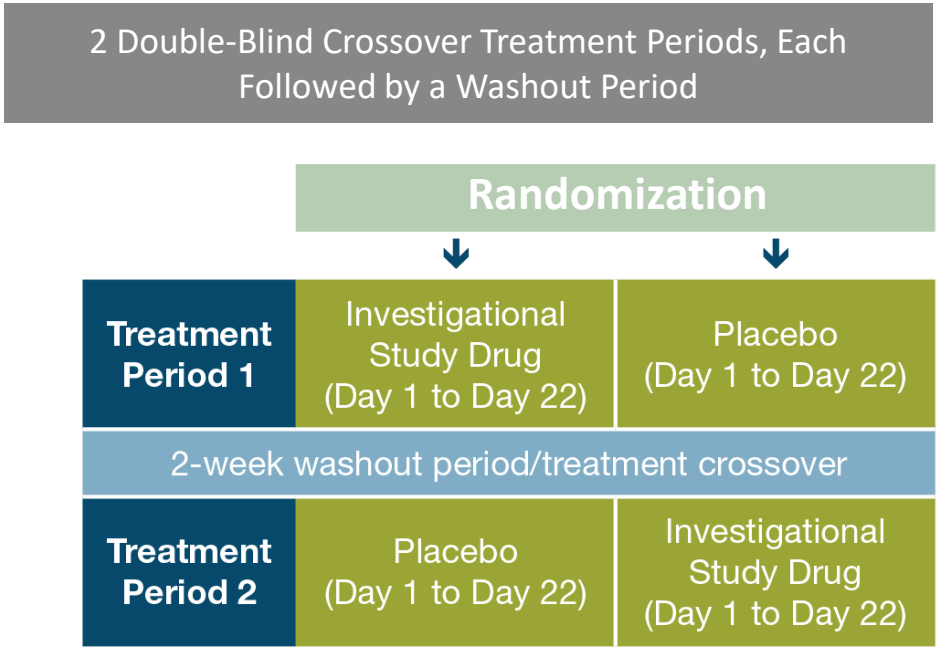
Mu, kappa and delta receptors found in the respiratory regions of the brain stem, lung and peripheral lung nerves

Endogenous opioids are believed to play an important role in modulating respiration (Lally, 2008)

- **Nalbuphine prevented sufentanil-induced cough during anesthesia induction** (Wang et al, 2020)

Vigeland CL et al, Respiratory Medicine 2017

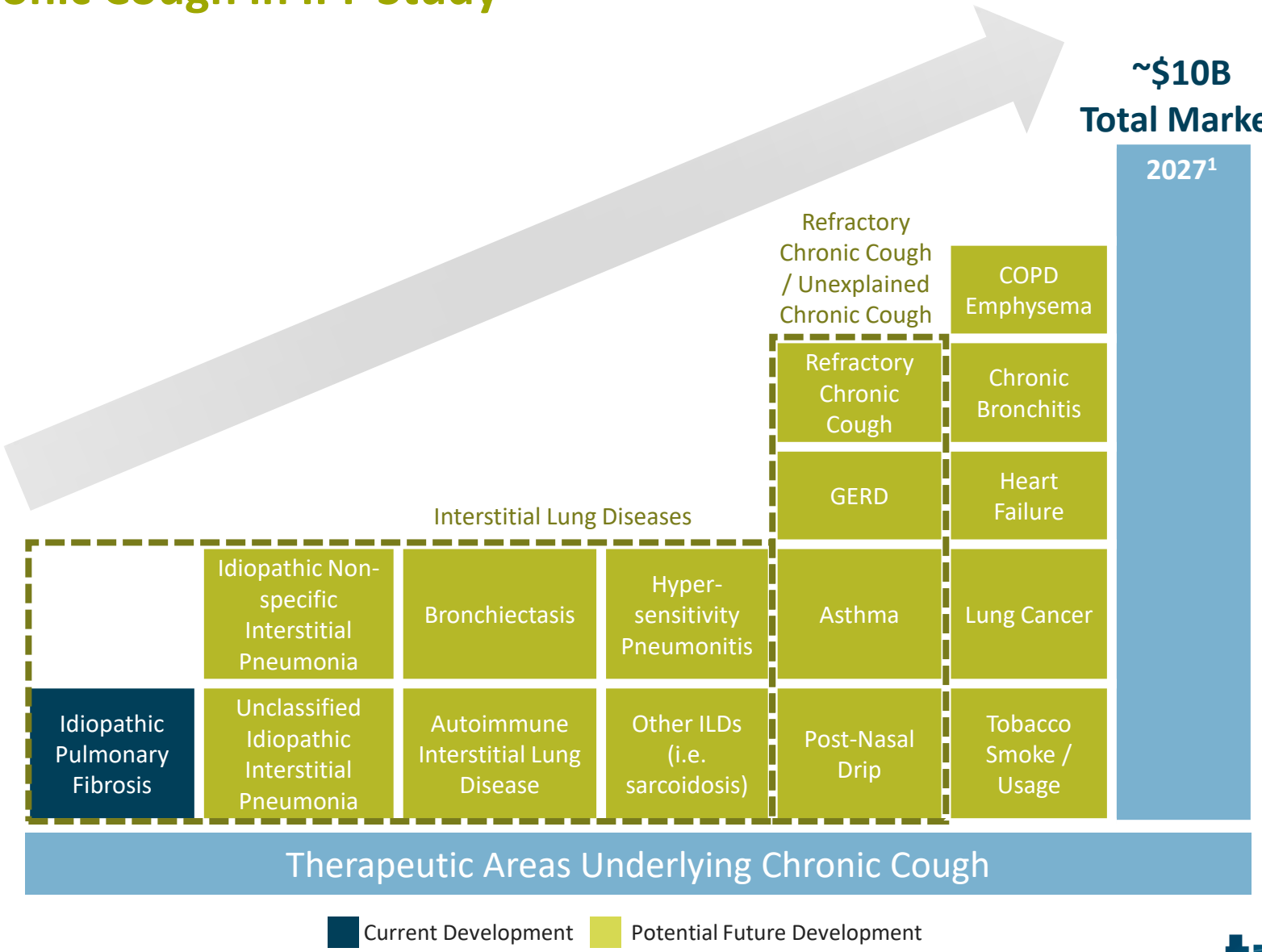
Chronic Cough in IPF Recruiting in the UK: Phase 2 Trial (N=44 Completers)



- **Amended study protocol (approved by MHRA) for fewer in-person visits and procedures to adapt to COVID restrictions**
- **Shelter in place restrictions lifted in the UK end of March**
- **Patient screening activity has resumed at multiple sites in the UK. Clinical team working to re-open all remaining sites**

- Enrollment of up to 60 patients with goal of 44 completers
- Primary endpoint is the 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 include cough, fatigue and dyspnea scales

Multiple Expansion Opportunities From Results in Chronic Cough in IPF Study



[1]The Insight Partners Jun 2020

Investment Highlights

Near-term Ph2b/3 Readout in Prurigo Nodularis

- FDA Fast Track designation granted for moderate to severe pruritus in PN
- Ph2b/3 enrollment expected to complete by 2H 2021 with top-line data four months after enrollment completion
- Only oral in development in a $3B+ category
- Ph2a data demonstrated potential for benefit/risk profile in severe pruritus

Ph2 Readout in Patients with Chronic Cough in Idiopathic Pulmonary Fibrosis

- Resumed screening subjects since COVID-19 shelter in place was lifted end of March in UK
- Opportunity to be first to market
- $4B market with significant unmet need

Strong Financial Position

- Cash balance as of 3/31/21 of $41.6 million
- Cash position will fund operations into the second quarter of 2022

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Thank You

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