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Gefapixant

U.S. Food & Drug Administration
Pulmonary-Allergy Drugs Advisory Committee
November 17, 2023

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Introduction

Lisa Bollinger, MD
Vice President, Regulatory Affairs
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Gefapixant Overview

Gefapixant is a $P2X_3$ antagonist developed *for the treatment of Refractory Chronic Cough (RCC) and Unexplained Chronic Cough (UCC) in adults*

Chronic Cough (CC) is defined as cough that persists >8 weeks

RCC	UCC
RCC is a chronic cough that persists despite optimal treatment of any underlying condition(s)	UCC is a cough for which no underlying etiology has been identified despite complete medical evaluation

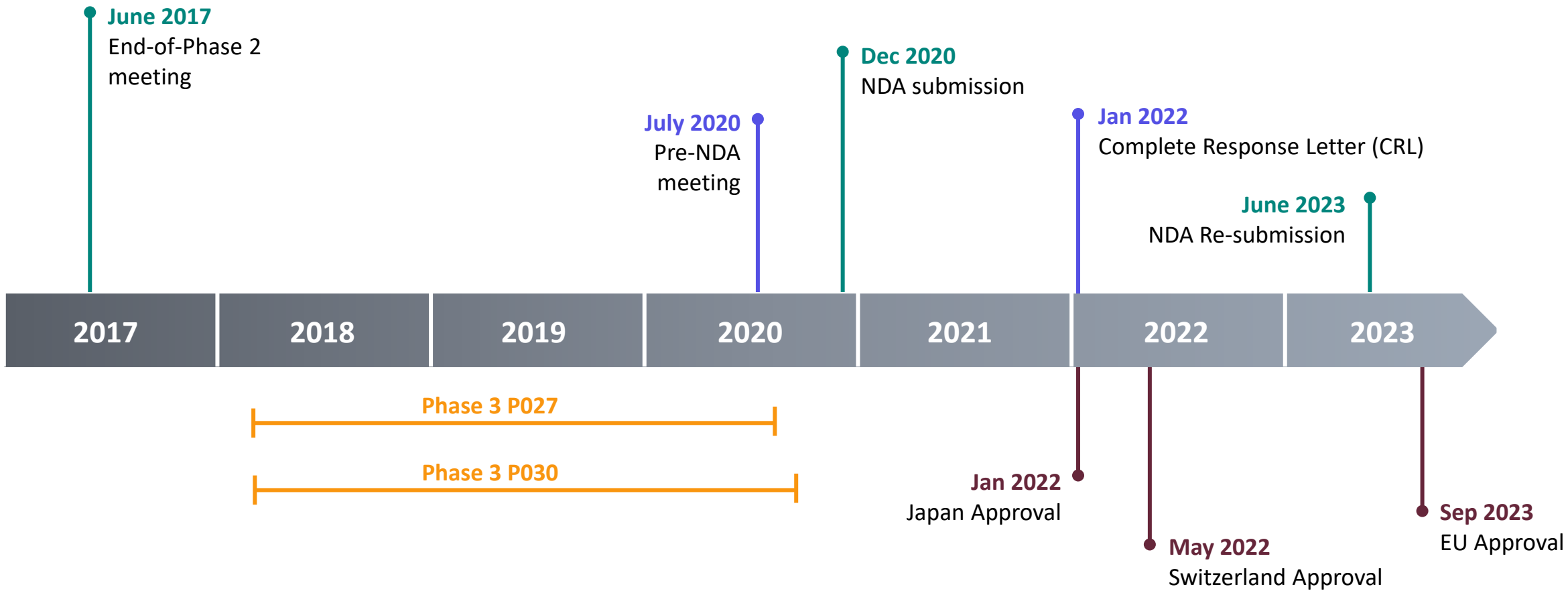
Gibson P, et al. *Chest*. 2016;149(1):27-44; Gibson PG. *J Allergy Clin Immunol Pract*. 2019;7(6):1724-1729; Lee KK, et al. *Chest*. 2021;159(1):282-293; Song WJ, et al. *Allergy Asthma Immunol Res*. 2017;9(5):394-402.

RCC/UCC: A **Serious Disease** with No Approved Treatments

- Chronic cough (CC) prevalence in US adults ~5%[a]
  - ~5-10% of CC patients have RCC/UCC[b]
  - Mostly women, aged 50 and above
- Patients with RCC/UCC suffer substantial disease burden
  - Physical
  - Social
  - Psychological
- No FDA-approved therapies

a) Meltzer EO, et al. *J Allergy Clin Immunol Pract*. 2021 Nov;9(11):4037-4044.e2; b) Gibson P, et al. *Chest*. 2016;149(1):27-44

Regulatory History for Gefapixant



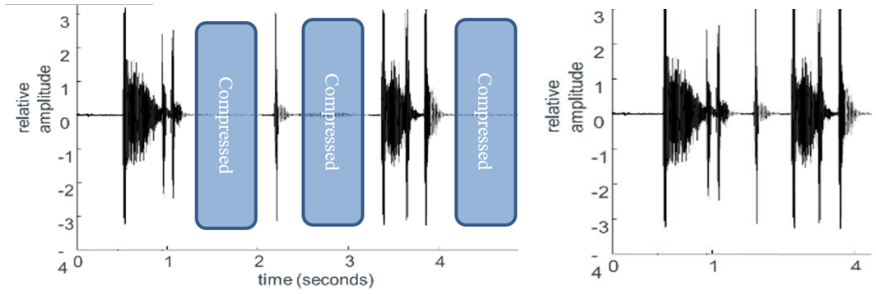
Methodology for Objective Cough Counting

1 RECORD

Digital 24-hr recording to capture cough sounds

2 COMPRESS

Algorithm removes silence and non-cough sounds



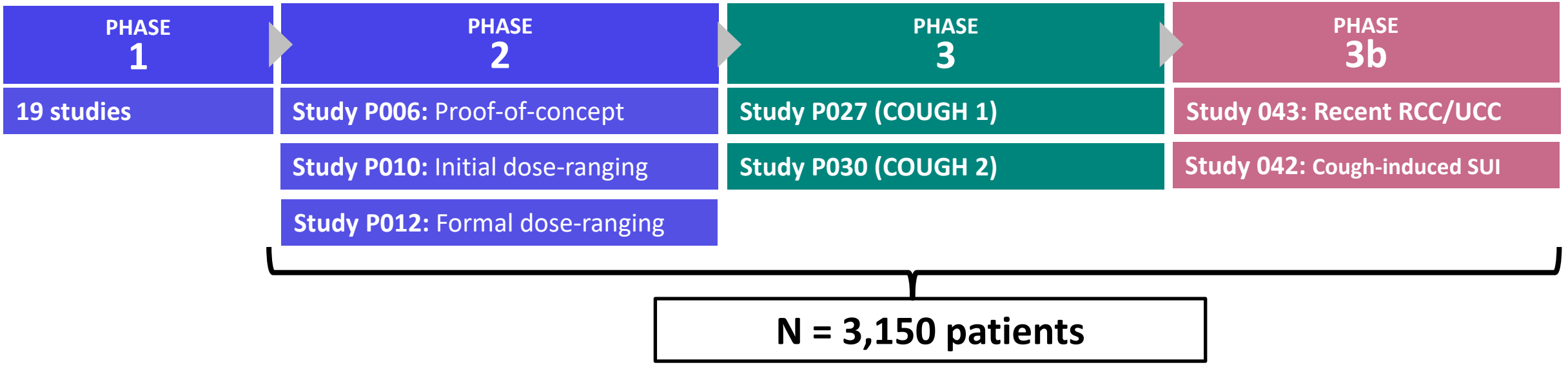
3 COUNT

Trained Raters review recordings and count coughs

Using both recordings

Development Program Has Demonstrated Efficacy and Safety of Gefapixant

- Proof of concept supported by nonclinical and Phase 1 and 2 studies
- Efficacy and Safety confirmed in two randomized, placebo-controlled, double-blind Phase 3 studies
- Clinical benefit also demonstrated in two Phase 3b studies



Agenda

Disease Background and Unmet Need	**Peter Dicpinigaitis, MD** Albert Einstein College of Medicine
Program Overview and Efficacy	**George Philip, MD** Merck Sharp & Dohme LLC
Patient Reported Outcomes	**Allison Martin Nguyen, MS** Merck Sharp & Dohme LLC
Clinical Safety	**English Willis, MD** Merck Sharp & Dohme LLC
Clinical Perspective	**Jaclyn Smith, MD, ChB, FRCP, PhD** The University of Manchester
Sponsor Closing	**Lisa Bollinger, MD** Merck Sharp & Dohme LLC

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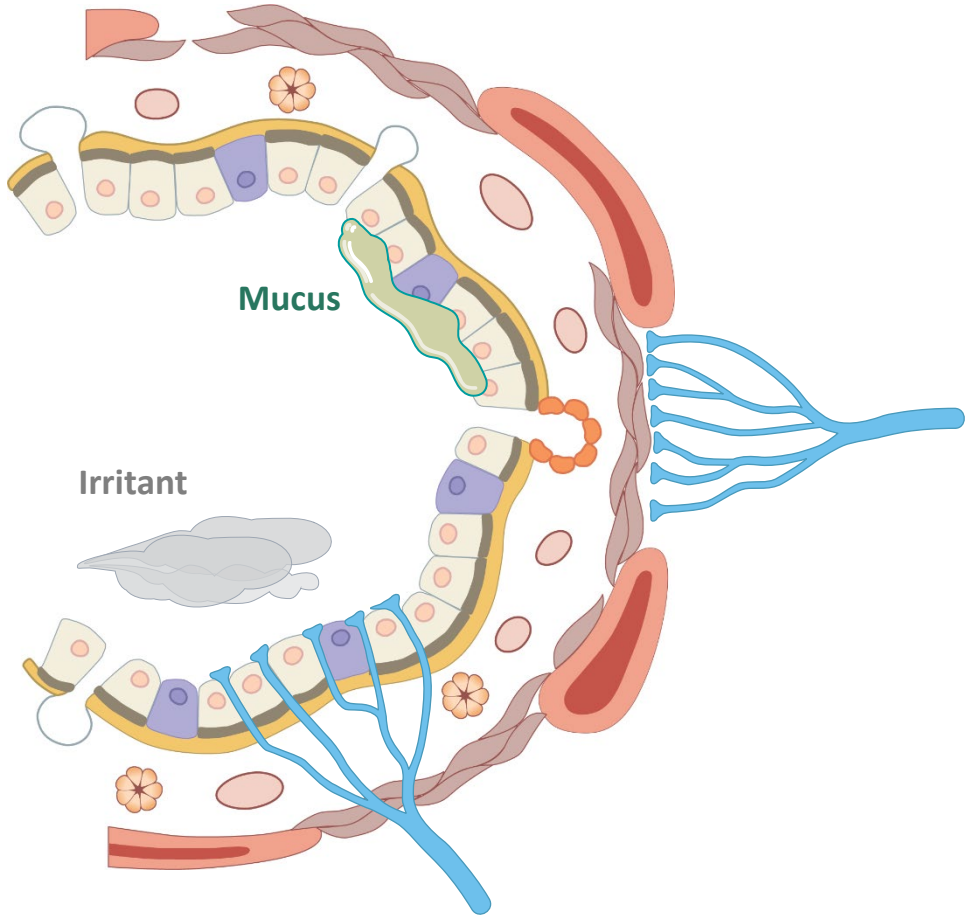
Disease Background and Unmet Need

Peter V. Dicpinigaitis, MD

Professor of Medicine, Albert Einstein College of Medicine
Director, Cough Center, Montefiore Medical Center, NY

Cough Is a Protective Reflex, But When Dysregulated, Can Become a Chronic Condition

- "**Protective** cough" in health
  - Clears mucus and foreign material
  - Initiated by various chemical irritants
- "Cough as a **symptom**": An important component of many acute and chronic conditions
- "Cough as its own **condition**": If the cough reflex itself becomes **dysregulated**, cough is triggered by low-level or innocuous stimuli[a-c]



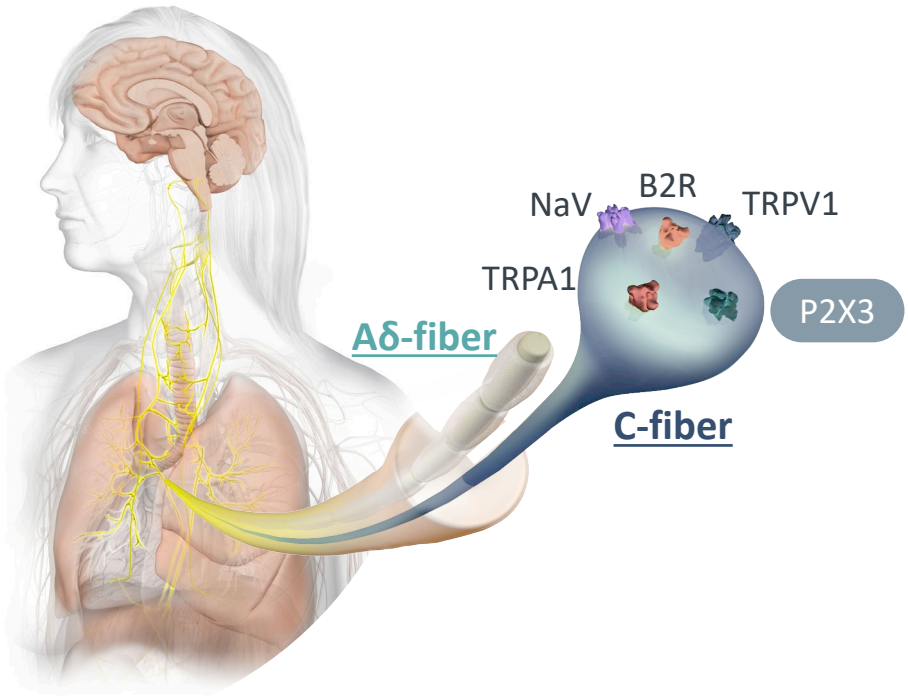
[a] Gibson PG. *J Allergy Clin Immunol Pract*. 2019;7(6):1724-1729; [b] Lee KK, et al. *Chest*. 2021;159(1):282-293; [c] Song WJ, et al. *Allergy Asthma Immunol Res*. 2017;9(5):394-402.

Two Sensory Pathways Within the Vagus Nerve in the Airways Have Distinct Functions[a]

Mechano-Sensitive Function

Aδ-fibers

- Initiate the protective cough reflex[a,b]
- Responsive to light touch, including mucus on the airway surface or inhaled foreign matter



Chemo-Sensitive Function

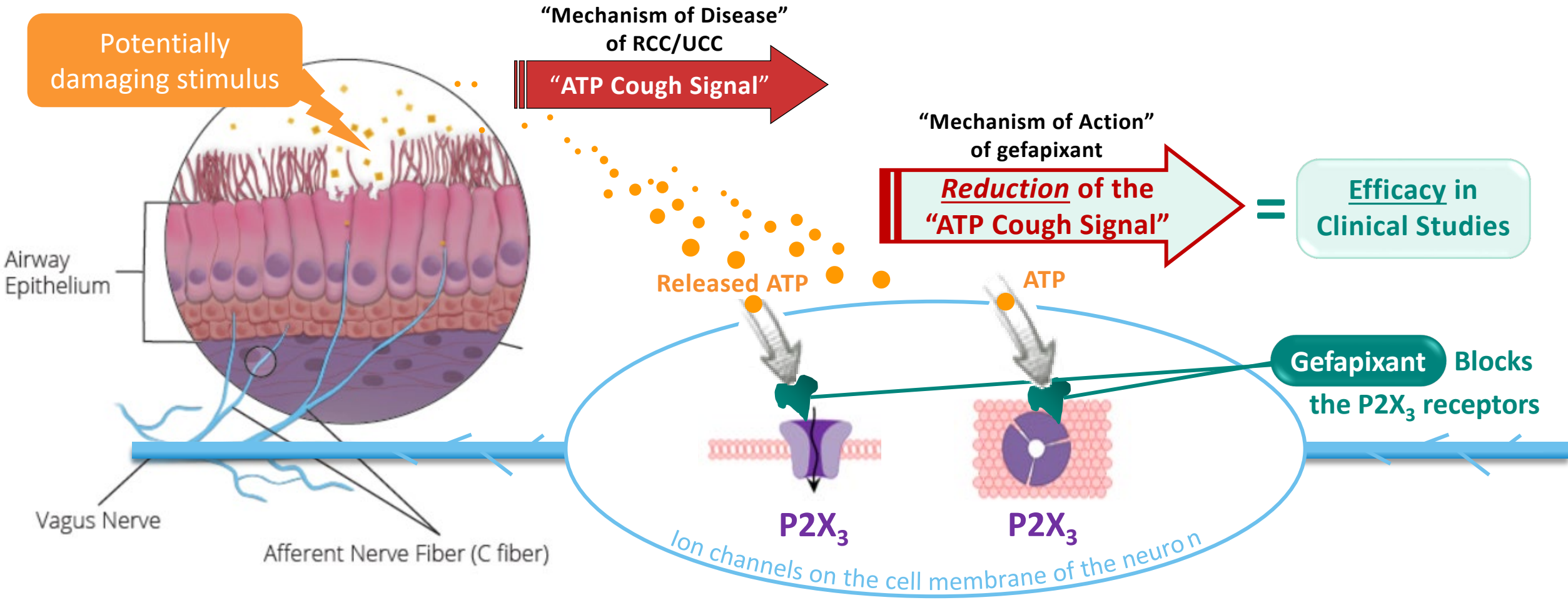
C-fibers

- Sense noxious stimuli
- Responsive to signaling molecules, inflammatory mediators, and other chemical stimuli (eg, capsaicin) via a variety of receptors[a]

Transient receptor potential (TRP) channels: TRPV1 and TRPA1, Purinergic receptors (P2X3), Bradykinin receptors (B2R), Voltage-gated sodium channels (NaV)

[a] Mazzone SB, Undem BJ. *Physiol Rev*. 2016;96(3):975-1024; [b] Sun H, et al. *Pulm Pharmacol Ther*. 2017;47:38-41.

Role of Extracellular ATP in Cough, and the Action of Gefapixant



RCC/UCC is Described by CHEST® Guidelines

Treatment of Unexplained Chronic Cough
CHEST Guideline and Expert Panel Report †

Peter Gibson, MBBS; Gang Wang, MD, PhD; Lorcan McGarvey, MD; Anne E. Vertigan, PhD, MBA, BAppSc (SpPath); Kenneth W. Altman, MD, PhD; and Surinder S. Birring, MB ChB, MD; on behalf of the CHEST Expert Cough Panel

Chronic Cough (>8 wk)

~5% of US Population[a,b] → **RCC/UCC**

5–10% of Chronic Cough[c]

BACKGROUND: Unexplained chronic cough (UCC) causes significant impairments in quality of life. Effective assessment and treatment approaches are needed for UCC.

† Gibson P, et al. *Chest*. 2016;149(1):27-44

[a] Meltzer EO, et al. *J Allergy Clin Immunol Pract* 2021;9:4037-44; [b] From 2018 National Health and Wellness Survey data (N=15,000). Prevalence was calculated as the proportion of respondents who reported having chronic cough (daily cough for at least 8 weeks) in the prior 12 months; [c] Gibson P, et al. *Chest*. 2016;149(1):27-44.

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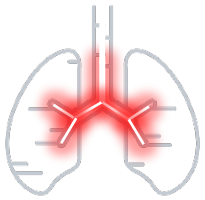
If

- Non-smoker, not on ACE inhibitor
- Physical exam: Non-contributory
- Chest x-ray: Normal/stable

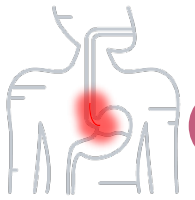
Then

Assess for common causes of Chronic Cough and treat



Asthma/NAEB

UACS



GERD

?

Refractory Chronic Cough (RCC)
Underlying condition(s) *identified* after investigation and *treated*, but cough persists

Unexplained Chronic Cough (UCC)
An underlying condition is ***not*** *identified* after investigation, but cough persists

† Gibson P, et al. Chest. 2016;149(1):27-44

NAEB, non-asthmatic eosinophilic bronchitis; UACS, upper airway cough syndrome; CC, Chronic Cough

RCC/UCC is Described by ERS Guidelines

ERS guidelines on the diagnosis and treatment of chronic cough in adults and children†

Alyn H Morice, Eva Millqvist, Kristina Bieksiene, Surinder S Birring, Peter Dicpinigaitis, Christian Domingo Ribas, Michele Hilton Boon, Ahmad Kantar, Kefang Lai, Lorcan McGarvey, David Rigau, Imran Satia, Jacky Smith, Woo-Jung Song, Thomy Tonia, Jan WK van den Berg, Mirjam J. G. van Manen, Angela Zacharasiewicz

In Adults

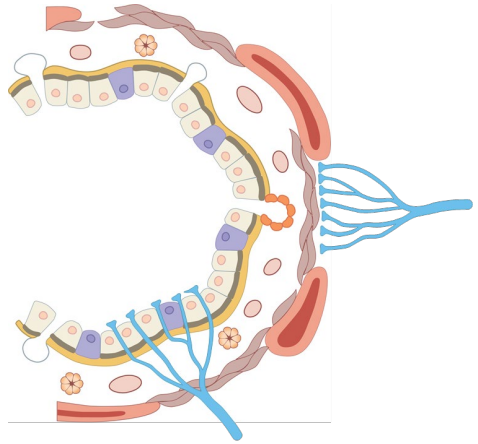
Here the term ***Chronic Refractory Cough*** is used to indicate that the cough is refractory to conventional treatment of cough-associated conditions or traits

Patients with chronic cough have persistent cough despite thorough investigation and treatment. Terms such as idiopathic chronic cough, ***Unexplained Chronic Cough*** and chronic refractory cough have been utilized to describe this condition

† Morice AH, et al. *Eur Respir J*. 2020;55(1):1901136.

Patients with RCC/UCC Have a Common *Clinical* Presentation[a-d]

- **Dry or minimally productive cough** persisting beyond 8 weeks (often months or years)
- **Bouts of cough** – "Cough hypersensitivity" observed on various exposures
  - Heightened sensitivity to exposures that can trigger cough (eg, strong chemical fumes or second-hand smoke)
  - Sensitivity to exposures that normally do not cause cough (eg, laughing or singing)



- **Cough with recurring sensations** (eg, "tickle in the throat," urge to cough)

This clinical phenotype may be explained by a dysregulation of the cough reflex

[a] Saita I, et al. *Clin Med (Lond)*. 2016;16(suppl 6):s92-s97; [b] Hilton E, et al. *Respir Med*. 2015;109(6):701-707; [c] McGarvey L, et al. *Pulm Pharmacol Ther*. 2009;22(2):59-64; [d] Gibson P, et al. *Chest*. 2016;149(1):27-44.

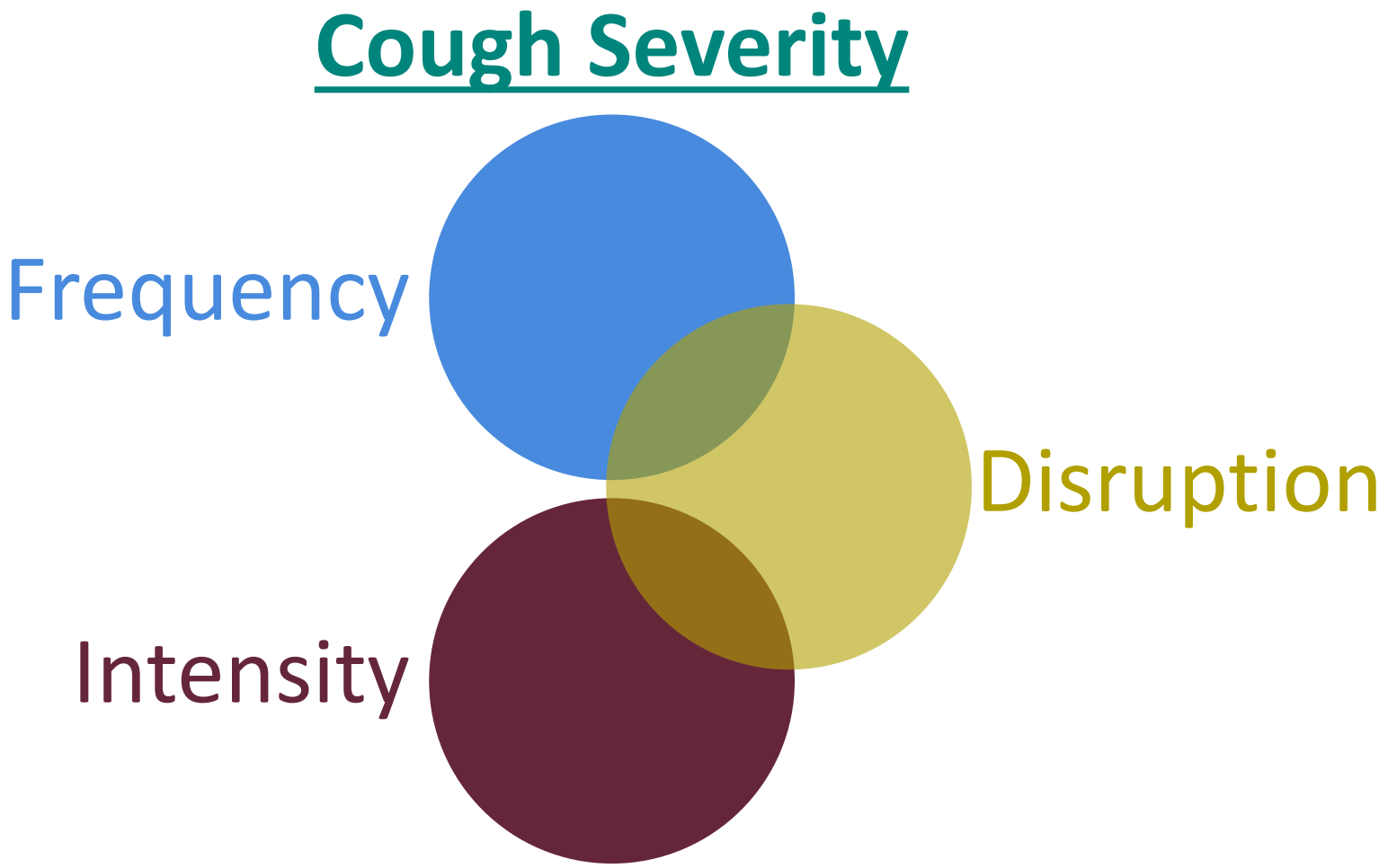
Cough Frequency Associated with Various Respiratory Conditions

Patient population	~ Coughs/day
Healthy[a-c]	8-30
Bronchitis[a]	106
Asthma[a]	107
COPD[a-c]	118-216
RCC/UCC (Phase 3 population)[d] [Q1-Q3 range]	**499** [265-874]*

* Based on pooled cough count data at baseline, the median is 499 coughs/day and Q1-Q3 is 265-874.

[a] Yousaf N, et al. *ERJ.* 2013;41:241-243; [b] Lee KK, et al. *Chest.* 2021;159(1):282-293; [c] Sumner H, et al. *Am J Respir Crit Care Med*. 2013;187(9):943-949; [d] McGarvey LP, et al. *Lancet*. 2022;399(10328):909-923.

RCC and UCC Contribute to Significant Patient Burden that Informed the Design of the Gefapixant Clinical Program



Patient Journey of RCC/UCC: Video Interviews of Patients *European Lung Foundation (Patient Advocacy Organization)*

"Started gentler then became more intensive; I did allergy tests with several doctors"

"I have been to my family doctor, to an ENT, a pulmonologist and got Chest x-ray, a GI for gastroscopy?"

"I went to the family doctor, who say we must cancel your medicine and take another. But no impact to the cough. Now I am with a lung doctor"

"because really, nobody seems to come up with any answers"

https://europeanlung.org/en/people-and-partners/your-experiences/my-experience-of-chronic-cough/

Burden of Chronic Cough in Patients Seeking Medical Attention

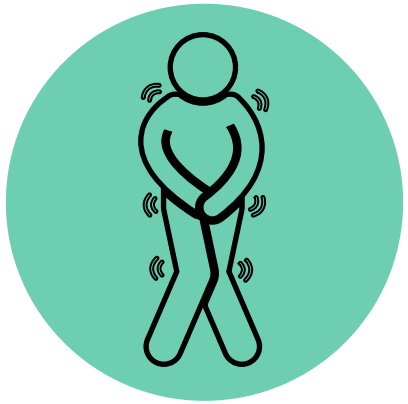
Work Life

Religious Services

Social Stigma

Personal Life

Incontinence



The Leicester Cough Questionnaire (LCQ) Measures Impact of Cough on Patients' Lives

Physical

8 items

item	
1	Chest or stomach pains
2	Bothersome phlegm/sputum production
3	Being tired
9	Exposure to paint or fumes
10	Sleep disturbance
11	Coughing fits/bouts
14	Suffering from hoarse voice
15	A lot of energy

Social

4 items

item	
7	Job/daily task interference
8	Life enjoyment interference
18	Interrupted conversations or phone calls
19	Annoyed partner, family or friends

Psychological

7 items

item	
4	Feeling in control of cough
5	Embarrassment
6	Anxiety
12	Frustration
13	Feeling fed up
16	Fear of serious illness
17	Concern others think something wrong with you

Birring et al. *Thorax* 2003;58:339-343

Cough-induced Stress Urinary Incontinence (C-SUI)

- A socially debilitating complication of chronic cough[a-c]
- Reported in 63% of women presenting for evaluation of chronic cough[d]
- Repeated episodes of incontinence daily[a-c]
- Incontinence episodes may be reduced with successful treatment of RCC/UCC[e]

[a]Wood LN, et al. *BMJ*. 2014;349:g4531; [b]Shariat SF, et al. *Urol Int*. 2009;83(2):181-6; [c]Hrisanfow E, et al. *J Clin Nurs*. 2013;22(1-2):97-105; [d]Dicpinigaitis PV. *ERJ Open Res*. 2021;7(1):00012-2021; [e]Irwin RS. *Chest*. 2006;129(1 Suppl):54S-58S

Treatment Goals

- 100% cough reduction is not the goal
- Even a partial reduction in cough *frequency* or *intensity* can be meaningful to a patient's QoL
  - Reducing *frequency* can make the patient comfortable enough to go out in public
  - Reducing *duration and intensity* of coughing bouts could disproportionately reduce or eliminate SUI

Limitations of Drugs Being Used for RCC/UCC

- No therapies are approved for RCC/UCC in the US

- Empiric use of centrally acting agents has notable safety/tolerability issues:
  - Opioids → **sedation, constipation, abuse potential**
  - Neuromodulators (eg, amitriptyline, gabapentin) → **sedation, other**

Unmet Need

- RCC/UCC (per CHEST and ERS) is an important clinical entity
  - Dysregulated cough reflex caused by otherwise innocuous triggers
- Patients with RCC/UCC carry a heavy burden
  - Impact on quality of life for patients and their relationships
- No treatment approved for RCC/UCC

Patients need safe and effective treatments for RCC/UCC

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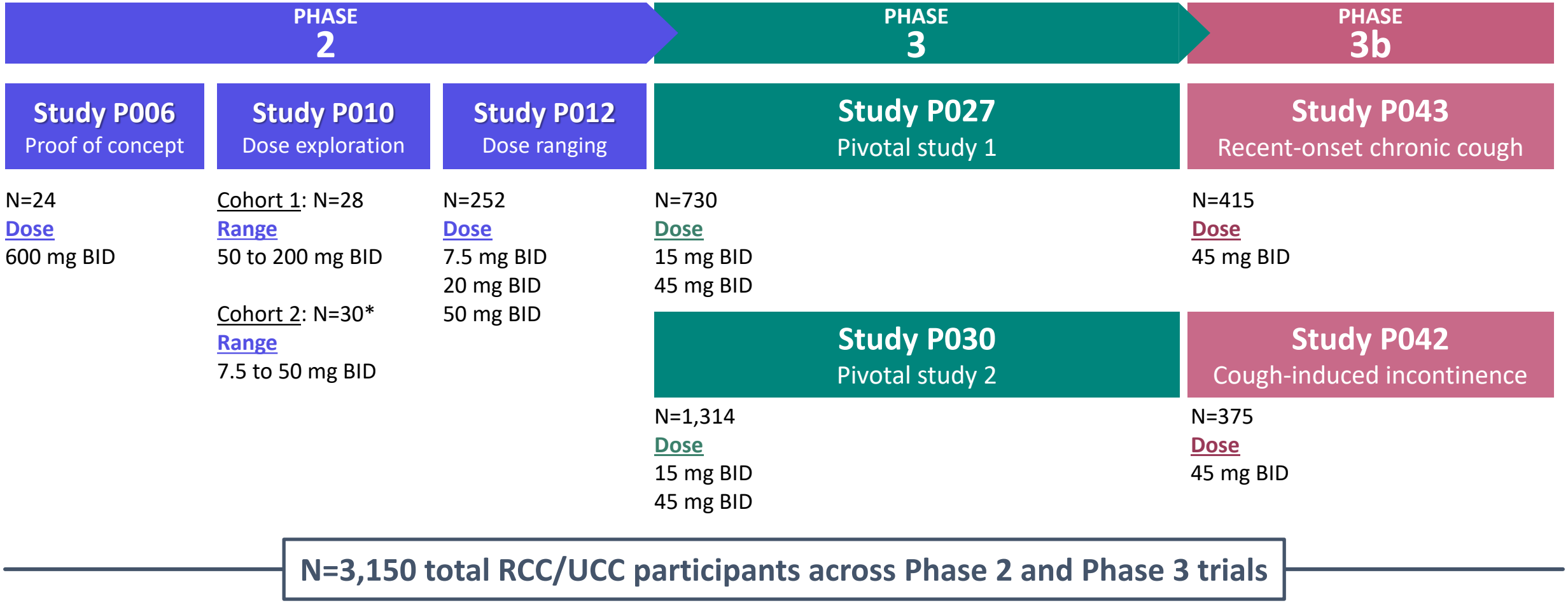
Program Overview and Efficacy Data

George Philip, MD
Executive Director, Medical Affairs
Merck Sharp & Dohme LLC

Gefapixant Development Program in RCC/UCC: Overview



*18 participants from Cohort 1 participated in Cohort 2

Gefapixant Phase 3: Key Entry Criteria
P027 and P030

Chronic Cough (>8 weeks)

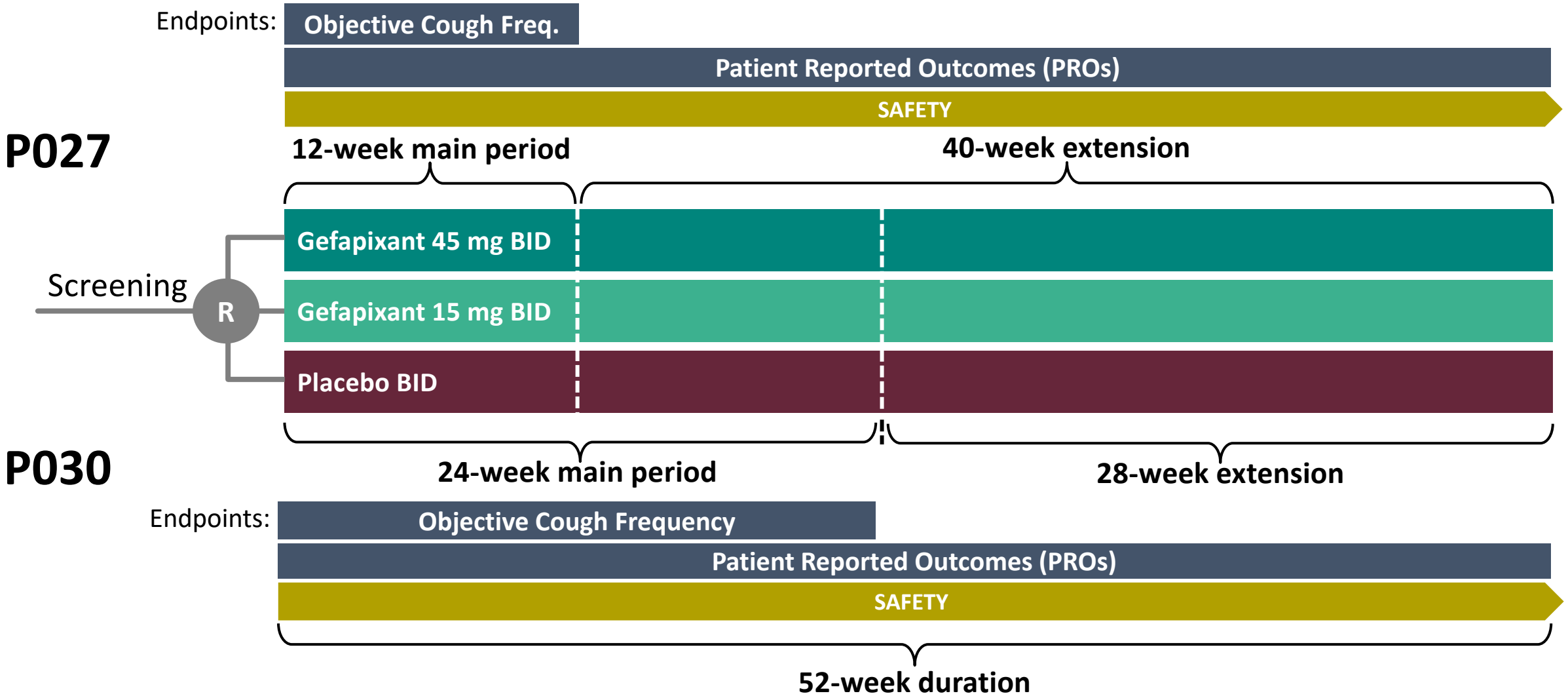
- Diagnosis per CHEST guidelines
  - Refractory Chronic Cough (RCC)
    - Conditions associated with chronic cough (eg, Asthma, UACS, GERD), which persist despite ≥2mo of stable therapy
  - Unexplained Chronic Cough (UCC)
    - No such co-morbid conditions identified, despite full evaluation
- Duration **≥1 yr**
- Cough severity visual analog scale (**VAS**) **score ≥40 mm**[a]

- Age ≥18 yr
- No smoking (for ≥1 yr, and ≤20 pack-yr)
- No recent ACE-I treatment
- No substantial abnormalities on chest x-ray (or chest CT) after onset of the cough, and within 5 yr of study start
- Spirometry: FEV_1/FVC ≥60%

[a] Rhatigan et al. J Allergy Clin Immunol Pract. 2023;9:S2213-2198(23)01007-3

Gefapixant Phase 3: Trial Designs

P027 and P030



Gefapixant Phase 3: Sequential Testing of Endpoints

P027 and P030

P027 (at 12 weeks) N=730 treated	**P030** (at 24 weeks) N=1,314 treated
Primary efficacy endpoint 1. **24-hour** cough frequency	**Primary efficacy endpoint** 1. **24-hour** cough frequency
Key Secondary efficacy endpoints 2. **Awake** cough frequency	**Key Secondary efficacy endpoints** 2. **Awake** cough frequency
	3. Proportion of participants with **≥1.3-point increase** from baseline in **Leicester Cough Questionnaire** (**LCQ**) total score[a]
3. Proportion of participants with **≥30% reduction** from baseline in **24-hour** cough frequency[b]	4. Proportion of participants with **≥30% reduction** from baseline in **24-hour** cough frequency[b]

[a]Raj et al. *Pharmacology and Therapeutics of Cough* 2009; 311-320; [b]Schelfhout et al. *Lung* 2022;200:717-724

Subject Disposition: 52-week Pooled Data

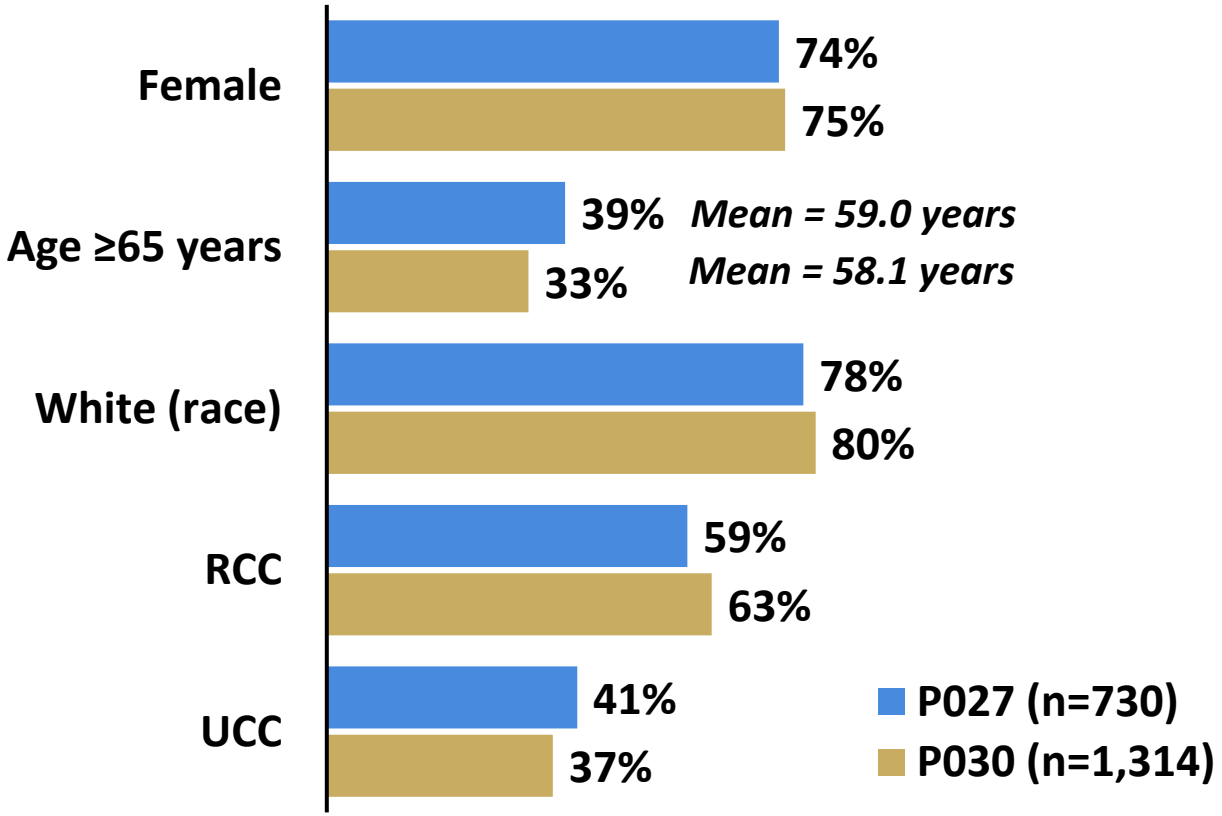
P027 and P030 Pooled

Treatment and Study Status	Participants, n (%)		
	Placebo N=680	Gefapixant 15 mg BID N=686	Gefapixant 45 mg BID N=683
Participants treated	**678**	**684**	**682**
Completed	**533 (78.6)**	**514 (75.1)**	**430 (63.0)**
Discontinued from treatment	145 (21.4)	170 (24.9)	252 (37.0)
Adverse event (AE)	**38 (5.6)**	**54 (7.9)**	**152 (22.3)**
Withdrawal by subject	**88 (13.0)**	**103 (15.1)**	**85 (12.5)**
Lost to follow-up	7 (1.0)	3 (0.4)	5 (0.7)
Non-compliance with study drug	3 (0.4)	2 (0.3)	4 (0.6)
Physician decision	4 (0.6)	2 (0.3)	5 (0.7)
Pregnancy	0	1 (0.1)	1 (0.1)
Death	2 (0.3)	2 (0.3)	0
Other	3 (0.4)	3 (0.4)	0
Discontinued from study	99 (14.6)	118 (17.2)	144 (21.1)

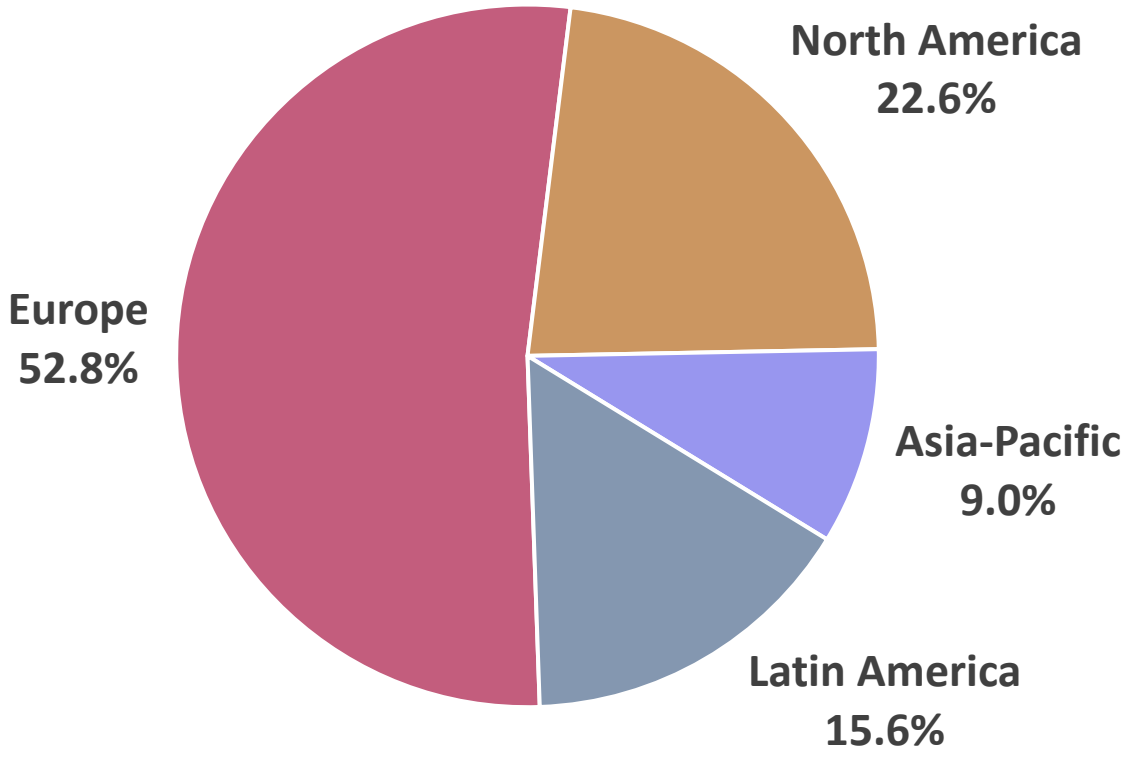
Baseline Characteristics are Consistent with Published Literature[a]

P027 and P030

Overall Baseline Characteristics



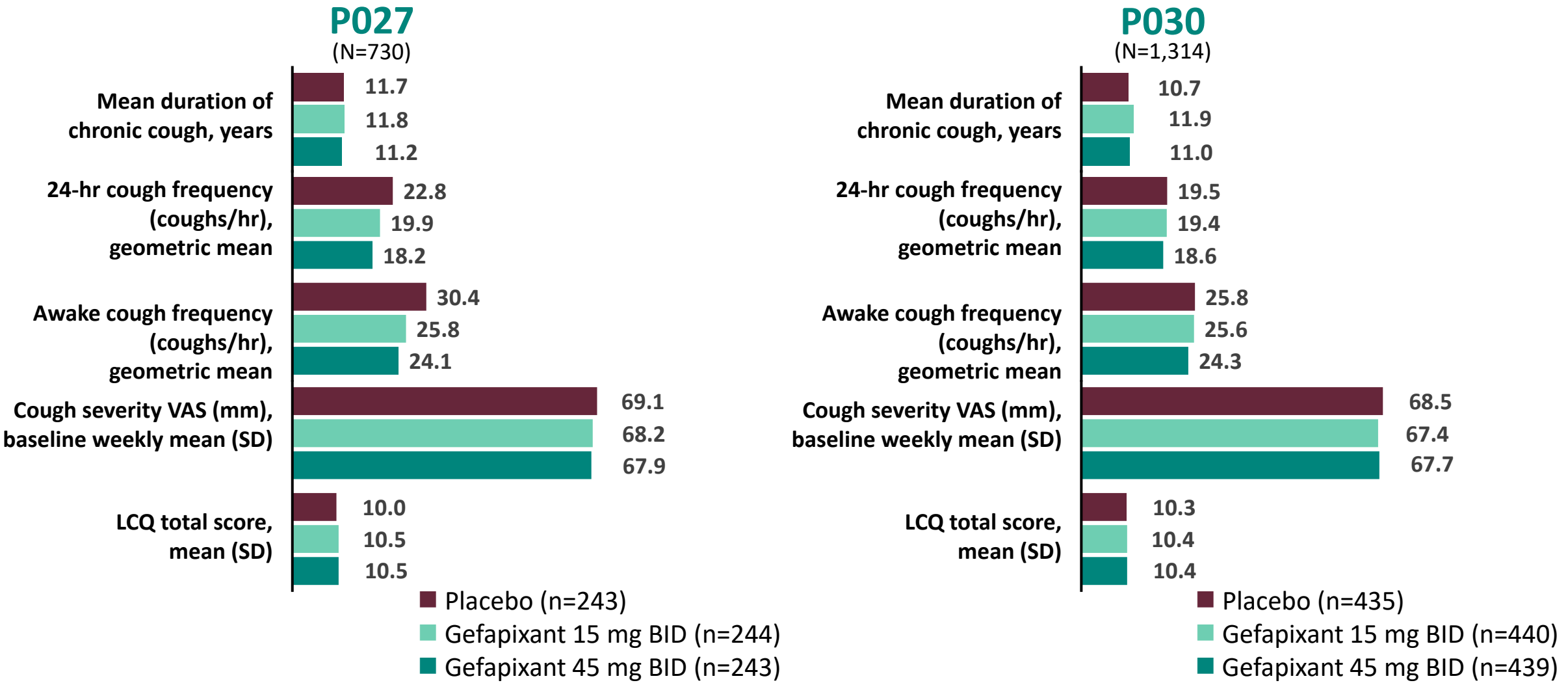
Regional Distribution (Pooled)



[a] Morice AH, et. al. *Eur Respir J.* 2014;44(5):1149-55.

Cough-Related Baseline Characteristics

P027 and P030

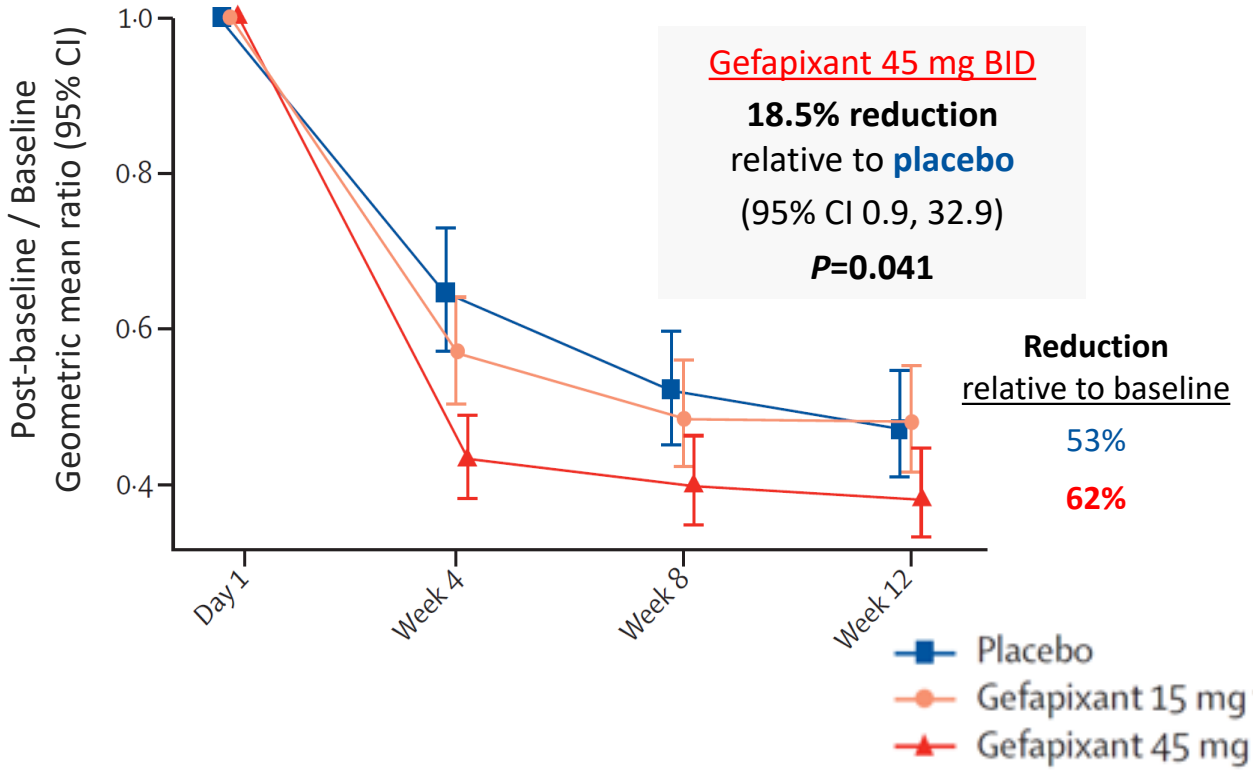


Gefapixant Reduces 24-hour Cough Frequency

P027 and P030 Primary Endpoint (Original Dataset: Prespecified Analyses)

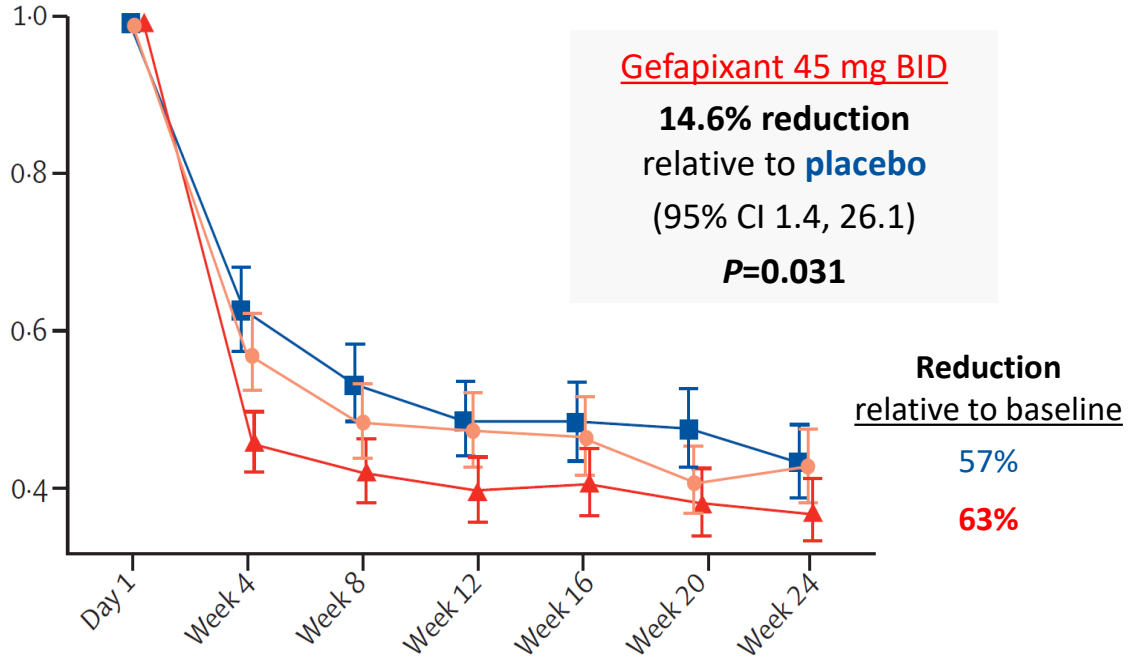
P027 ("COUGH-1")

Through Week 12



P030 ("COUGH-2")

Through Week 24



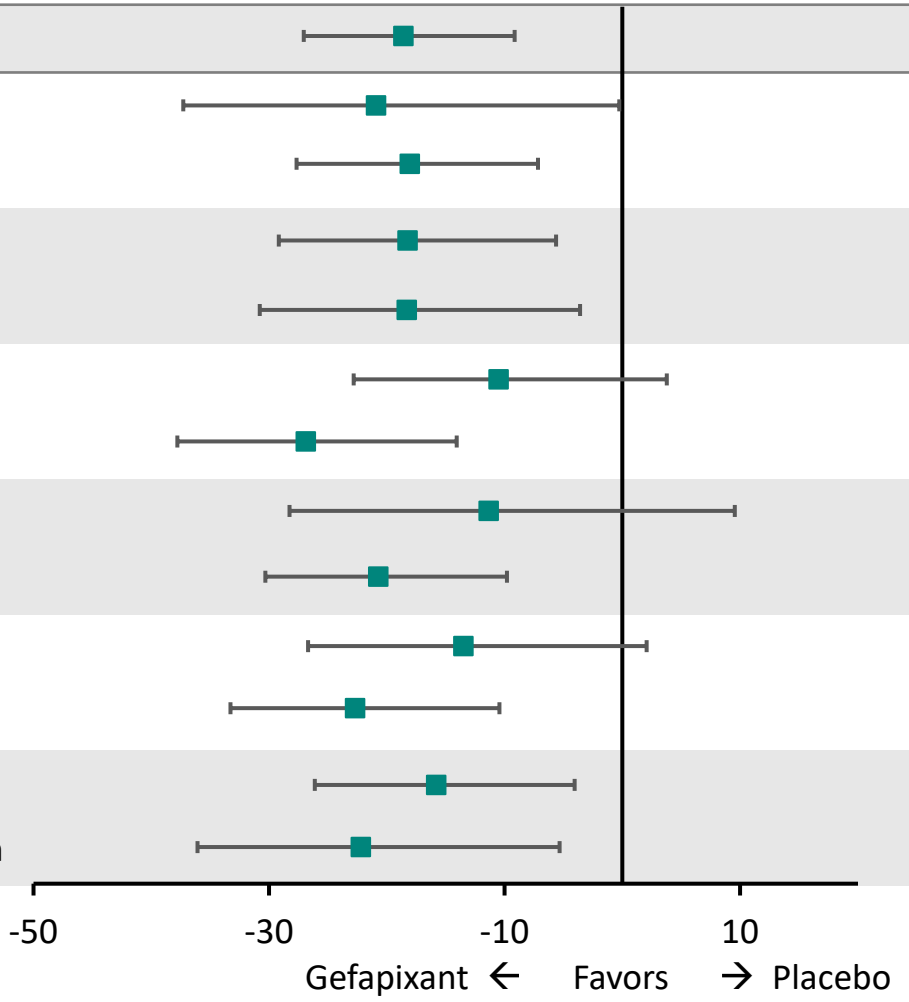
Placebo
Gefapixant 15 mg twice per day
Gefapixant 45 mg twice per day

McGarvey LP, et al. *Lancet*. 2022;399(10328):909-923.

Gefapixant Demonstrated Consistent Efficacy Across Subgroups

P027 and P030 Pooled 24-hour Cough Frequency

		Participants, n	
		Placebo	Gefapixant
ALL PATIENTS		641	626
Gender	Male	161	156
	Female	480	470
Age	<65 yr	415	405
	≥65 yr	226	221
Duration of cough	<10 yr	348	360
	≥10 yr	293	266
Baseline mean weekly Cough severity VAS category	<60 mm	191	178
	≥60 mm	448	446
Baseline 24-hour cough frequency	<20 coughs / hr	295	317
	≥20 coughs / hr	346	309
Primary diagnosis	Refractory Chronic Cough	404	390
	Unexplained Chronic Cough	237	236



Prespecified subgroups.
Estimated Relative Reduction over Placebo (%)

McGarvey LP, et al. *Lancet*. 2022 Mar 5;399(10328):909-923.

Analyses of Cough Frequency Data in Studies P027 and P030

Before the CRL

Original Dataset

Compression methodology was refined during Phase 3 trials

Pre-Specified Analysis

L-ANCOVA[†] – Excludes patients without baseline or post-baseline data

After the CRL

Recount Dataset

A single compression method was applied to all compressed recordings

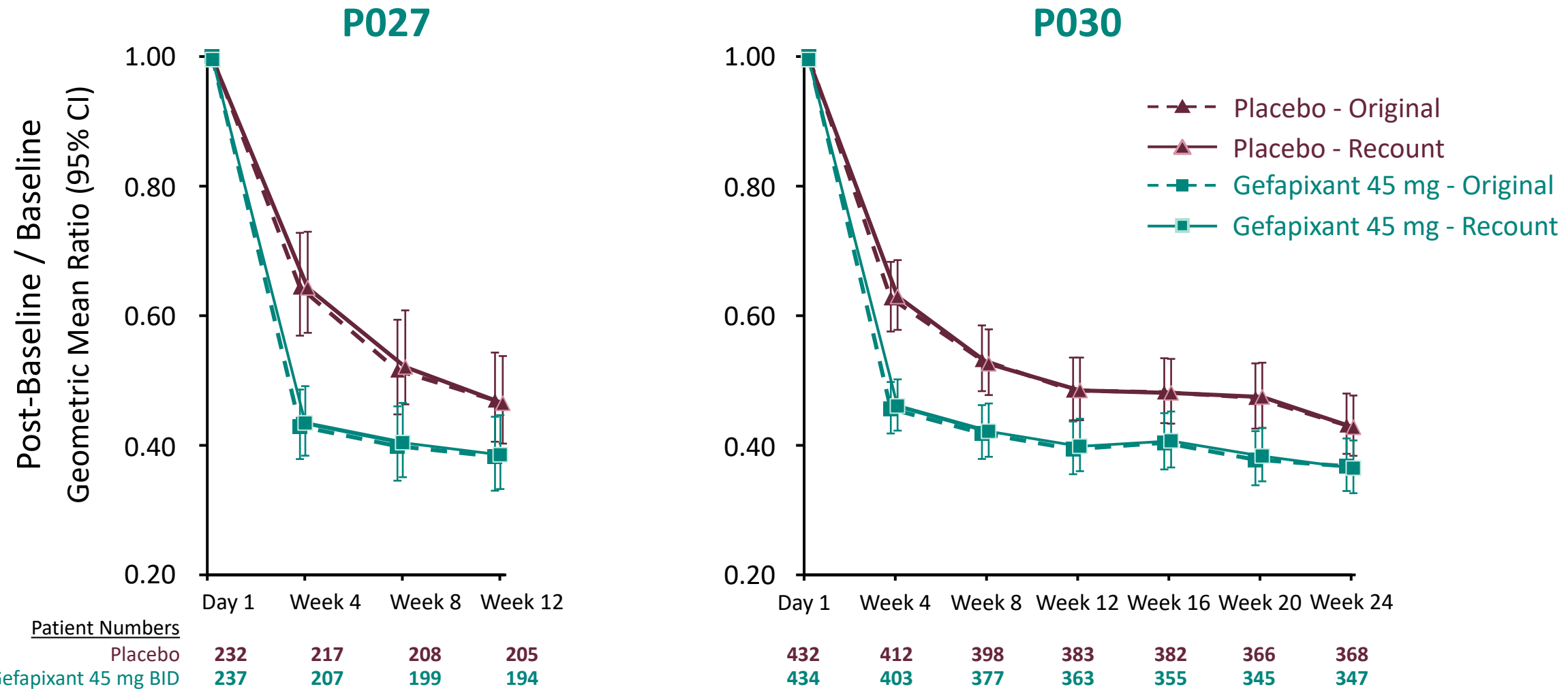
Supportive Analyses

1) **L-ANCOVA**[†] – Excludes patients without baseline or post-baseline data
2) **MI+ANCOVA** – Imputes data for patients with missing values

[†] 'Longitudinal ANCOVA' also referred to as 'MMRM'

24-hour Cough Frequency: Original Dataset versus Recount Dataset

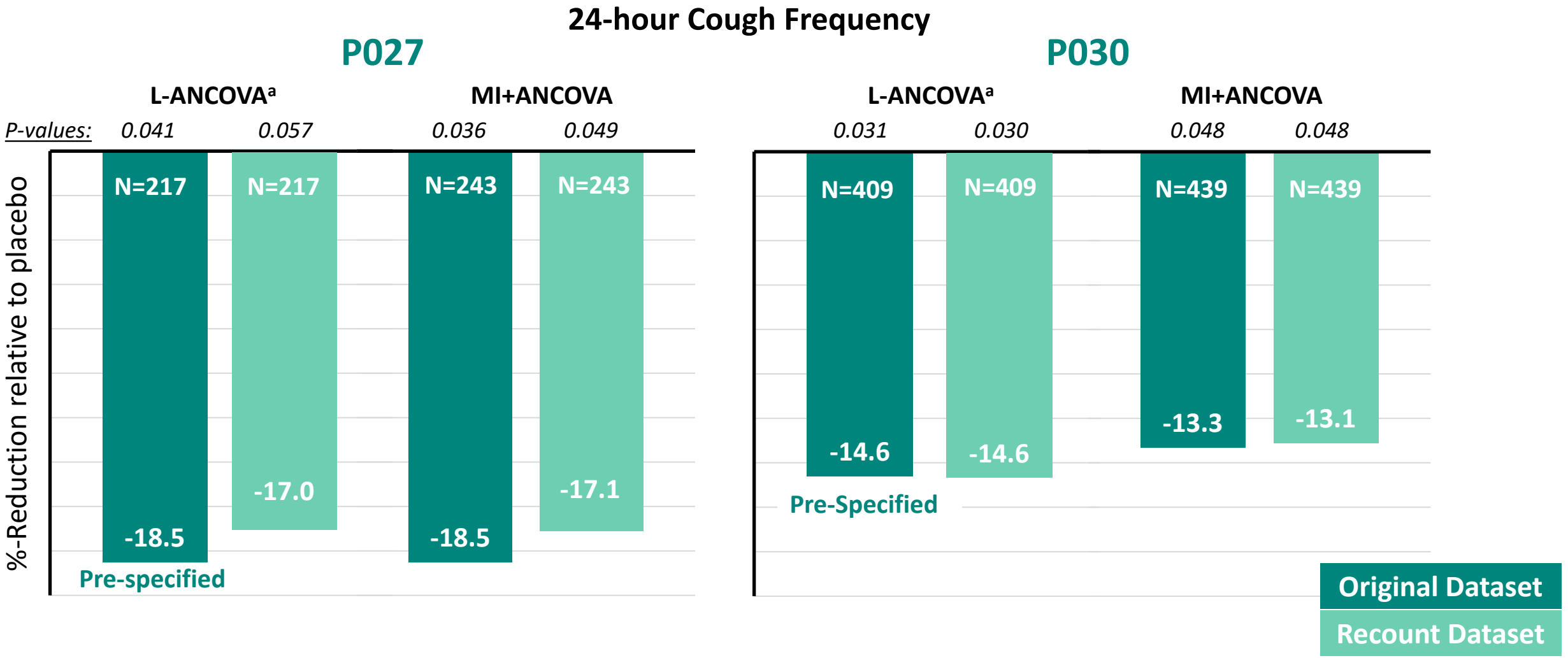
L-ANCOVA[a]



[a] 'Longitudinal ANCOVA' also referred to as 'MMRM'

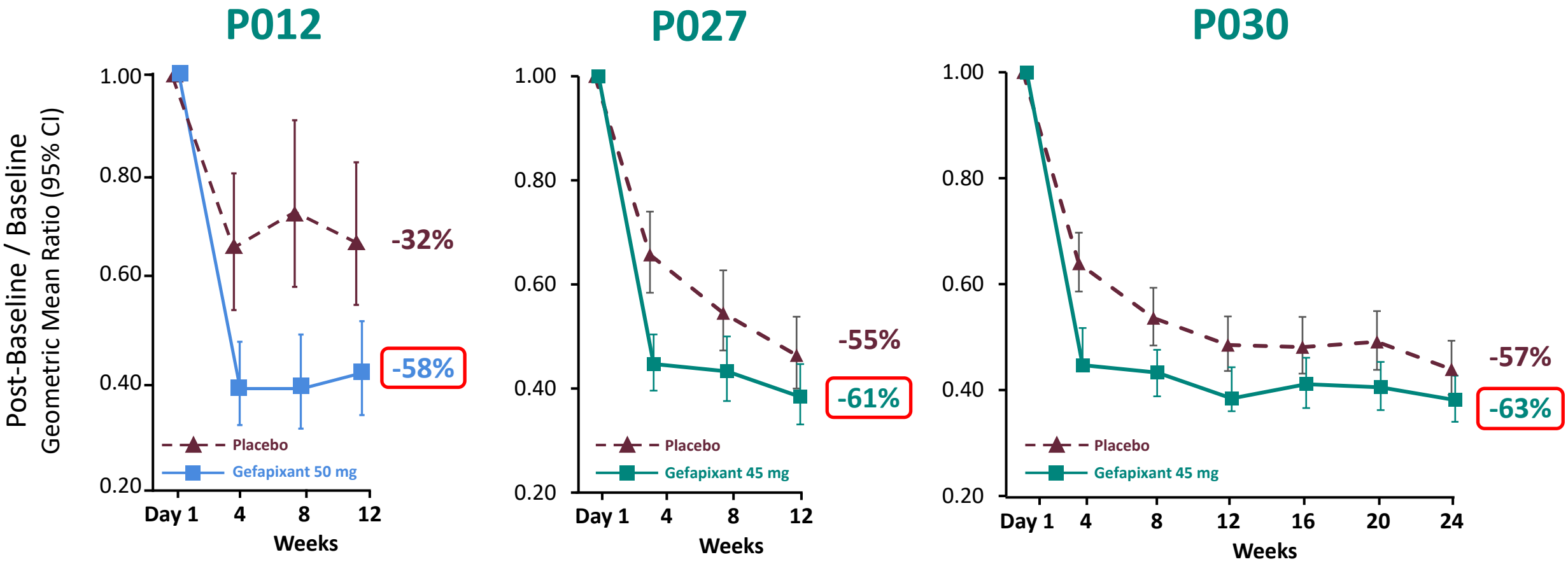
Consistent Reduction in Cough Frequency Across Datasets and Analyses

P027 and P030 Primary Endpoint



[a] 'Longitudinal ANCOVA' also referred to as 'MMRM"

Gefapixant Demonstrated Consistent Reduction in 24-hr Cough Frequency Across Phase 2b and Phase 3 (Recount) Studies



Data Do Not Support that Efficacy is Driven by Taste-related AEs

- In Phase 2 (P010): Taste-related AEs continued to increase (up to 200mg) while efficacy plateaued beyond 50mg
- In Phase 3: In the placebo group (with no pharmacologic effects), patients with taste-related AEs did *not* experience more cough reduction than patients without taste-related AEs

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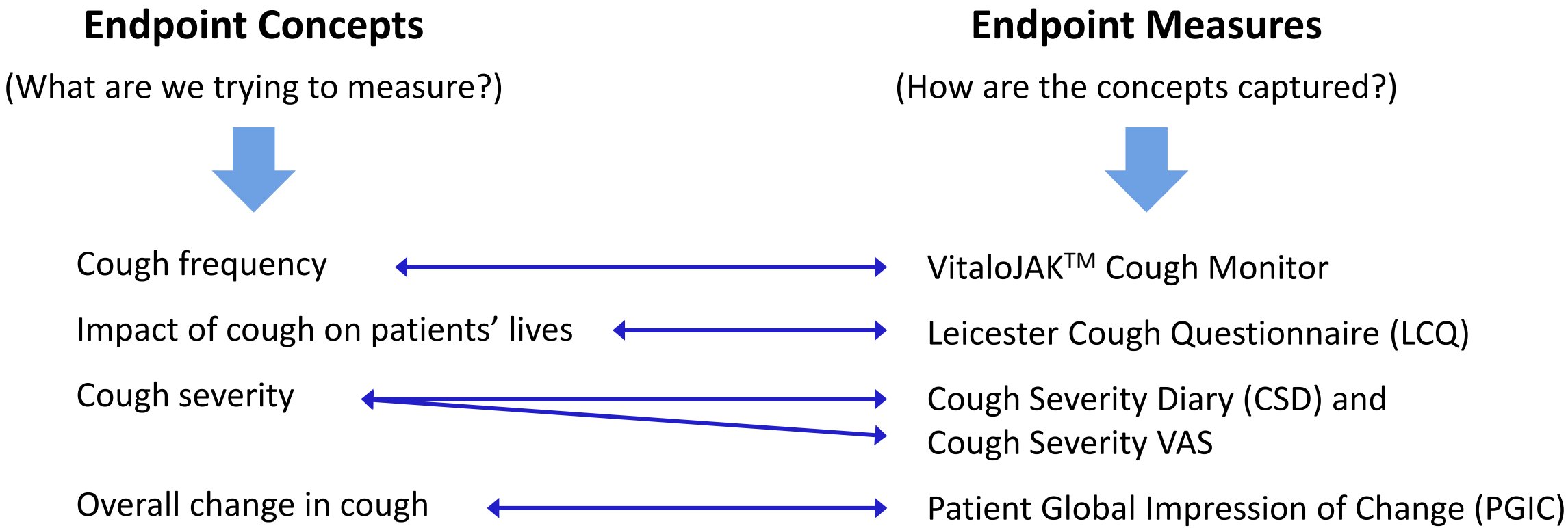
Patient Reported Outcomes

Allison Martin Nguyen, MS
Executive Director, Epidemiology
Patient-Centered Endpoints & Strategy (PaCES)
Merck Sharp & Dohme LLC

Comprehensive Patient-Focused Endpoint Strategy



LCQ is Valid to Assess Impact of Cough on Patients with RCC/UCC

Physical

8 items

item	
1	Chest or stomach pains
2	Bothersome phlegm/sputum production
3	Being tired
9	Exposure to paint or fumes
10	Sleep disturbance
11	Coughing fits/bouts
14	Suffering from hoarse voice
15	A lot of energy

Social

4 items

item	
7	Job/daily task interference
8	Life enjoyment interference
18	Interrupted conversations or phone calls
19	Annoyed partner, family or friends

Psychological

7 items

item	
4	Feeling in control of cough
5	Embarrassment
6	Anxiety
12	Frustration
13	Feeling fed up
16	Fear of serious illness
17	Concern others think something wrong with you

Birring et al. *Thorax* 2003;58:339-343

Leicester Cough Questionnaire: Sample Items

From Physical Domain

11. In the last 2 weeks, how many times a day have you had coughing fits?

1	2	3	4	5	6	7
All of the time (continuously)	Most of the time during the day	Several times during the day	Sometimes during the day	Occasionally through the day	Rarely	None

From Social Domain

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

From Psychological Domain

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

Addressing LCQ Concerns from FDA

- Content Validity = Evidence that the LCQ items are based on input from patients with RCC/UCC
  - ✓ Original development included patients with RCC/UCC
  - ✓ Subsequent Merck study confirmed content validity of the LCQ
- Use of total score to assess impact of cough on patients' lives
  - ✓ Psychological, Social, and Physical domains are important
  - ✓ Consistently supports improvements in cough frequency
- Clinical meaningfulness of the 1.3-point threshold for LCQ total score

Estimating Meaningful Change Thresholds for the LCQ Total Score

- The thresholds of ≥1.3, 3.3, and 4.1 points were based on:
  - **Developer publication[a]**
    - 1.3 was determined by anchoring mean LCQ total score change against patient global ratings of change
  - **Phase 2 pooled analyses[b]**
    - Data anchoring LCQ total score changes to PGIC ratings of 'minimally improved', resulting in a range from 1.3 to 2.3
  - **Subsequent analyses of Phase 2 data per FDA request**
    - 2 higher thresholds of 3.3 and 4.1 corresponding to PGIC ratings of ‘much improved’ and ‘very much improved’

[a] Raj et al. *Pharmacology and Therapeutics of Cough* 2009;311-320; [b] Nguyen et al. *Ther Adv Respir Dis* 2022;16:1-13

PGIC is a Valuable Metric for Assessing Change in Cough

Patient's Global Impression of Change

Compared to the start of treatment, how would you describe your cough now?

- ◯ Very much improved
- ◯ Much improved
- ◯ Minimally improved
- ◯ No change
- ◯ Minimally worse
- ◯ Much worse
- ◯ Very much worse

Correlations between PGIC and Changes in Cough Frequency & PROs

P012 (Week 12)

	Polyserial	Spearman
24-hour Cough Frequency		
% Change	0.65	0.67
Absolute Change	0.26	0.49
LCQ Total Score	-0.76	-0.72
CSD Total Score	0.61	0.62
Cough Severity VAS	0.61	0.60

Clinically Meaningful Improvement in LCQ Total Score

P030 and P027/P030 Pooled

P030 (at Week 24)

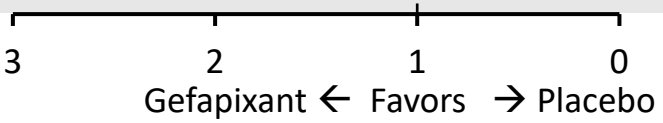
≥ 1.3-point Increase from Baseline

	n (%) of Responders	Odds Ratio[a] vs Placebo (95% CI)	*P*-value
Placebo (N=355)	245 (69.0)		
Gefapixant 45 mg BID (N=342)	262 (76.6)	**1.41** (1.02, 1.96)	**0.040**

P027 and P030 Pooled

LCQ Responder Analyses

	Threshold (points improved)	Estimated Odds Ratio	Participants, n: Placebo	Participants, n: Gefapixant
Week 12	≥ 1.3	**1.42** (1.11, 1.83)	358	391
	≥ 3.3	**1.48** (1.17, 1.88)	229	273
	≥ 4.1	**1.52** (1.19, 1.95)	184	231
Week 24	≥ 1.3	**1.37** (1.06, 1.77)	369	391
	≥ 3.3	**1.48** (1.16, 1.88)	244	283
	≥ 4.1	**1.44** (1.13, 1.84)	207	243
Week 52	≥ 1.3	**1.72** (1.31, 2.27)	351	383
	≥ 3.3	**1.59** (1.24, 2.04)	250	290
	≥ 4.1	**1.49** (1.16, 1.91)	221	253



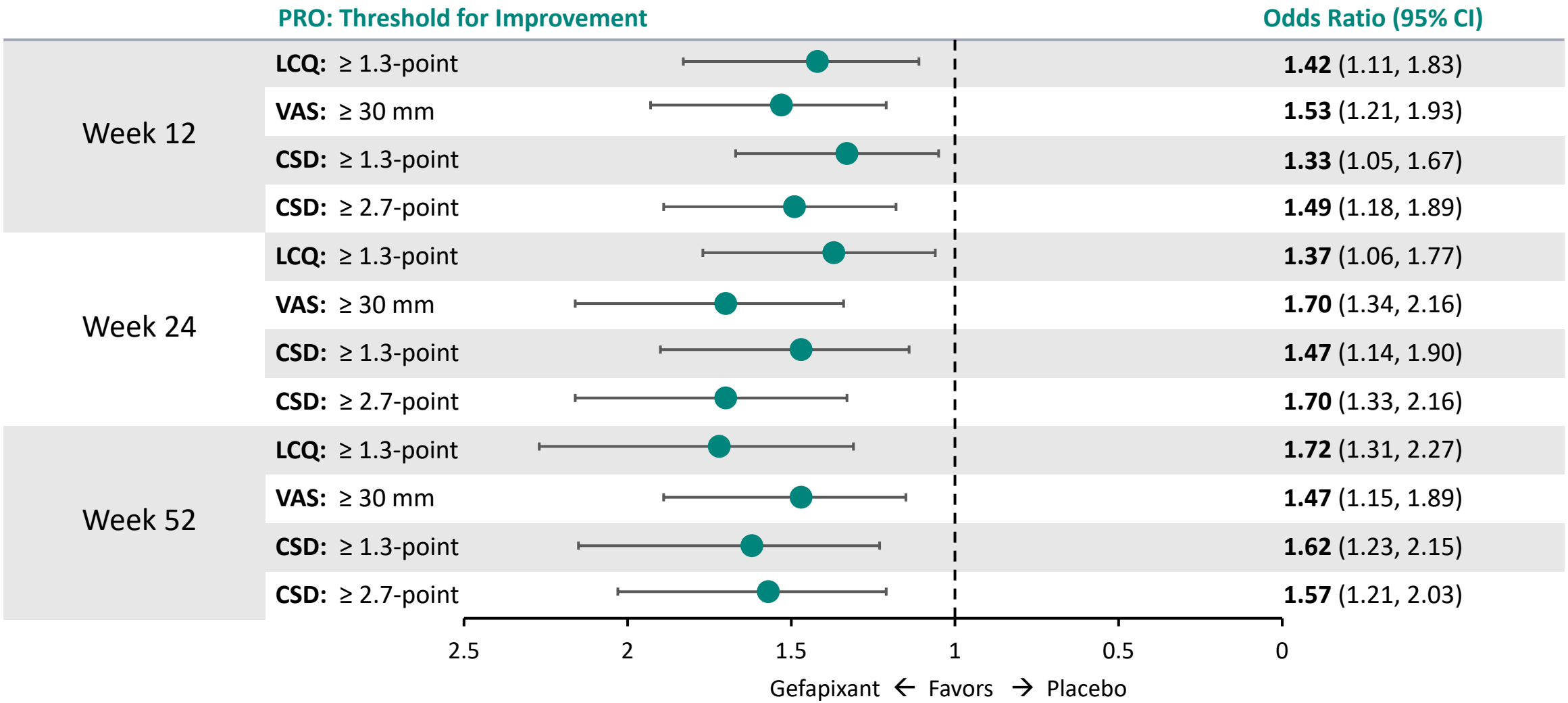
N=Number of subjects with available data at Week 12/24; n, Number of responders at Week 12/24.

[a] Estimated based on the logistic regression model.

Covariates include treatment, visit, treatment-by-visit interaction, gender, region, baseline LCQ total score, and interaction of baseline LCQ total score by visit.

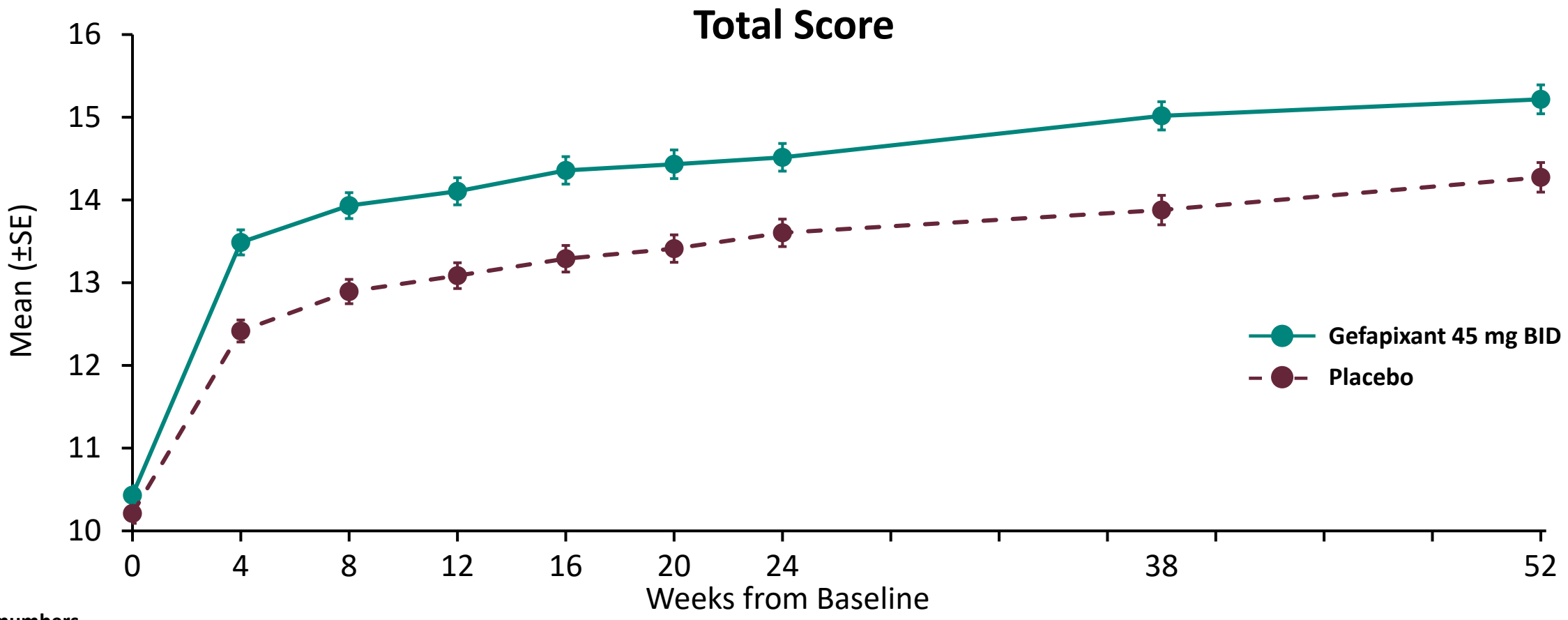
Responder Analyses are Consistent Across Other Cough PROs

P027 and P030 Pooled



LCQ Total Score Demonstrates Long-Term Durability

P027 and P030 Pooled (52-week data)

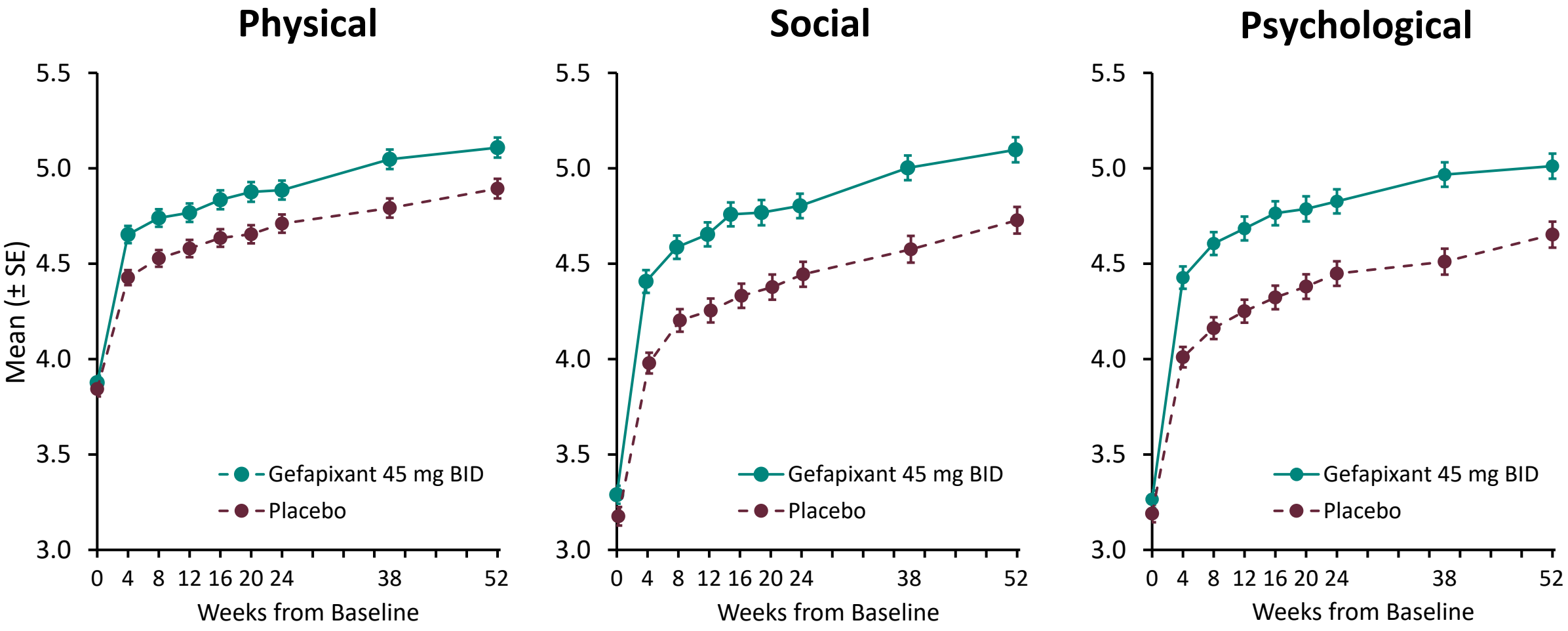


Patient numbers

Gefapixant	655	580	576	565	554	508	544	529	500
Placebo	644	621	608	596	589	543	578	552	538

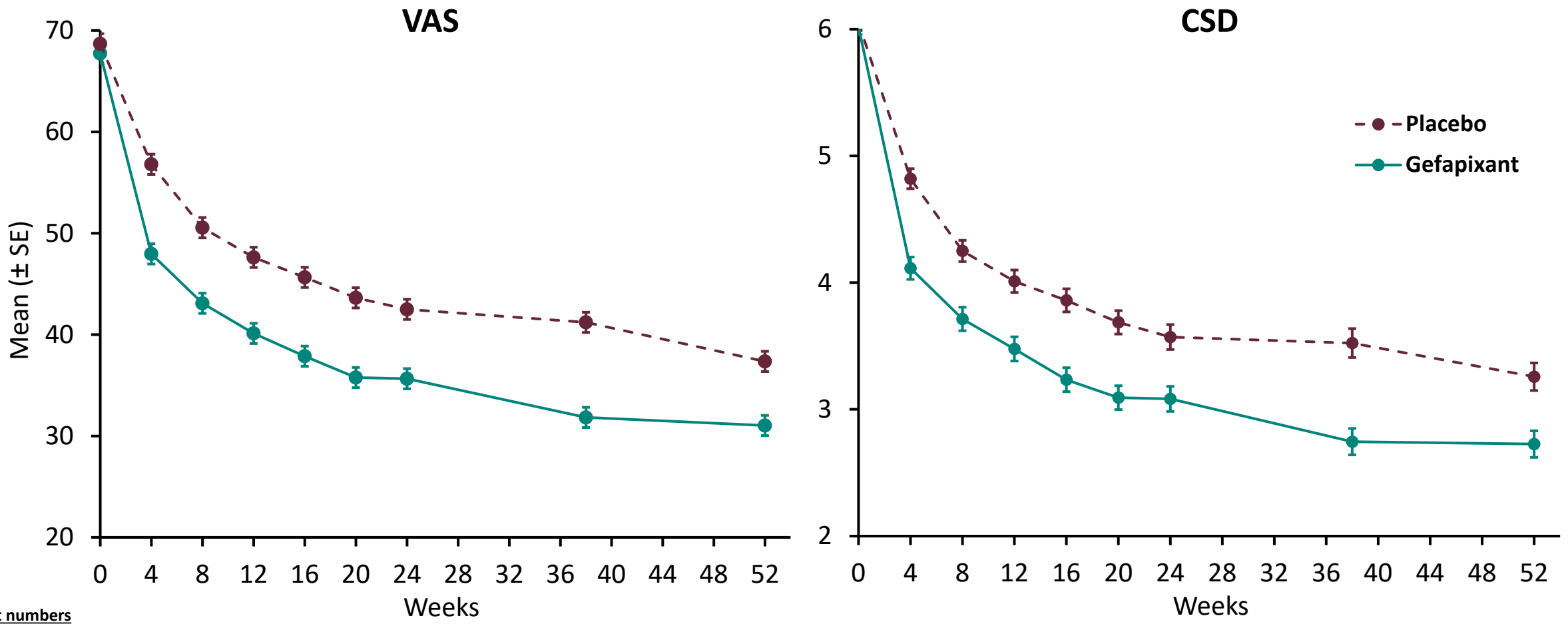
LCQ Individual Domains Demonstrate Durability Over 52 Weeks

P027 and P030 Pooled



Cough Severity VAS Score and Cough Severity Diary (CSD) Over Time

P027 and P030 Pooled

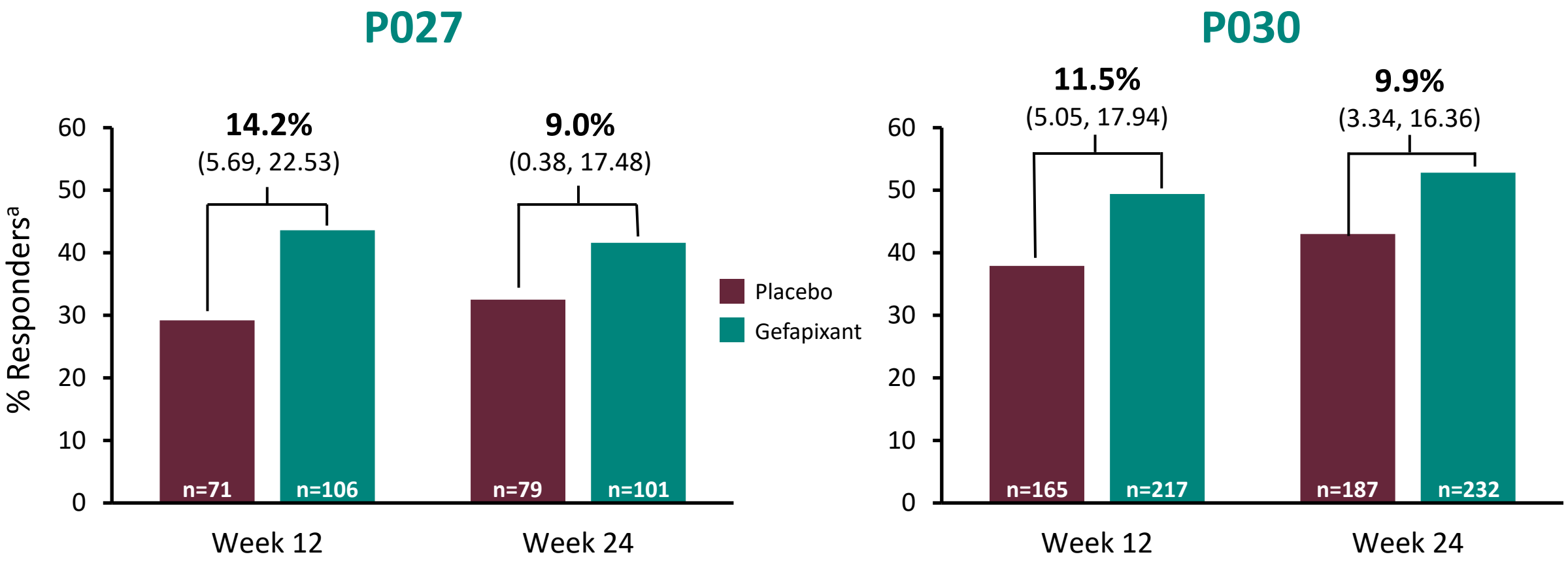


Patient numbers

Placebo	675	658	632	610	602	588	528	428	460	675	658	632	610	602	588	528	429	460
Gefapixant 45 mg BID	680	645	598	579	554	544	512	404	427	680	645	598	579	554	544	512	404	427

Responders Based on Patient Global Impression of Change (PGIC)

Studies P027 and P030



[a] Responders = Defined by self-ratings of “Much improved” or “Very much improved” on 7-point Likert scale

Patients Reported Clinically Meaningful Improvements

LCQ

- In P030, which was powered for LCQ total score, gefapixant demonstrated statistically significant and clinically meaningful benefits
- Across LCQ total and domain scores: Meaningful improvements versus placebo, based on each of the 3 thresholds for total score (≥1.3 / 3.3 / 4.1-pt increases)

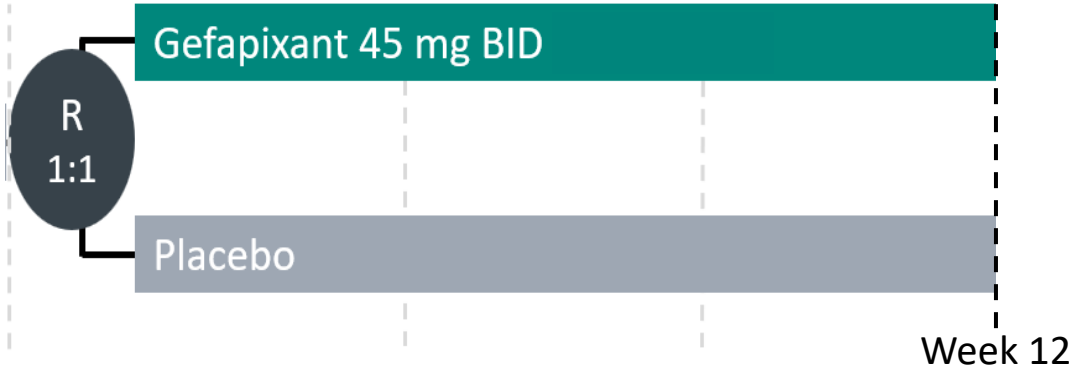
Cough Severity VAS, Cough Severity Diary, and PGIC

- VAS & CSD: Odds for achieving clinically meaningful response were higher for gefapixant, versus placebo, at each timepoint for each endpoint
- PGIC: Patients reported greater improvement on gefapixant than on placebo

Phase 3b Randomized, Placebo-Controlled Studies

P043: “Recent-Onset Chronic Cough (ROCC)”

P042: “Cough-induced Stress Urinary Incontinence (C-SUI)”



- Both met the primary endpoint (PROs)
- Provided additional safety data with no new findings
- Improvements in cough PROs were consistent with pivotal trials
- This improvement in cough led to reductions in C-SUI episodes

Gefapixant Shows Clinically Meaningful and Consistent Efficacy

- Positive results on the primary endpoint in all 7 efficacy studies
- Consistent treatment effect across original and recount datasets
- Reductions in 24-hr Cough Frequency are clinically meaningful and supported by PROs
  - >60% cough reduction relative to baseline
  - PROs show meaningful responses across multiple responder thresholds
  - Long-term durability in PROs over 52 weeks
- Phase 3b studies support efficacy, including in cough-induced stress urinary incontinence

Totality of data provides substantial evidence of effectiveness of gefapixant for RCC/UCC

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Safety

English Willis, MD

Executive Director, Clinical Safety and Risk Management
Merck Sharp & Dohme LLC

Overall Exposure to Gefapixant Across the Development Program

Studies	Participants
Phase 1	460
Phase 2	690
Phase 3[a]	2,019
Total	3,169

[a] Includes the 2 pivotal studies (P027 and P030), local Phase 3 studies (P038 (Japan) and P30 China specific study), and Phase 3b studies (P042 and P043)

Duration of Exposure in Pivotal Phase 3 Trials

P027 and P030 Pooled

Duration of Exposure[a]	Participants[b]
Any exposure	1,369
≥12 weeks	1,130
≥24 weeks	1,033
≥52 weeks	633

[a]All participants as treated from P027/P030 Pool

[b]Each participant is counted once on each applicable duration category row. Duration of exposure is calculated assuming one day of dosing=one day of exposure. One day of dosing means one day with at least one tablet of gefapixant. The cutoff days for duration of exposure ≥12 weeks, ≥24 weeks, and ≥52 weeks are 84, 168, and 360, respectively.

Summary of Adverse Events

P027 and P030 Pooled – 52 Weeks

	Participants, n (%)		
	Placebo N=675	Gefapixant 15 mg BID N=686	Gefapixant 45 mg BID N=683
Participants with ≥1 AEs	**533 (79.0)**	**559 (81.5)**	**607 (88.9)**
Drug-related AEs[a]	138 (20.4)	194 (28.3)	470 (68.8)
Serious AEs	39 (5.8)	41 (6.0)	38 (5.6)
Deaths	2 (0.3)	2 (0.3)	0
Discontinued drug due to AE[b]	39 (5.8)	55 (8.0)	151 (22.1)
Discontinued due to taste-related AEs	2 (0.3)	9 (1.3)	95 (13.9)

AE=adverse event.

[a] Determined by the investigator to be related to the drug.

[b] Participants with one or more AEs for which the action taken is listed as 'drug withdrawn'.

Adverse Events ≥5% by PT (Gefapixant > Placebo)

P027 and P030 Pooled – 52 Weeks

Events	Participants, n (%)	
	Placebo N=675	Gefapixant 45 mg BID N=683
Dysgeusia	36 (5.3)	281 (41.1)
Ageusia	6 (0.9)	100 (14.6)
Hypogeusia	4 (0.6)	73 (10.7)
Nausea	45 (6.7)	64 (9.4)
Taste disorder	3 (0.4)	61 (8.9)
Cough	28 (4.1)	49 (7.2)
Dry mouth	17 (2.5)	45 (6.6)
Upper respiratory tract infection	36 (5.3)	43 (6.3)
Diarrhea	32 (4.7)	39 (5.7)
Oropharyngeal pain	29 (4.3)	37 (5.4)

Every participant is counted a single time for each applicable row and column.

Taste-Related Adverse Events

P027 and P030 Pooled – 52 Weeks

	Participants, n (%)	
	Placebo N=675	Gefapixant 45 mg BID N=683
Participants with any taste-related AE	**47 (7.0)**	**447 (65.4)**
Dysgeusia	36 (5.3)	281 (41.1)
Ageusia	6 (0.9)	100 (14.6)
Hypogeusia	4 (0.6)	73 (10.7)
Taste disorder	3 (0.4)	61 (8.9)
Hypergeusia	2 (0.3)	5 (0.7)

Every participant is counted a single time for each applicable row and column.

Serious Adverse Events (≥2 Participants)

P027 and P030 Pooled – 52 Weeks

	Participants, n (%)	
	Placebo N=675	Gefapixant 45 mg BID N=683
Participant with ≥1 serious AE	**39 (5.8)**	**38 (5.6)**
Cough	0	2 (0.3)
Osteoarthritis	1 (0.1)	2 (0.3)
Asthma	2 (0.3)	1 (0.1)
Gastritis	2 (0.3)	0
Laryngeal stenosis	2 (0.3)	0
Urosepsis	2 (0.3)	0

Every participant is counted a single time for each applicable row and column.

Characterization of Taste-Related Adverse Events

P027 and P030 Pooled – 52 Weeks

Participants with Any Taste-Related AE	Placebo N=47	Gefapixant 45 mg BID N=447
Time to onset		
Median, days (range)	33 (1 to 138)	**2** (1 to 169)
Intensity, n (%)		
Mild	41 (87.2)	**289 (64.7)**
Moderate	6 (12.8)	**141 (31.5)**
Severe	0	17 (3.8)
Duration[a]		
Participants with AEs of known duration, n	41	432
Median, days (range)	60 (1 to 510)	**194** (1 to 555)

Taste-related AEs resolved in 96% of gefapixant patients

- While on treatment: 25% (median 65 days)
- After the last dose: 63% (median 5 days)

[a] Data collected up to date of data lock

Potential Clinical Sequelae: Participants With and Without Taste-Related AEs

P027 and P030 Pooled – 52 Weeks

	Participants *With* Taste-Related AEs		Participants *Without* Taste-Related AEs	
	Placebo N=47 n (%)	Gefapixant 45 mg BID N=447 n (%)	Placebo N=628 n (%)	Gefapixant 45 mg BID N=236 n (%)
Participants with ≥1 potential clinical sequelae	**4 (8.5)**	**35 (7.8)**	**7 (1.1)**	**4 (1.7)**
Decreased appetite	4 (8.5)	21 (4.7)	3 (0.5)	4 (1.7)
Weight decreased	0	7 (1.6)	3 (0.5)	1 (0.4)
Thirst	0	9 (2.0)	0	0
Dehydration	0	1 (0.2)	3 (0.5)	0

No meaningful changes in weight, BUN, or creatinine compared with baseline

Every subject is counted a single time for each applicable row and column.

Adverse Events Leading to Discontinuation (≥1%)

P027 and P030 Pooled – 52 Weeks

	Participants, n (%)	
	Placebo N=675	Gefapixant 45 mg BID N=683
Participants with ≥1 AE	**39 (5.8)**	**151 (22.1)**
Dysgeusia	1 (0.1)	59 (8.6)
Ageusia	0	25 (3.7)
Taste disorder	0	11 (1.6)
Cough	3 (0.4)	11 (1.6)
Nausea	4 (0.6)	7 (1.0)

Every participant is counted a single time for each applicable row and column.

Safety and Tolerability Conclusions

- Gefapixant 45 mg BID in adults with RCC or UCC has an acceptable safety and tolerability profile
  - Few serious AEs were reported, incidences were similar to placebo, and none were taste-related
  - The most frequently reported AEs were related to taste
  - Taste-related events were mostly mild, not associated with clinical sequelae; most patients tolerated the events and remained on treatment
  - Taste-related events were reversible and resolved in 96% of patients

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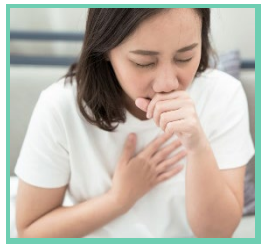
Clinical Perspective on the Benefit-Risk Relationship

Jaclyn Smith, MD, ChB, FRCP, PhD

Division of Infection, Immunity and Respiratory Medicine

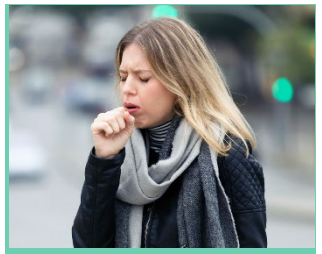
University of Manchester, UK

The Diagnostic Journey of Patients with RCC/UCC is Burdensome



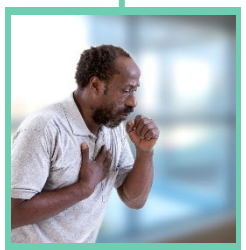
It lasts…

It lasts…

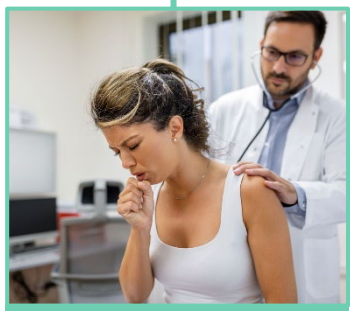


It lasts…

Can be 10 years or more

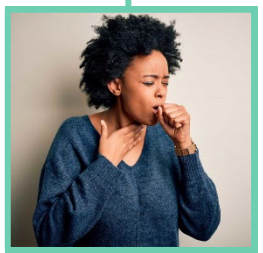


It starts



It’s evaluated…

It’s evaluated again…



It’s painful

It’s isolating

Meltzer EO, et al. *J Allergy Clin Immunol Pract* 2021;9:4037-44.

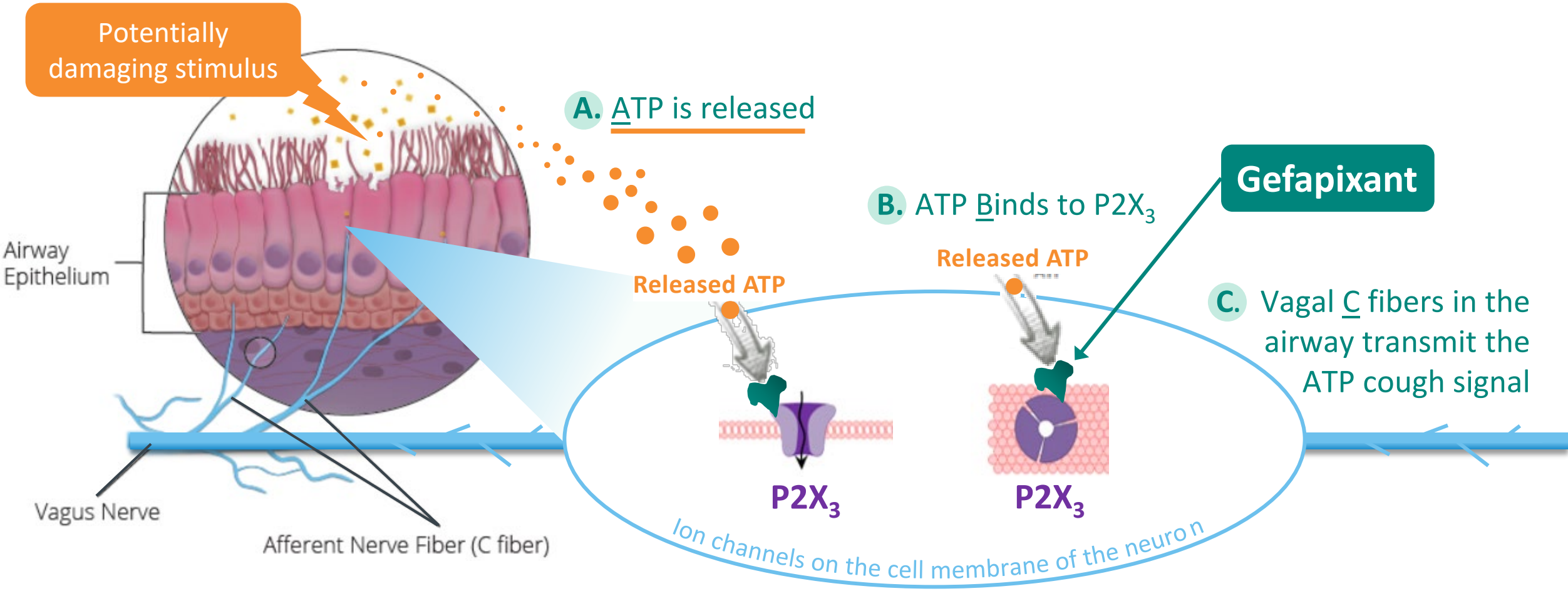
Patients with RCC/UCC Have No Approved Treatment Options

- Off-label treatments that have been used:
  - Opioids
  - Neuromodulators (gabapentin)
  - Other antitussives

Centrally acting agents lead to CNS-related AEs

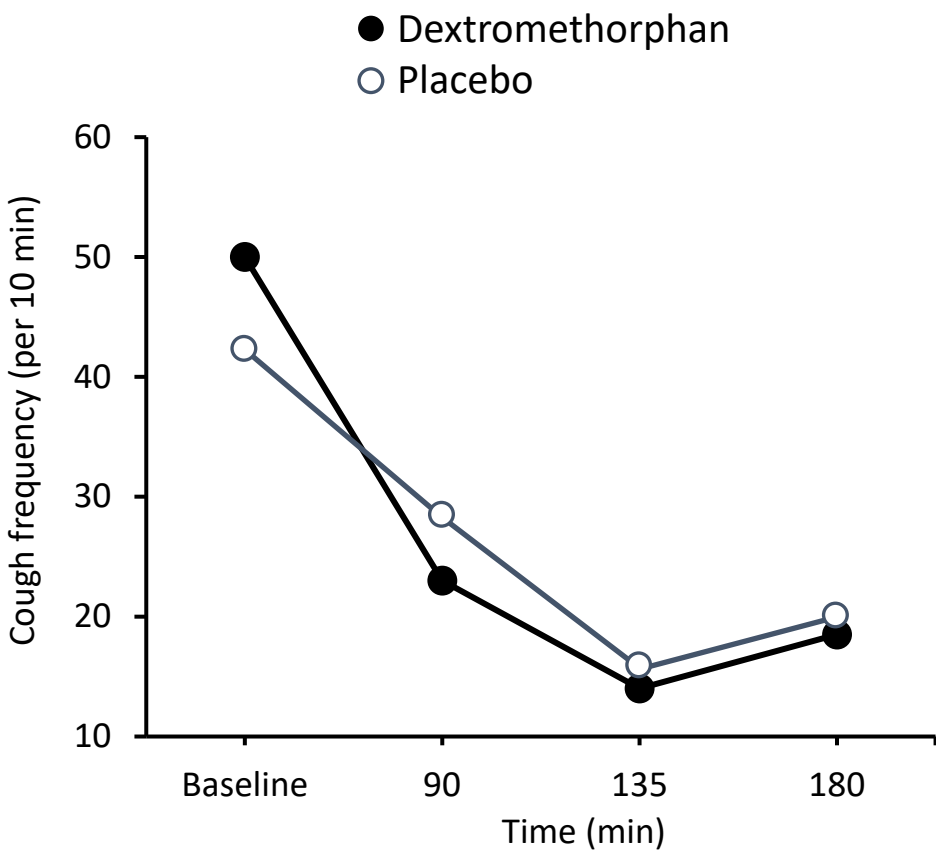
- Limitations of off-label treatments:
  - Lack of robust evidence
  - Substantial safety concerns
  - Abuse potential
  - Highly variable use

Gefapixant is Specific to the P2X3 Receptor in the Periphery

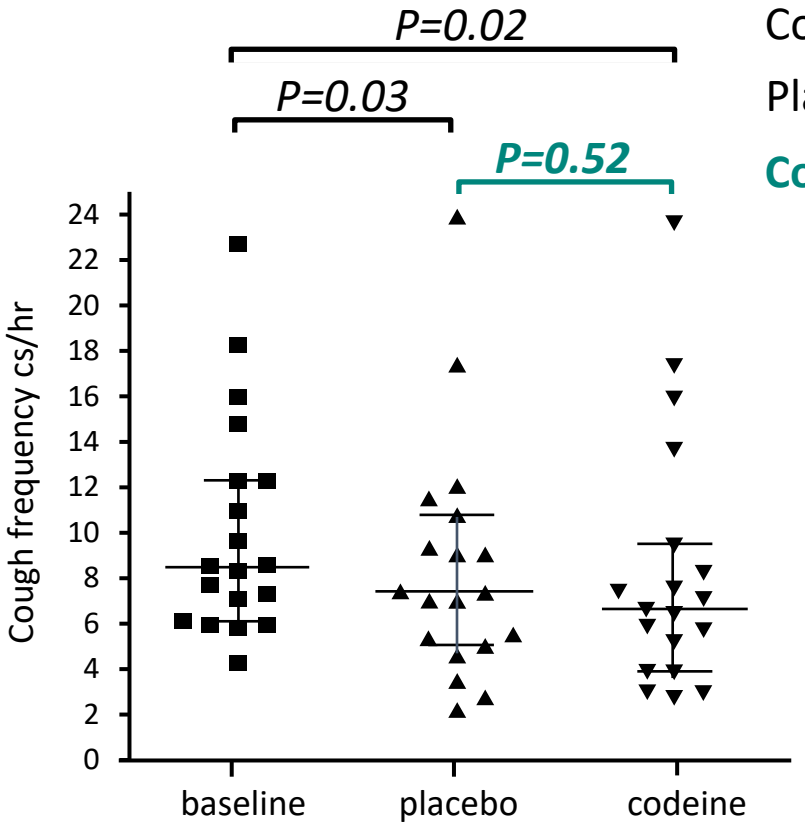


Placebo Response in Other Cough Studies

Cough due to URTI [a]



Cough due to stable COPD [b]



Codeine vs. Baseline

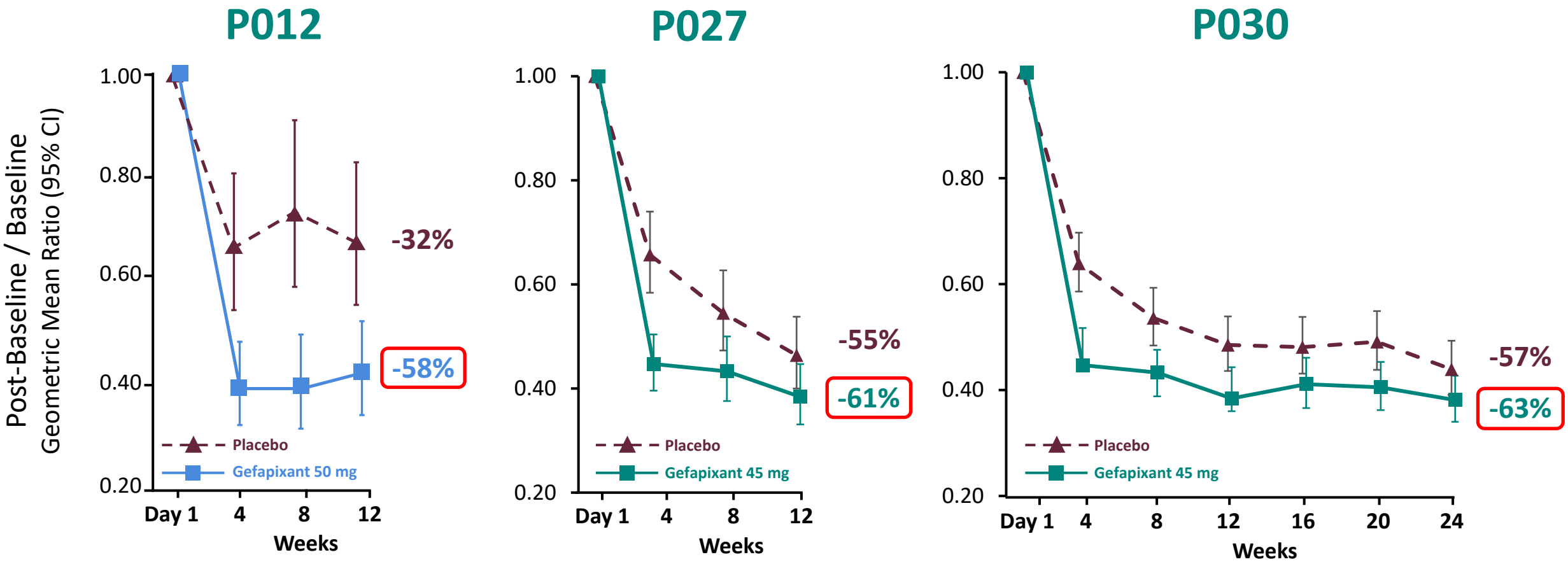
Placebo vs. Baseline

Codeine vs. Placebo

Horizontal lines = median time spent coughing; *error bars* = IQR

[a] Left panel reprinted from Lee PCL, et al. *J Pharm Pharmacol*. 2000;52(9):1137-42; [b] Right panel adapted from Smith J, et al. *J Allergy Clin Immunol*. 2006;117(4):831-5.

Gefapixant Demonstrated Consistent Reduction in 24-hr Cough Frequency Across Phase 2b and Phase 3 (Recount) Studies

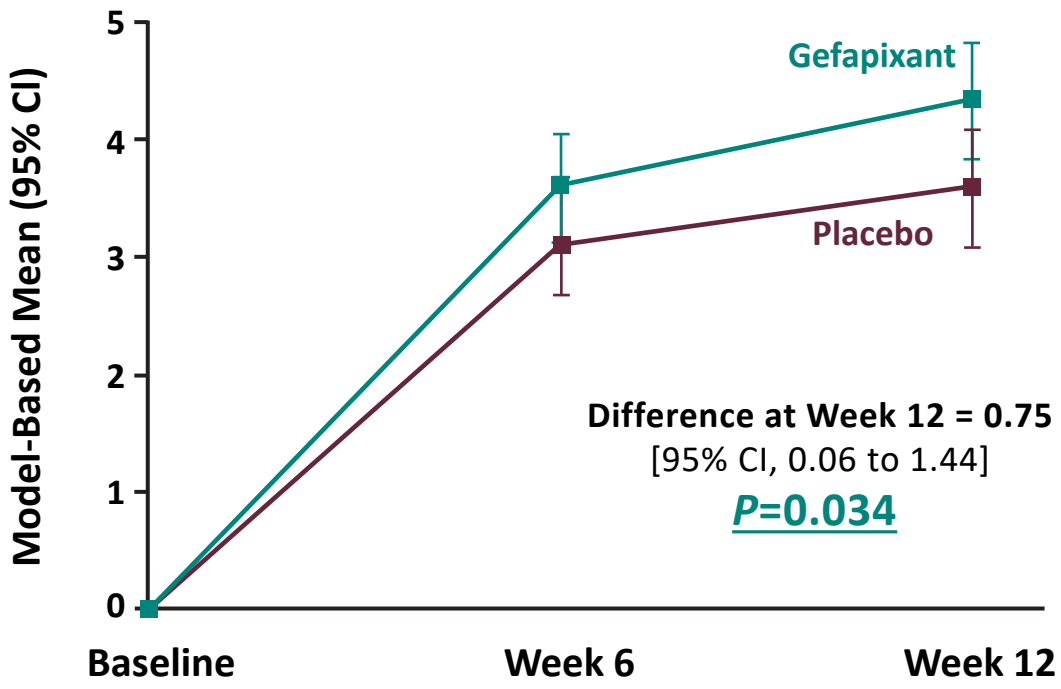


Phase 3b: Recent-Onset Chronic Cough Results are Consistent

P043 (Week 12) and P027/P030 Pool (Week 52)

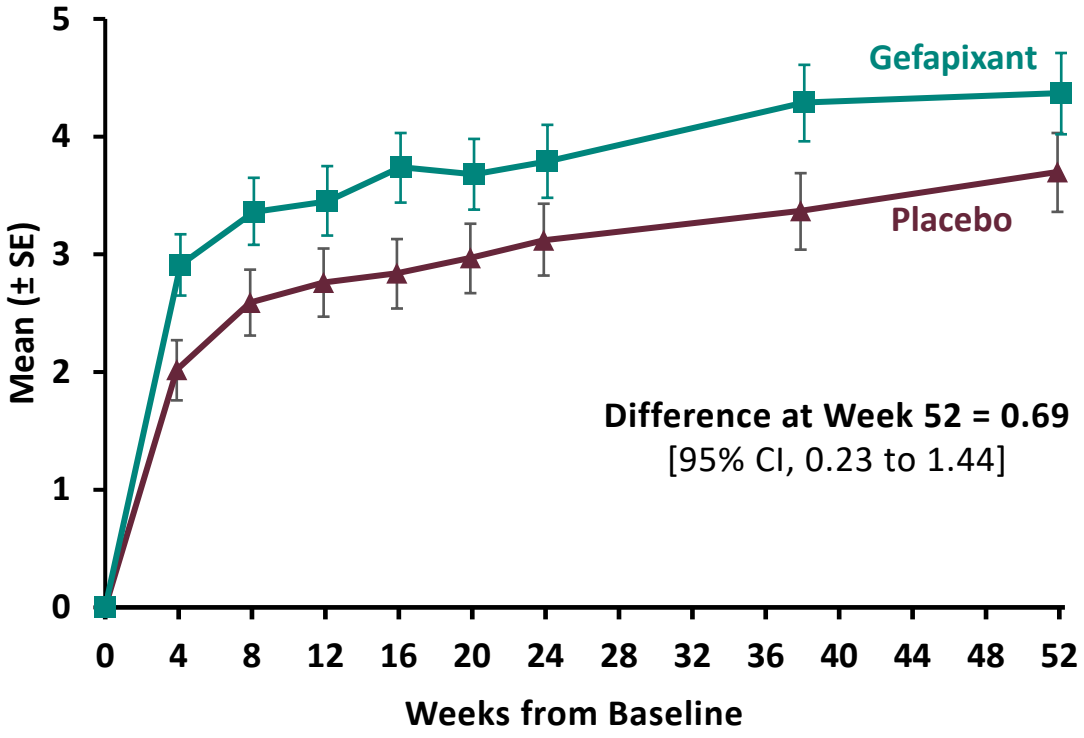
P043

LCQ Change from Baseline (Week 12)



P027 and P030 Pool

LCQ Change from Baseline (Week 52)



McGarvey L, et al. *Lung*. 2023;201(2):111-118.

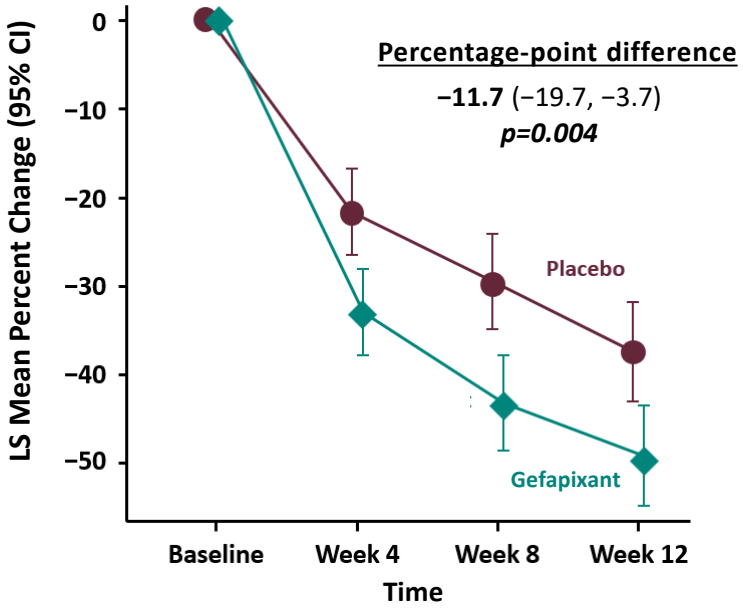
Phase 3b: RCC/UCC with Cough-Induced Urinary Incontinence

P042 (Week 12) and P027/P030 Pool (Week 52)

P042

Cough-induced Incontinence

(Episodes/day, %-Change from Baseline)



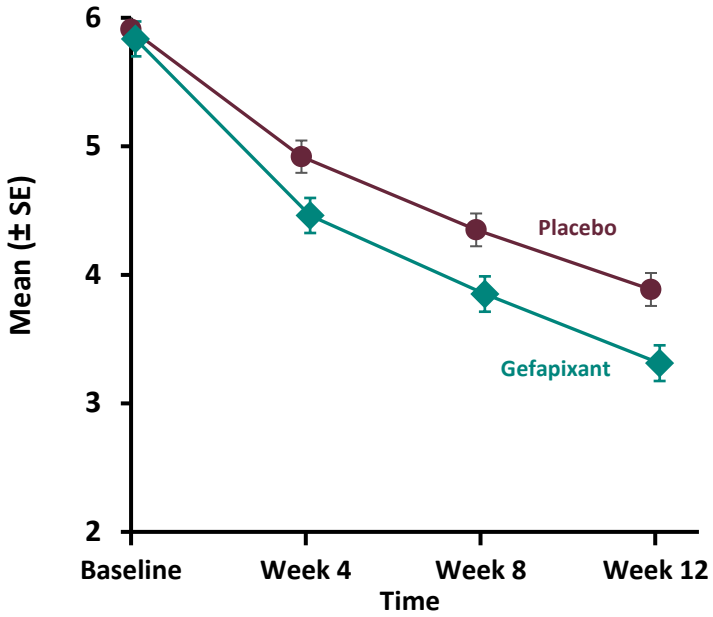
Baseline values, mean (SD)

4.73 (4.22) Episodes/day

4.73 (3.00) Episodes/day

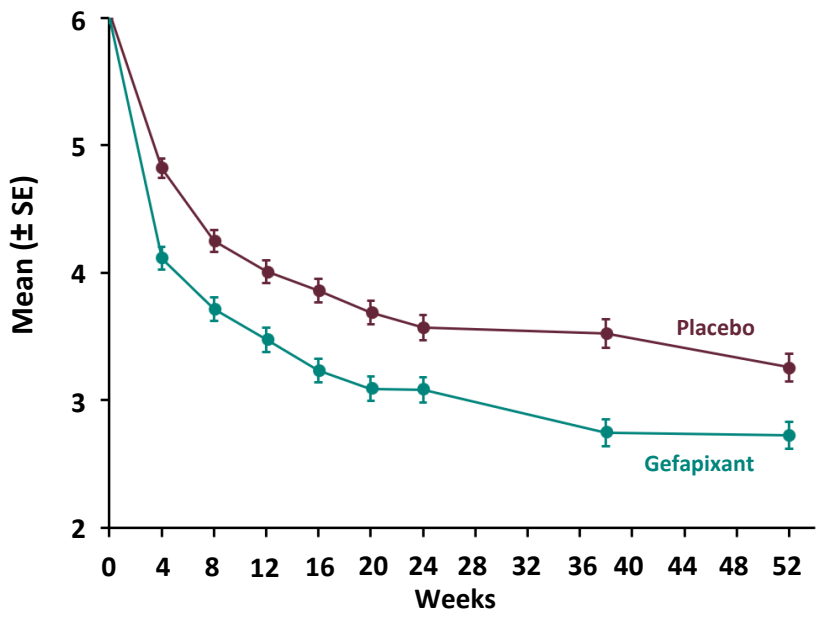
P042

Cough Severity Diary

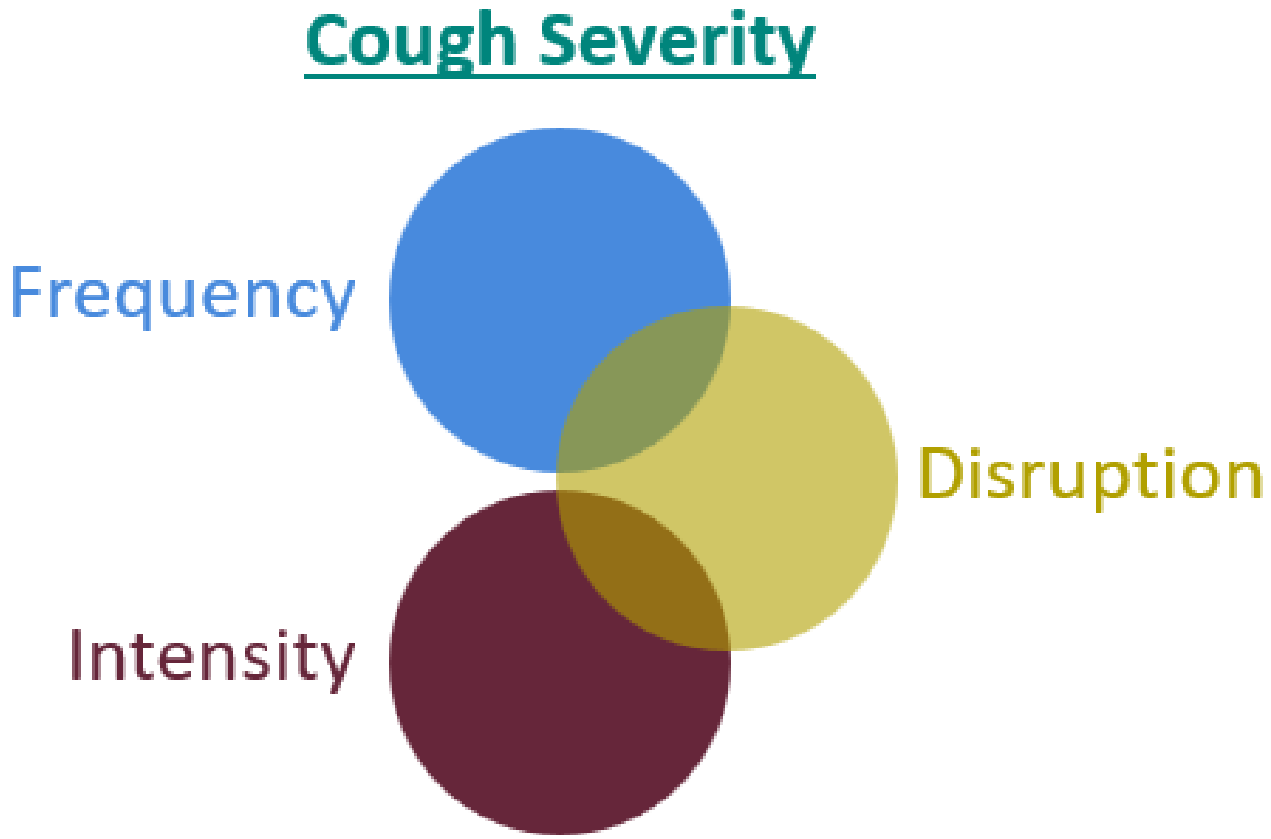


P027/P030 Pool

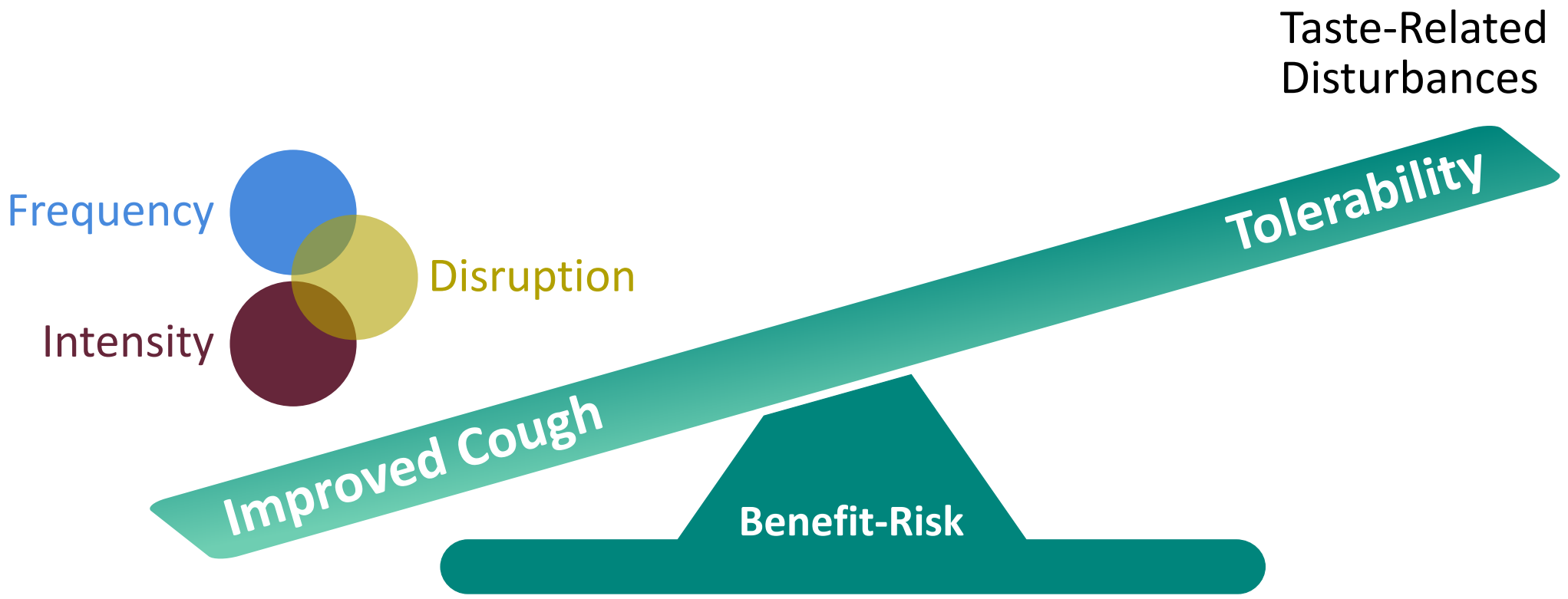
Cough Severity Diary



RCC and UCC Contribute to Significant Patient Burden, Informing the Design of the Gefapixant Clinical Program



Clinical Perspective on the Benefit-Risk of Gefapixant



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Closing Summary

Lisa Bollinger, MD
Vice President, Regulatory Affairs
Merck Sharp & Dohme LLC

Determining Clinically Meaningful Efficacy of Gefapixant in RCC/UCC

"Clinical meaningfulness of group differences must be determined by a multi-factorial evaluation of the benefits and risks of the treatment and of other available treatments for the condition in light of the primary goals of therapy."

-- Dworkin RH, et al. Pain. 2009

Factors that inform Clinically Meaningful Efficacy[a]	For gefapixant…
Statistical significance of primary efficacy analyses	Consistent treatment effect across original/recount datasets.
Magnitude of improvement in primary efficacy outcome	>60% reduction from baseline in 24hr cough frequency
Treatment effect size, compared with approved treatments	No approved treatments for RCC/UCC, no established treatment effect
Results of responder analyses	Multiple analyses support the primary endpoint
Rapid onset of treatment benefit	As early as 4 weeks (on primary endpoint)
Durability of treatment benefit	Through 52 weeks
Results for secondary efficacy endpoints	PRO results support meaningful cough reduction
Safety and tolerability	Well characterized, few serious AEs (similar to placebo and not drug related)
Different mechanism of action vs. existing treatments	1st in class MoA: Targets the unique pathophysiology
Limitations of available treatments	Off-label and unproven use of opioids and neuromodulators with known risks

[a] Uses framework to interpret clinical importance of group differences, established by Dworkin RH, et al. *Pain.*2009;146:238–244.

Gefapixant has a Favorable Benefit-Risk Assessment in RCC/UCC

Dimension	Conclusions and Reasons
Analysis of Condition	• RCC/UCC is its own condition recognized in guidelines, and recruited in Phase 3 • Significant Unmet Need
Current Treatment Options	• No approved or proven treatments

Benefit	• Totality of Data provides Substantial Evidence of Effectiveness
	  • Treatment effect not a chance finding
	  • Meaningful to patients

Risk and Risk Management	• Taste-related AEs are a tolerability consideration • Safety is well-characterized with no serious drug-related adverse events

Conclusions Regarding Benefit-Risk

The benefits of gefapixant, balanced against its well-characterized safety profile, support approval for RCC/UCC in adults, a debilitating disease with no approved treatment.

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Gefapixant
Supporting Slides

U.S. Food & Drug Administration

Pulmonary-Allergy Drugs Advisory Committee

November 17, 2023

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Gefapixant for the treatment of Refractory Chronic Cough (RCC) and Unexplained Chronic Cough (UCC) in adults

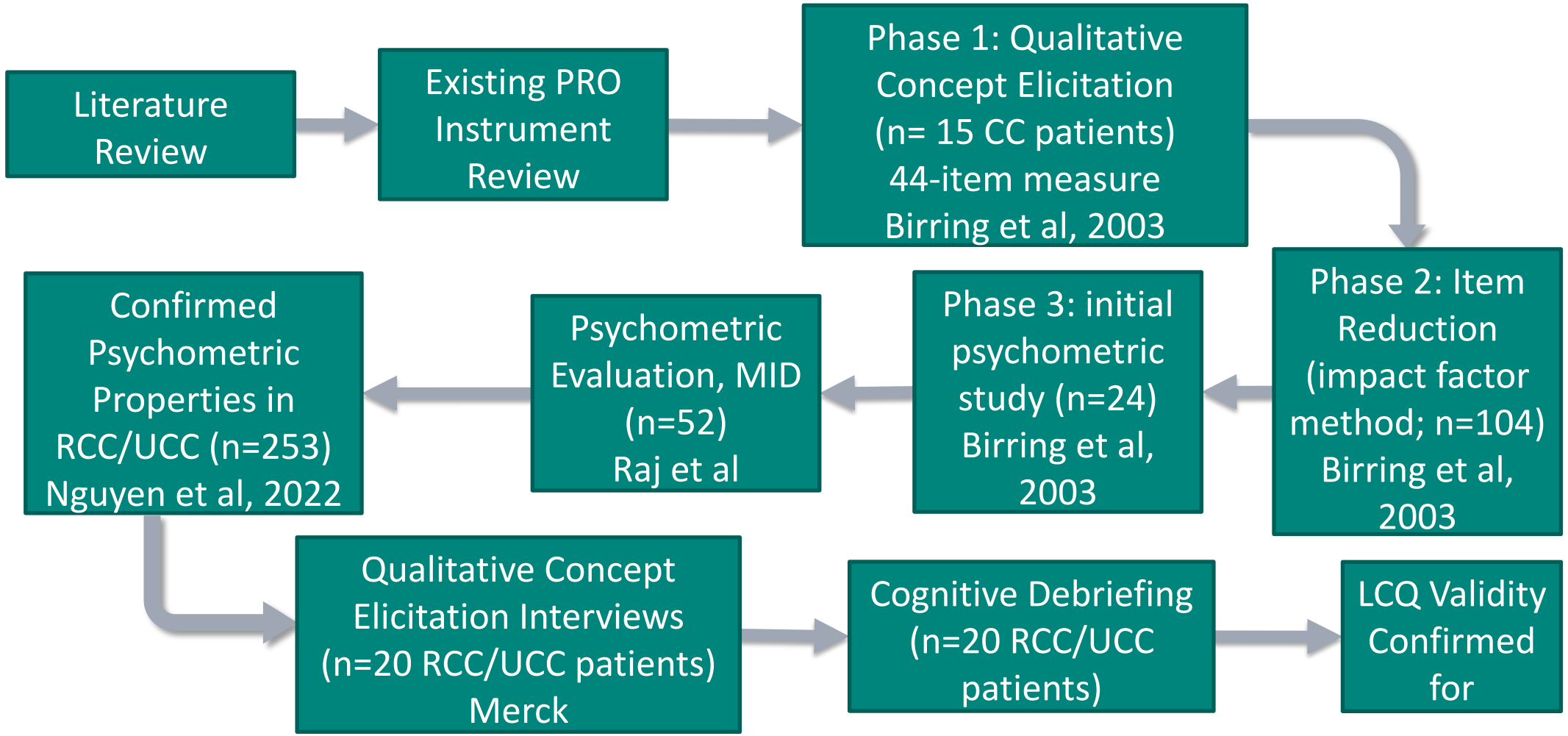
- Significant unmet need
- Totality of data provides evidence of meaningful efficacy
- Acceptable safety and tolerability profile

Patients With Taste-Related AEs Did Not Have More Benefit Than Patients Without Taste-Related AEs

P027 and 030 Pooled (Recount)

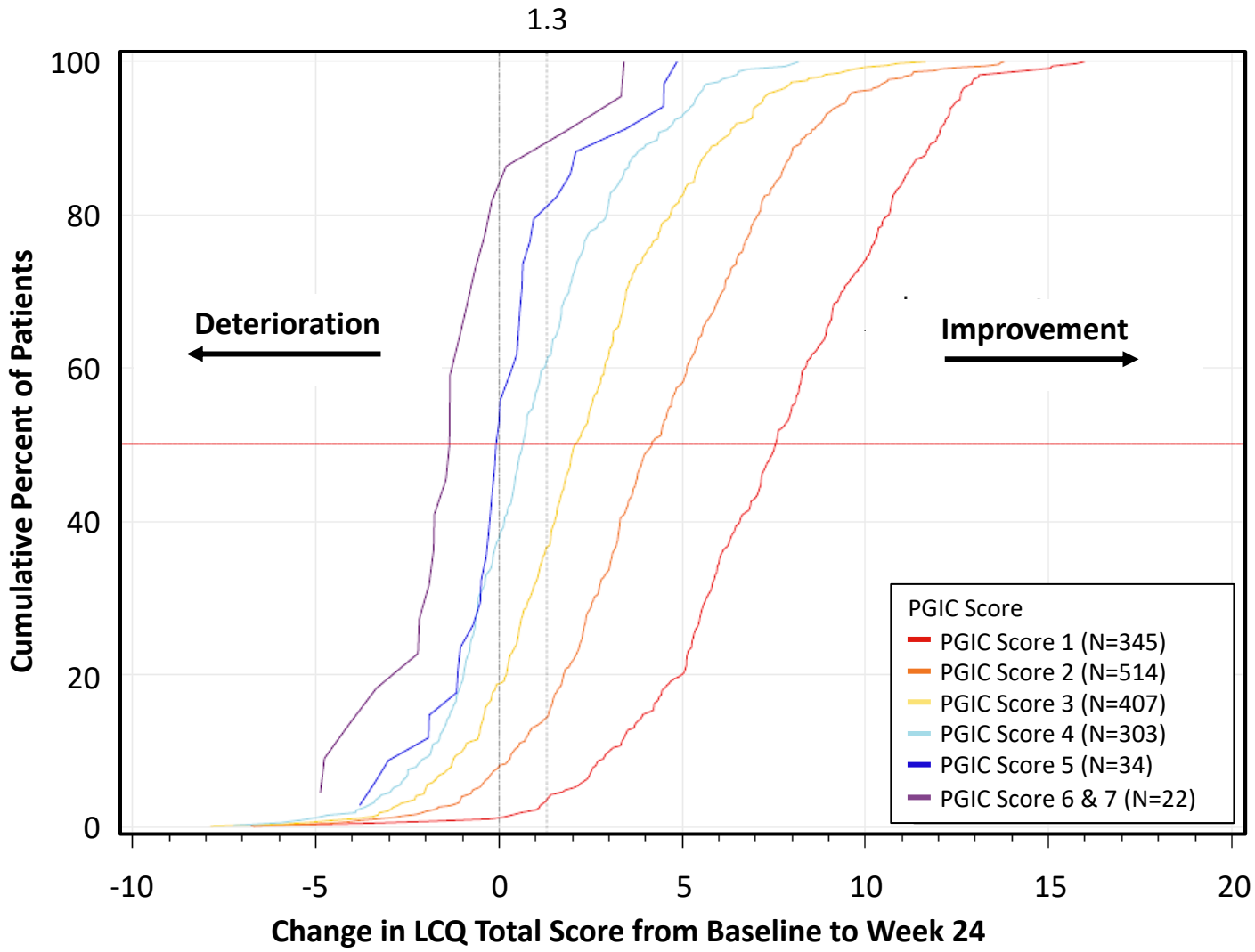
	n	With Taste AE	n	Without Taste AE
24-hour Cough Frequency: Reduction from Baseline, % (95% CI)				
Placebo (Week 12)	39	**47** (26, 62)	602	**52** (48, 56)
LCQ Total Score: Responders, % (95% CI)				
Placebo (Week 24)	42	**71.4** (57.7, 85.1)	506	**67.0** (62.9, 71.1)
Placebo (Week 52)	41	**61.0** (46.1, 75.9)	473	**68.9** (64.7, 73.1)

LCQ: Rigorous Process to Develop & Validate for RCC/UCC



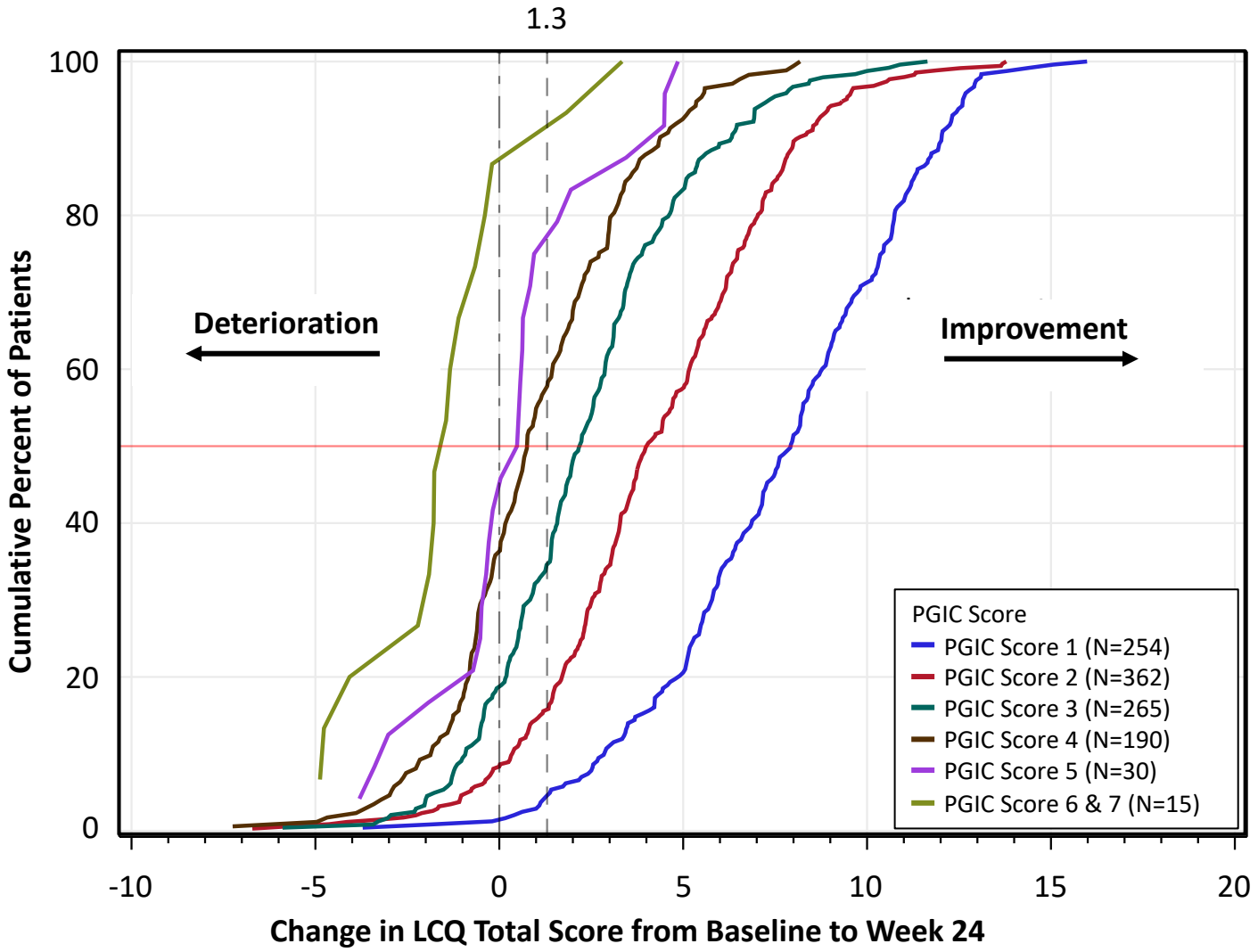
Cumulative Distribution of Change from Baseline in LCQ Total Score, by PGIC Category

P027 and P030 Pool, Week 24

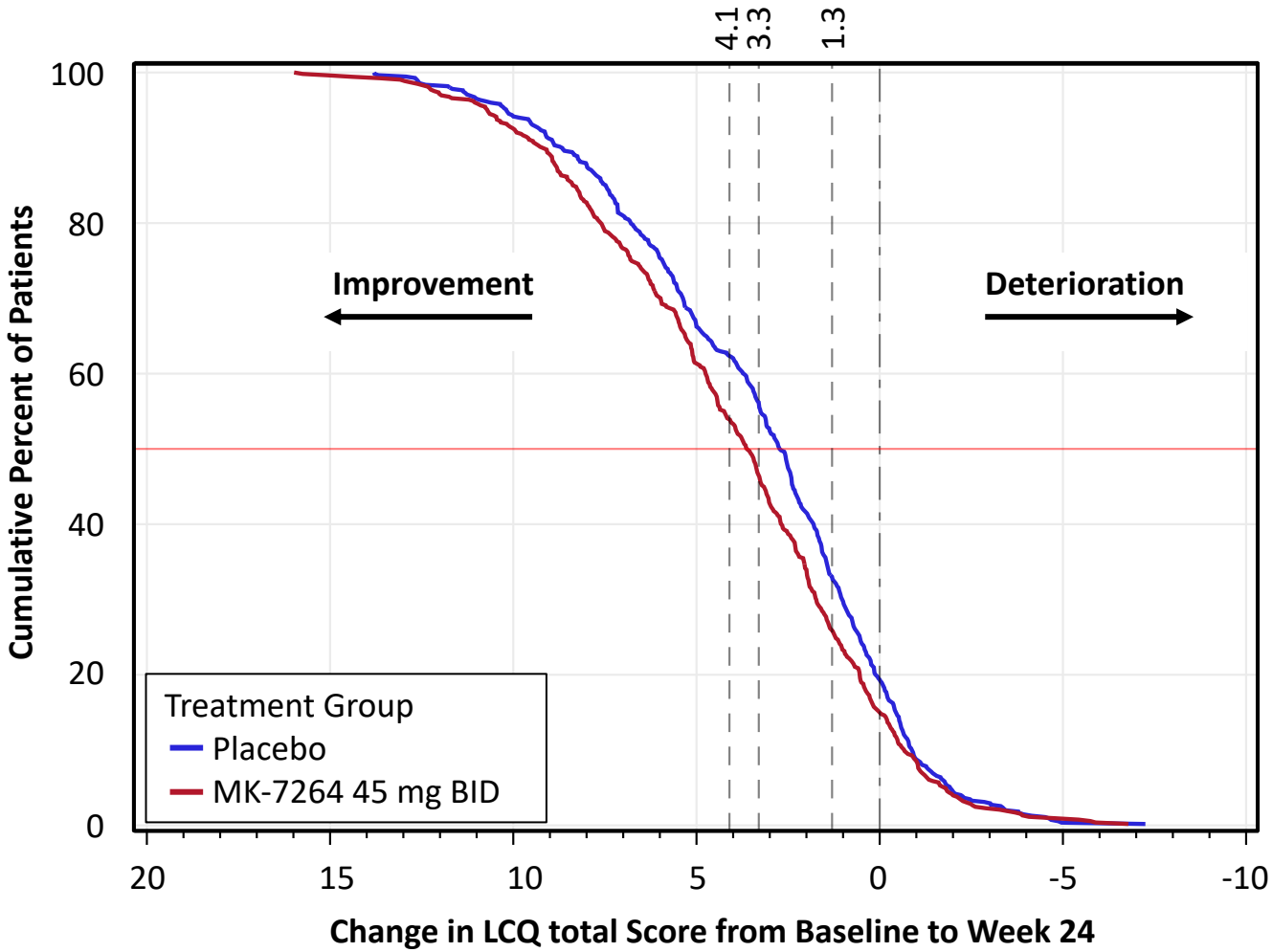


Cumulative Distribution of Change from Baseline in LCQ Total Score, by PGIC Category

P030, Week 24



Cumulative Distribution of LCQ total score, by treatment group, Baseline to Week 24, P027/P030 Pool



Analysis of 24-Hour Cough at Week 12 by Taste AE

P027 and P030 Pooled (Recount)

Improvement from Baseline % (95% CI)

Treatment	N	With Taste AE	N	Without Taste AE
Gefapixant 45mg BID	405	**64** (59, 68)	221	**56** (49, 61)

LCQ responder: ≥1.3 point increase in total score

Analysis of LCQ Responders at Week 24/52 by Taste AE

P027 and 030 Pooled

Week 24

Treatment	N/n	With Taste AE	N/n	Without Taste AE
Gefapixant 45mg BID	349/266	**76.2** (71.7, 80.7)	178/125	**70.2** (63.5, 76.9)

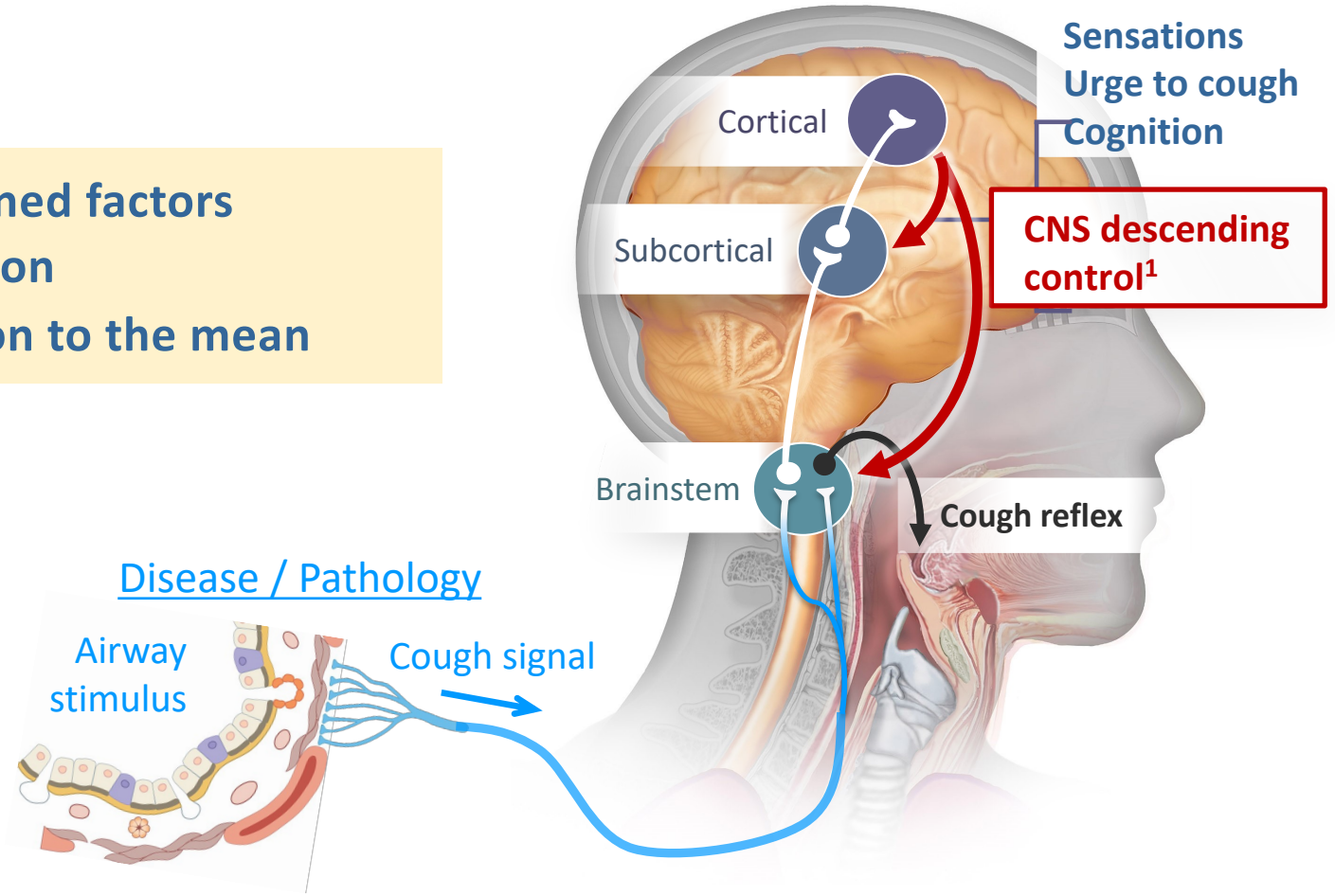
Week 52

Treatment	N/n	With Taste AE	N/n	Without Taste AE
Gefapixant 45mg BID	321/260	**81.0** (76.7, 85.3)	164/123	**75.0** (68.4, 81.6)

LCQ responder: ≥1.3 point increase in total score

Placebo Effect is Multifactorial

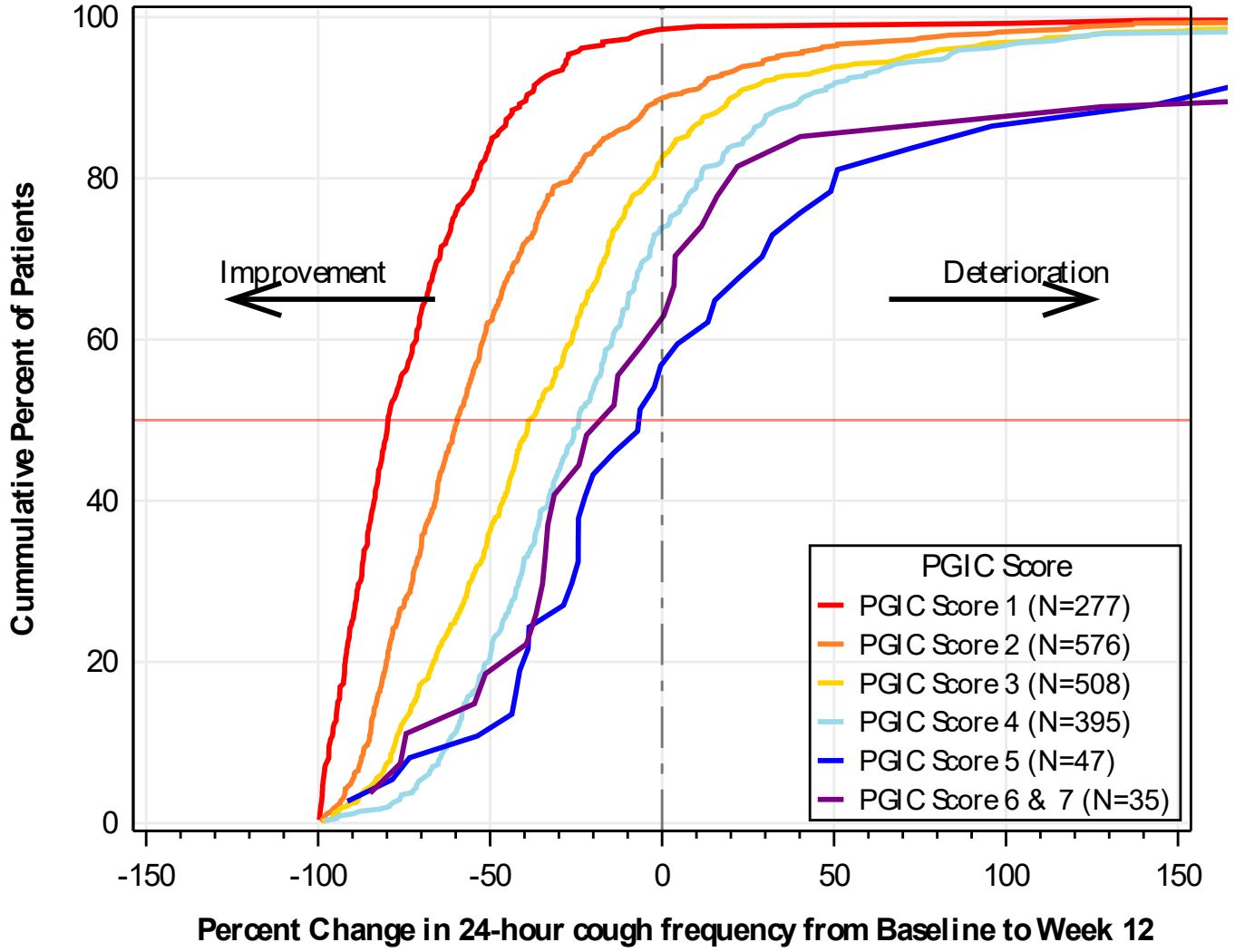
1. **Unexplained factors**
2. **Expectation**
3. **Regression to the mean**



1. Geuter et al. *Annu Rev Neurosci* 2017;40:167-188.

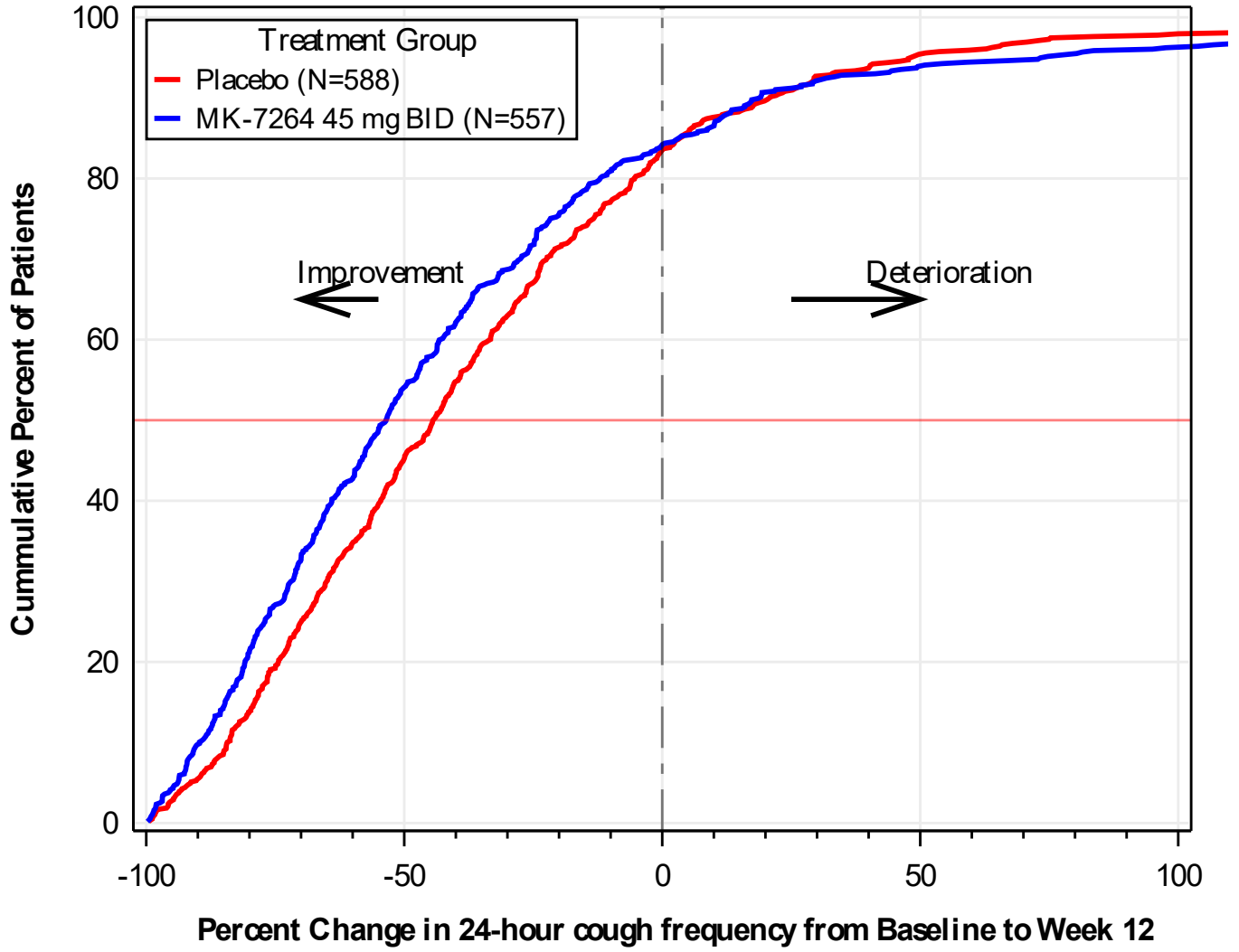
Cumulative Distribution Functions – Percentage Change from Baseline in Cough Frequency by PGIC

Pooled P027 and P030 – Recount Data



Cumulative Distribution Functions – Percentage Change from Baseline in Cough Frequency, by Treatment Groups

Pooled P027 and P030 – Recount Data



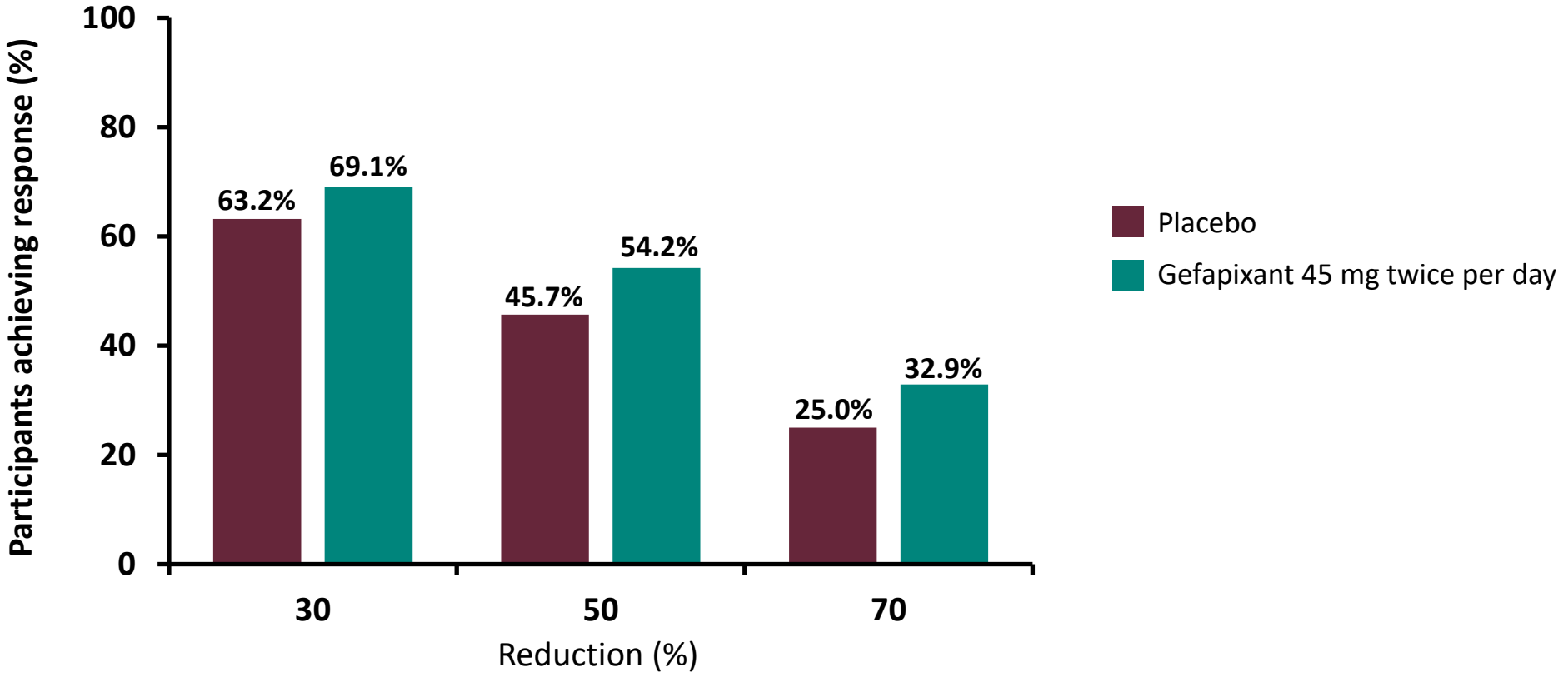
Analysis of 24-Hour Cough at Week 12 by Taste AE

P027 and P030 Pooled (Recount)

	With Taste AE by Week 12		Without Taste AE by Week 12	
Treatment	N	Reduction from Baseline % (95% CI)	N	Reduction from Baseline % (95% CI)
Placebo	39	**47** (26, 62)	602	**52** (48, 56)
Gefapixant 45 mg BID	405	**64** (59, 68)	221	**56** (49, 61)

24-hour Cough Frequency at Week 12: Responder analysis (30%, 50%, 70% decrease from baseline)

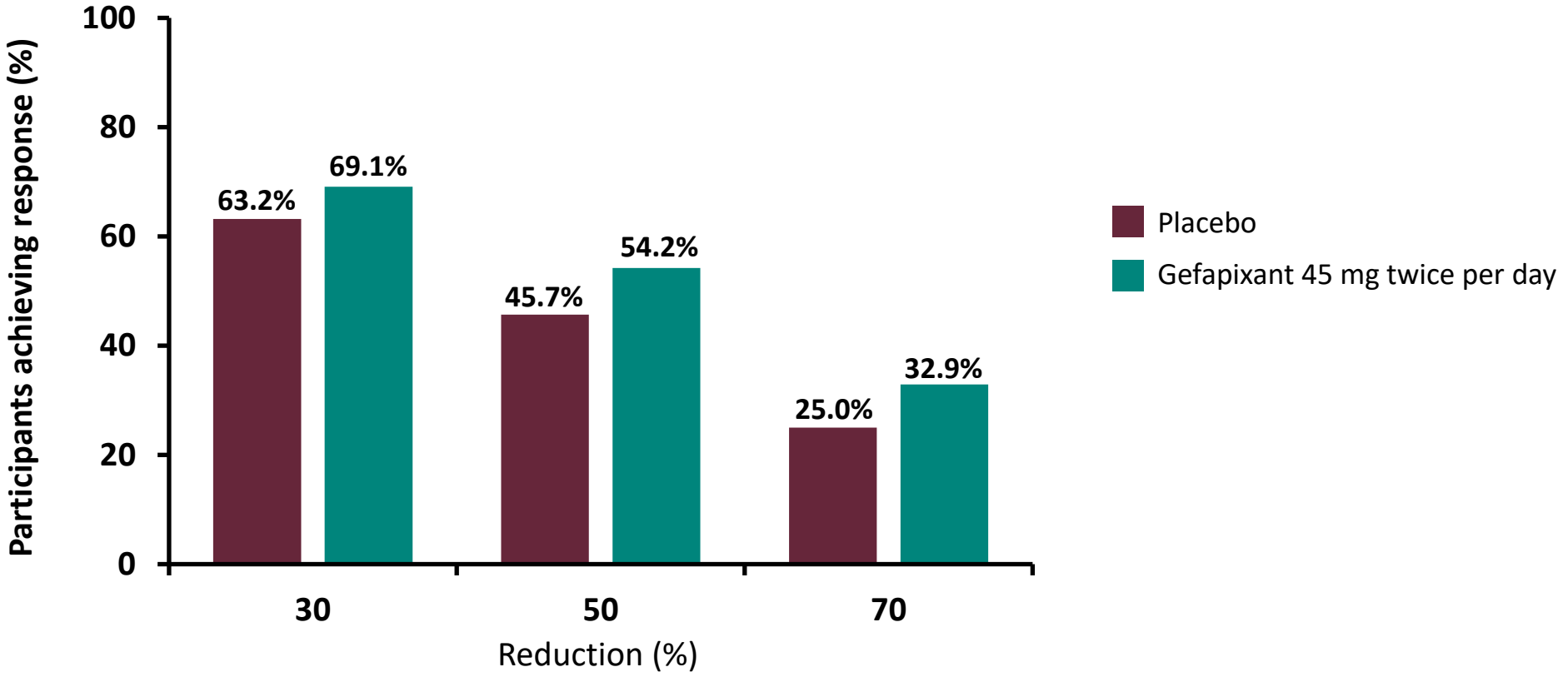
P027 and P030 Pooled: Full Analysis Set (Recount)



	30	50	70
Estimated difference Gefapixant 45 mg vs Placebo (95% CI)	**5.92 (-0.36, 12.15)**	**8.48 (2.15, 14.80)**	**7.97 (2.32, 13.86)**
Odds Ratio vs Placebo (95% CI)	**1.30 (1.01, 1.69)**	**1.40 (1.11, 1.77)**	**1.48 (1.14, 1.91)**

24-hour Cough Frequency at Week 12: Responder analysis (30%, 50%, 70% decrease from baseline)

P027 and P030 Pooled: Full Analysis Set (Recount)



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Significant (p<0.0001) Correlation Between 24-Hr Cough Frequency & PROs, PN012

Measure	Week 12
LCQ (total)	-0.56
LCQ (physical)	-0.54
LCQ (psychological)	-0.55
LCQ (social)	-0.50
CSD Total Score	0.48
CSD (frequency)	0.49
CSD (intensity)	0.46
CSD (disruption)	0.43
Cough Severity VAS	0.54

Schelfhout et al, 2022

Spearman correlation coefficients reported

LCQ = Leicester Cough Questionnaire; CSD=Cough Severity Diary; VAS = visual analog scale

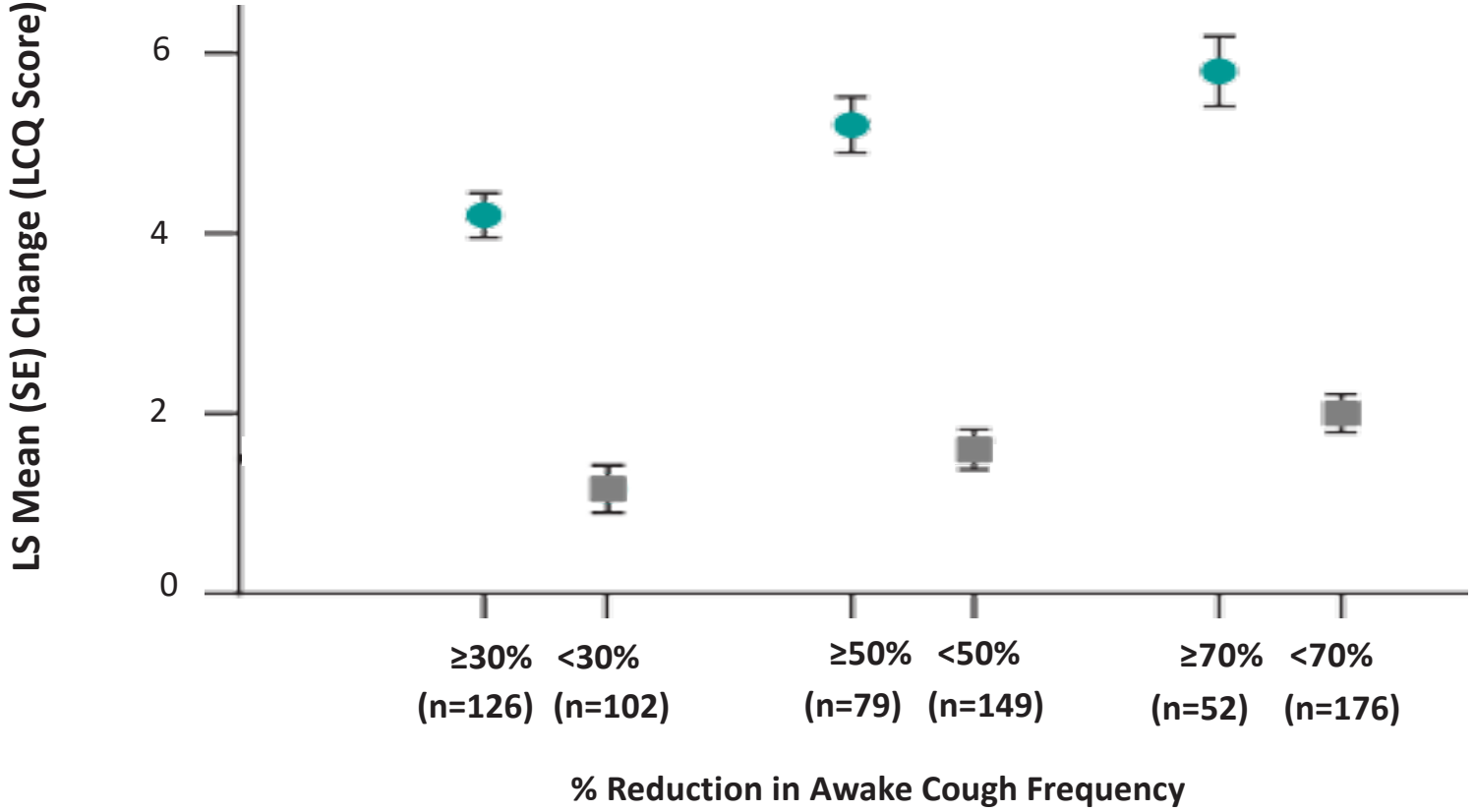
24-hr Cough Frequency Differs Significantly Across LCQ Severity Groups, PN012

	LCQ Severity Groups at Baseline						
	Total Score <8		Total Score >8 to ≤13		Total Score >13		
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	
24-hr Cough Frequency	25	66.8 (7.5)	141	28.9 (3.1)	85	19.5 (4.1)	p<0.0001

Schelfhout et al, 2022

Greater Improvement in LCQ Total Scores Among Cough Frequency Responders

LCQ Total Score Change from Baseline to Week 4, by Cough Frequency Response
P012 Pooled Data



Nguyen et al, 2022