FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
FDA Opening Remarks

NDA 215010: Gefapixant for the Treatment of Refractory or Unexplained Chronic Cough in Adults

Stacy Chin, MD
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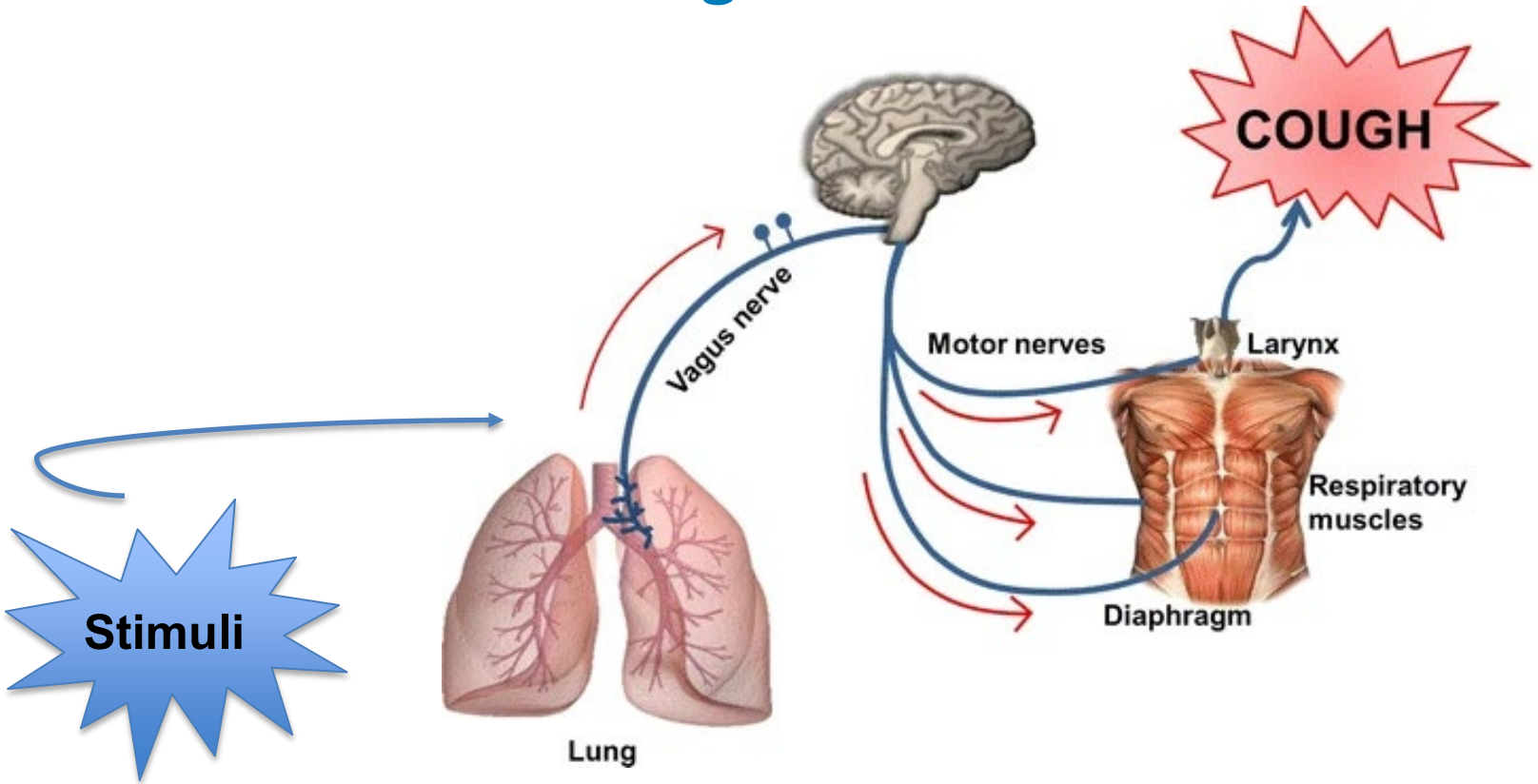
Office of Immunology and Inflammation / Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
November 17, 2023

Gefapixant

- Mechanism of action: oral P2X3 antagonist
- New molecular entity (NME), first in class, not approved in US
- Proposed indication
  - Treatment of adults with refractory or unexplained chronic cough
- Proposed dosage
  - 45 mg oral tablet twice daily

Cough Reflex Arc



Source: Adapted from Bonvini, S.J., Birrell, M.A., Smith, J.A. *et al., 2015,* Targeting TRP channels for chronic cough: from bench to bedside. *Naunyn-Schmiedeberg's Arch Pharmacol* **388**, 401–420

Epidemiology of Chronic Cough

- Defined by chronicity > 8 weeks
- Common, 5% US population
- Adults
  - Average age 55 years
  - Onset most common in 6th decade of life
- Females > Males
- Natural history not well-characterized

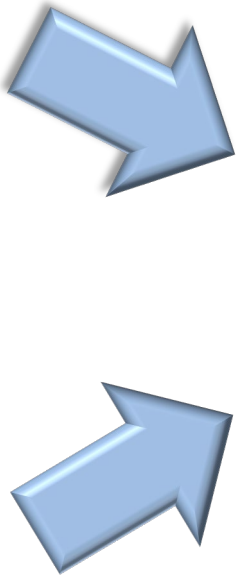
Morice AH, et al. 2020. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J.;55(1):1901136
Gibson, P, et. al, 2016, Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report, Chest, 149(1):27-44.

Refractory Chronic Cough (RCC)

- Underlying etiology identified (asthma, eosinophilic bronchitis, gastroesophageal reflux, postnasal drip, medications, etc.)
- Symptoms persist despite treatment

Unexplained Chronic Cough (UCC)

- No underlying etiology identified
- No response to empiric treatment



Chronic Cough (CC)

Current Treatment Options

- Off-label therapy – e.g., opioids, gabapentin, pregabalin, antitussives
- Speech language therapy
- No approved therapies → unmet need

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Gefapixant Clinical Development Program

Trial Identity	Trial Population	Trial Design	Number Treated, Regimen	Primary Endpoint	No. of Sites and Countries
Phase 3 Pivotal Efficacy and Safety Trials					
P030	Adults with RCC or UCC	52-week, R, DB, PC, PG	Total treated: 1314 • Gef 45 mg: 439 • Gef 15 mg: 440 • Placebo: 435	24-hour cough frequency at Week 24	175 sites in 20 countries
P027	Adults with RCC or UCC	52-week, R, DB, PC, PG	Total treated: 730 • Gef 45 mg: 243 • Gef 15 mg: 244 • Placebo: 243	24-hour cough frequency at Week 12	156 sites in 17 countries
Phase 3b Supplementary Efficacy and Safety Trials					
P042	Adult females with stress urinary incontinence and RCC or UCC	12-week, R, DB, PC, PG	Total treated: 375 • Gef 45 mg: 185 • Placebo: 190	Daily episodes of cough-induced stress urinary incontinence at Week 12	90 sites in 12 countries
P043	Adults with recent-onset (<12 months) RCC or UCC	12-week, R, DB, PC, PG	Total treated: 415 • Gef 45 mg: 206 • Placebo: 209	LCQ total score at Week 12	91 sites in 12 countries
Phase 3 Supplementary Safety Trial					
P030 China specific extension	Adults with RCC or UCC	52-week R, DB, PC, PG	Total treated: 160 • Gef 45 mg: 66 • Gef 15 mg: 27 • Placebo: 67	24-hour cough frequency at Week 24	20 sites in China

Source: Clinical reviewer. All treatment doses were given twice daily.
Abbreviations: DB, double-blind; Gef, gefapixant; LCQ, Leicester Cough Questionnaire; PC, placebo-controlled; PG, parallel group; R, randomized; RCC, refractory chronic cough; UCC, unexplained chronic cough

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P030 and P027 Primary Endpoint Results

Variable 24-hour cough frequency (coughs/hour)	Trial P030 (Week 24)		Trial P027 (Week 12)	
	Placebo	Gefapixant 45 mg	Placebo	Gefapixant 45 mg
N	419	409	222	217
Geometric mean[1] at baseline	20.4	19.4	23.6	18.9
Geometric mean[1] at Week 24 or 12	8.7	7.1	10.6	7.4
Primary endpoint/analysis/p-value				
Relative reduction (%) in geometric mean ratio (95% CI)[2]		-14.6 (-26.0, -1.5)		-17.0 (-31.5, 0.6)
p-value[2]		0.030		0.057
Median[3] cough frequency at baseline (min, max)	21.3 (0.7, 184)	19.9 (0.2, 230)	26.1 (0.3, 1054)	20.9 (0.2, 399)
Median[3] cough frequency at Week 24 or 12	11.4	7.7	11.6	8.7
Median[3] change from baseline in cough frequency at Week 24 or 12	-8.7	-9.8	-8.9	-10.5

Source: FDA Briefing Document, Table 1. N: number of subjects who had baseline and postbaseline values; CI: confidence interval; MMRM: mixed model repeated measures.
[1] Geometric means were used because these frequency data were log-transformed. [2] Based on MMRM model for response variable of change from baseline in log-transformed 24-hour cough frequency, adjusted for covariates including treatment, visit, the interaction of treatment by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit. The estimated relative reduction (relative to placebo) is calculated by 100 (e^{DIFF} -1). DIFF is the treatment difference in change from baseline at Week 12 or 24 based on the log-transformed data. [3] Median values were from post hoc analyses on all available observations at specific visits.

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P030/P027 Multiplicity-Controlled Secondary Endpoint Results

Variable Statistic	Trial P030 (Week 24) Placebo	 Gefapixant 45 mg	Trial P027 (Week 12) Placebo	 Gefapixant 45 mg
Awake cough frequency				
N [a]	419	409	222	217
Geometric mean at baseline	26.9	25.2	31.4	25.0
Geometric mean at Week 24 or 12	11.3	9.0	13.8	9.6
Geometric mean ratio (95% CI) [bc]	0.43 (0.38, 0.47)	0.36 (0.32, 0.40)	0.46 (0.40, 0.53)	0.39 (0.33, 0.45)
Relative reduction (%) in geometric mean ratio (95% CI) [c]		-15.5 (-27.0, -2.3)		-16.3 (-31.2, 1.9)
p-value		0.023		0.076
≥ 1.3-point increase from baseline in LCQ total score				
n^d/N^d (%)	245/355 (69)	262/342 (77)		
Odds ratio vs. placebo (95% CI) [e]		1.4 (1.0, 2.0)		
p-value[e]		0.040		
Responder/N (%)[f]	245/415 (59)	262/419 (63)		
Estimated difference (%) (95% CI)[g]		3.3 (-3.3, 9.9)		
≥30% reduction from baseline in 24-hr cough frequency				
n^d/N^d (%)	245/368 (67)	248/347 (72)	135/205 (66)	133/194 (69)
Odds ratio vs. placebo (95% CI) [e]		1.2 (0.9, 1.7)		1.2 (0.8, 1.8)
p-value[e]		0.188		0.435
Responder/N (%)[f]	245/432 (57)	248/434 (57)	135/232 (58)	133/237 (56)
Estimated difference (%) (95% CI)[g]		0.4 (-6.1, 7.0)		-2.2 (-11.2, 6.8)

[a] N=Number of subjects who had baseline and postbaseline assessments. [b] Based on subjects with nonmissing values at baseline and Week 24. [c] Based on the MMRM model for response variable of change from baseline in log-transformed 24-hour cough frequency, adjusted for covariates including treatment, visit, the interaction of treatment by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit . The estimated relative reduction (relative to placebo) is calculated by 100 (e^{DIFF} -1). DIFF is the treatment difference in change from baseline at Week 24 based on the log-transformed data. [d] N=Number of subjects with available data at Week 24; n=number of responders at Week 24. [e] Based on the logistic regression model with terms of treatment, visit, treatment-by-visit interaction, gender, region, baseline, and baseline-by-visit interaction among subjects who had baseline and post baseline values. [f] N=number of subjects who had baseline values. Subjects with nonmissing baseline data but missing Week 24 data are imputed as nonresponders. [g] Based on the Mietinnen and Nurminen method.

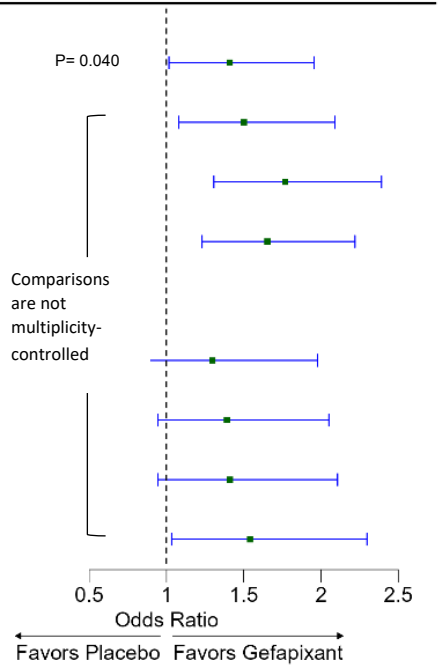
Source: FDA Statistical Reviewer

P030/P027 Patient Reported Outcome (PRO) Secondary Endpoint Results: Odds ratios

Only multiplicity controlled endpoint

Change from Baseline in Secondary Endpoints

Variable	Gefapixant n/N[a]	Placebo n/N[a]	Percent Responders (%) (Gefapixant v. Placebo)	Odds Ratio v. Placebo (95% CI)
Study P030				
≥1.3 increase in LCQ total score	262/342	245/355	76.6 v 69.0	1.4 (1.0, 2.0)
≥1.3 reduction in mean weekly CSD total score	253/331	237/346	76.4 v 68.5	1.5 (1.1, 2.1)
≥2.7 reduction in mean weekly CSD total score	186/331	154/346	56.2 v 44.5	1.8 (1.3, 2.4)
≥30 mm reduction in Cough Severity VAS score	178/331	150/346	53.8 v 43.4	1.7 (1.2, 2.2)
Study P027				
≥1.3 increase in LCQ total score	134/194	123/196	69.1 v 62.8	1.3 (0.9, 2.0)
≥1.3 reduction in mean weekly CSD total score	129/204	112/211	63.2 v 53.1	1.4 (0.9, 2.1)
≥2.7 reduction in mean weekly CSD total score	84/204	65/211	41.2 v 30.8	1.4 (0.9, 2.1)
≥30 mm reduction in Cough Severity VAS score	87/204	63/211	42.6 v 29.9	1.5 (1.0, 2.3)



Source: FDA Briefing Document, Figure 1
Gefapixant: gefapixant 45 mg. Change from baseline at Week 24 (Trial P030)/12 (Trial P027).
n, number of responders; N, number of subjects with available data at Week 24 for Trial P030 (Week 12 for Trial P027) Abbreviations: CI, confidence interval; CSD, cough severity diary; LCQ, Leicester Cough Questionnaire; VAS, visual analog scale

Safety

- Taste disturbance
  - Common (2/3 of subjects)
  - Rapid onset (median 2 days)
  - Reversible upon discontinuation
  - Mild to moderate intensity
  - Impacts tolerability

Key Findings

- Wide variability in baseline cough frequency
- High placebo response
- Small reduction in cough frequency compared to placebo
  - Relative reduction in geometric mean ratio 15-17%
  - Median absolute reduction ~1-2 coughs/hour beyond placebo
  - Statistical significance in 1 of 2 trials using validated recount cough data and prespecified analysis
- Small effect on some PRO endpoints
- Taste disturbances common

Issues for Discussion

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    - Clinically meaningful improvements not established
    - Concerns about Leicester Cough Questionnaire (LCQ)
    - Lack of multiplicity control for other PRO endpoints

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    - Concerns about Leicester Cough Questionnaire (LCQ)
    - Lack of multiplicity control for other PRO endpoints
  - Potential unblinding due to taste disturbances

Statute and Regulations

- 1962 Drug Amendments (Kefauver-Harris) to the Federal Food, Drug, and Cosmetic Act (FD&C Act) included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence" before approval

- An NDA can be rejected if, among other reasons:

"…there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; …" (21 U.S.C. § 355(d)

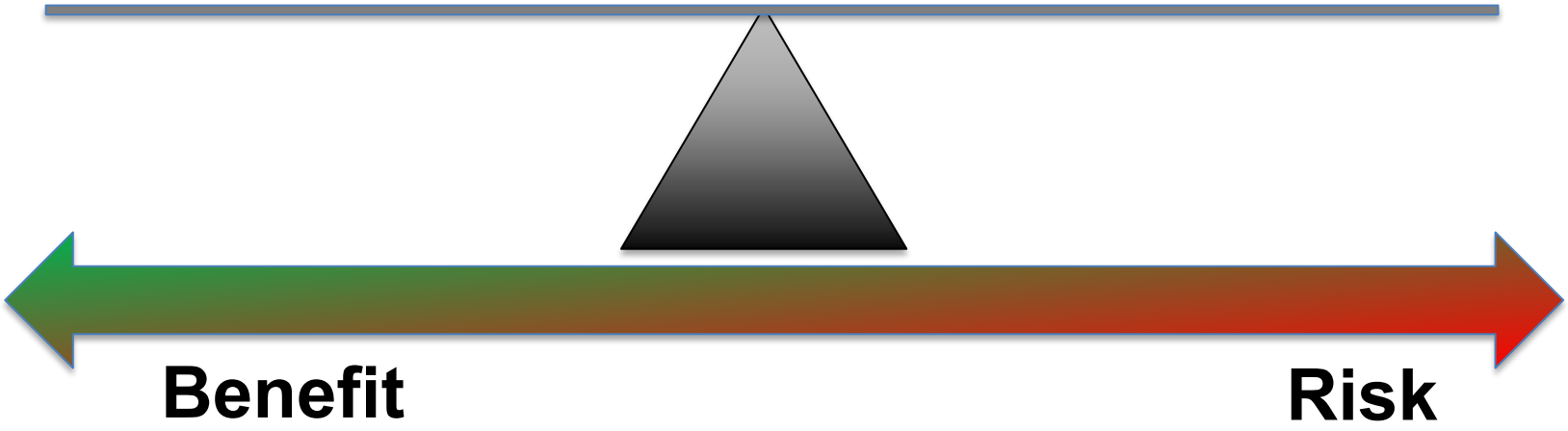
- "Totality of evidence" not in regulations

Statutory Standard for Substantial Evidence of Effectiveness

- Substantial evidence is defined as:

  *"evidence consisting of **adequate and well-controlled investigations**, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" (21 U.S.C. § 355(d))*

Benefit / Risk Framework



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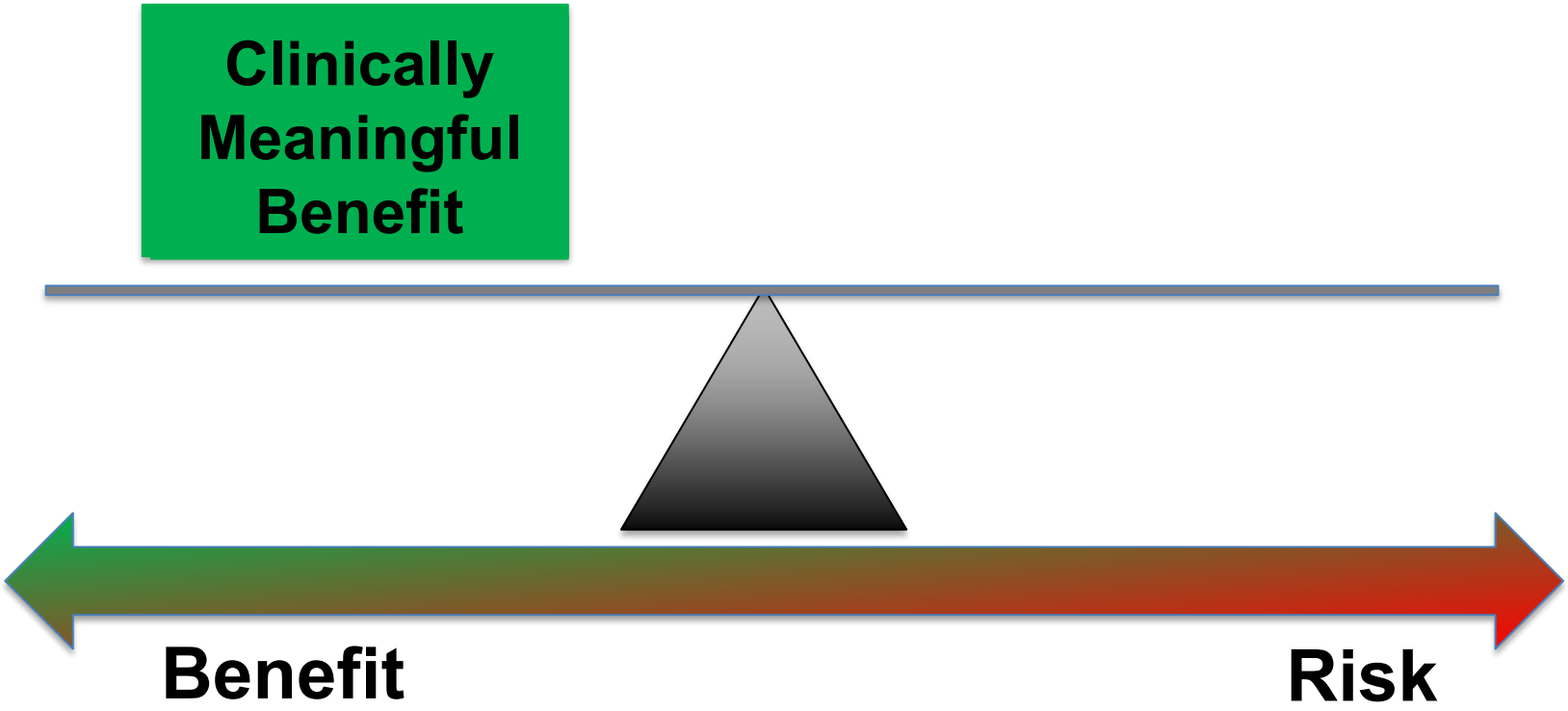

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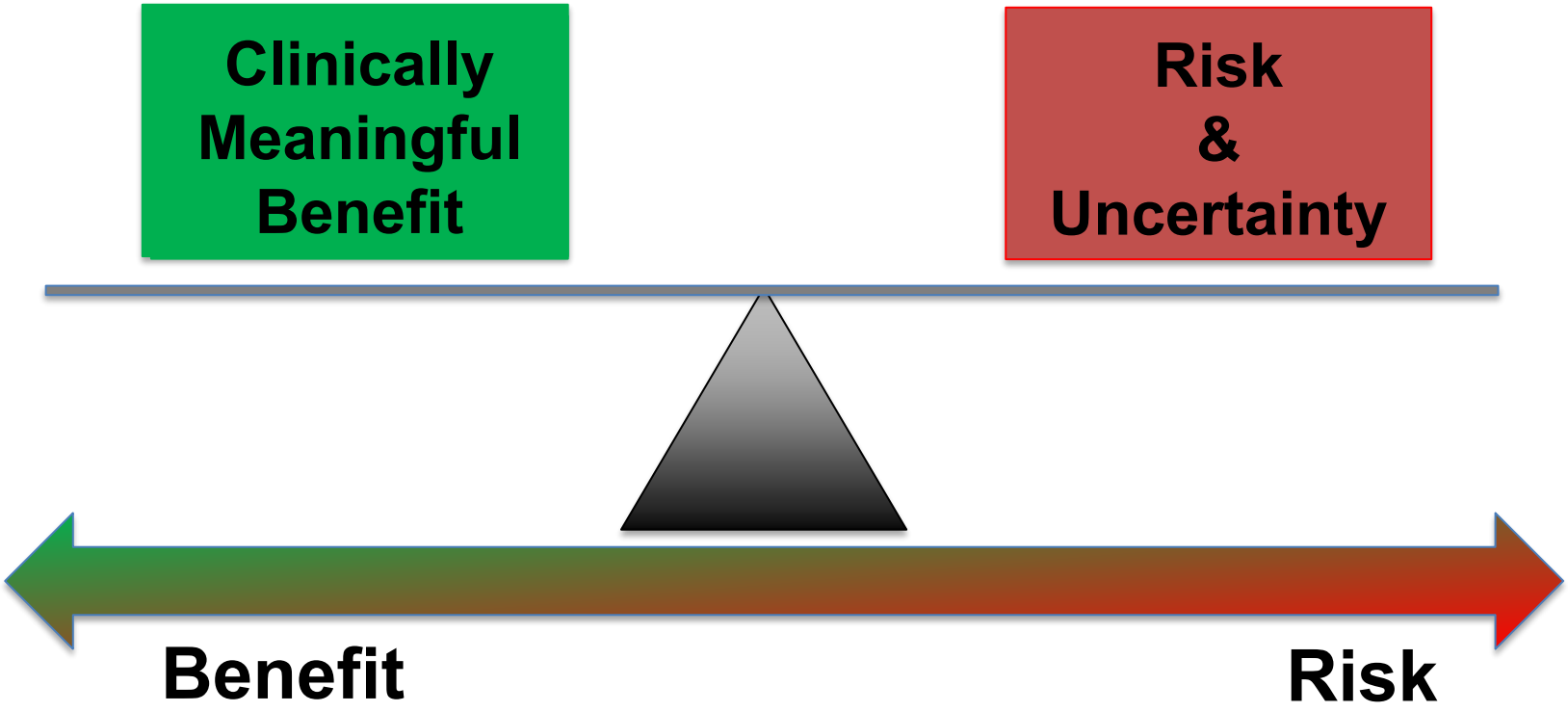

Discussion Points

- Discuss the evidence of effectiveness for gefapixant for the treatment of refractory or unexplained chronic cough in adults. Specifically address the following:
  - The small reduction in cough frequency compared to placebo and the clinical meaningfulness of the reduction in cough frequency
  - The observed results from PROs and whether these results provide compelling evidence to inform the clinical meaningfulness of the reduction in cough frequency
  - Potential unblinding of patients due to taste disturbance and its impact on interpretation of cough frequency and PRO results

Discussion Points

- Discuss the overall benefit/risk assessment of gefapixant for the treatment of adults with refractory or unexplained chronic cough, a symptomatic condition.

Voting Question

- Does the evidence demonstrate that gefapixant provides a clinically meaningful benefit to adult patients with refractory or unexplained chronic cough, given the small reduction in cough frequency and results from PROs? Provide a rationale for your vote.
  - If you conclude that there is insufficient evidence of a clinically meaningful benefit, describe the evidence that could be collected to show a benefit that is clinically meaningful.


FDA
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ADMINISTRATION

FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
Clinical and Statistical Presentation

NDA 215010: Gefapixant for the Treatment of Refractory or Unexplained Chronic Cough in Adults

Rachel Bean, MD
Medical Officer
Division of Pulmonology, Allergy, and Critical Care (DPACC)
Office of Immunology and Inflammation (OII)
Office of New Drugs (OND)

Susan Mayo, MS
Statistical Reviewer
Division of Biometrics III (DB III)
Office of Biostatistics (OB)
Office of Translational Science (OTS)

Center for Drug Evaluation and Research (CDER)

U.S. Food and Drug Administration (FDA)

November 17, 2023

Outline

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  - Rachel Bean, MD
- Statistical Review of Efficacy
  - Susan Mayo, MS
- Clinical Considerations
  - Rachel Bean, MD

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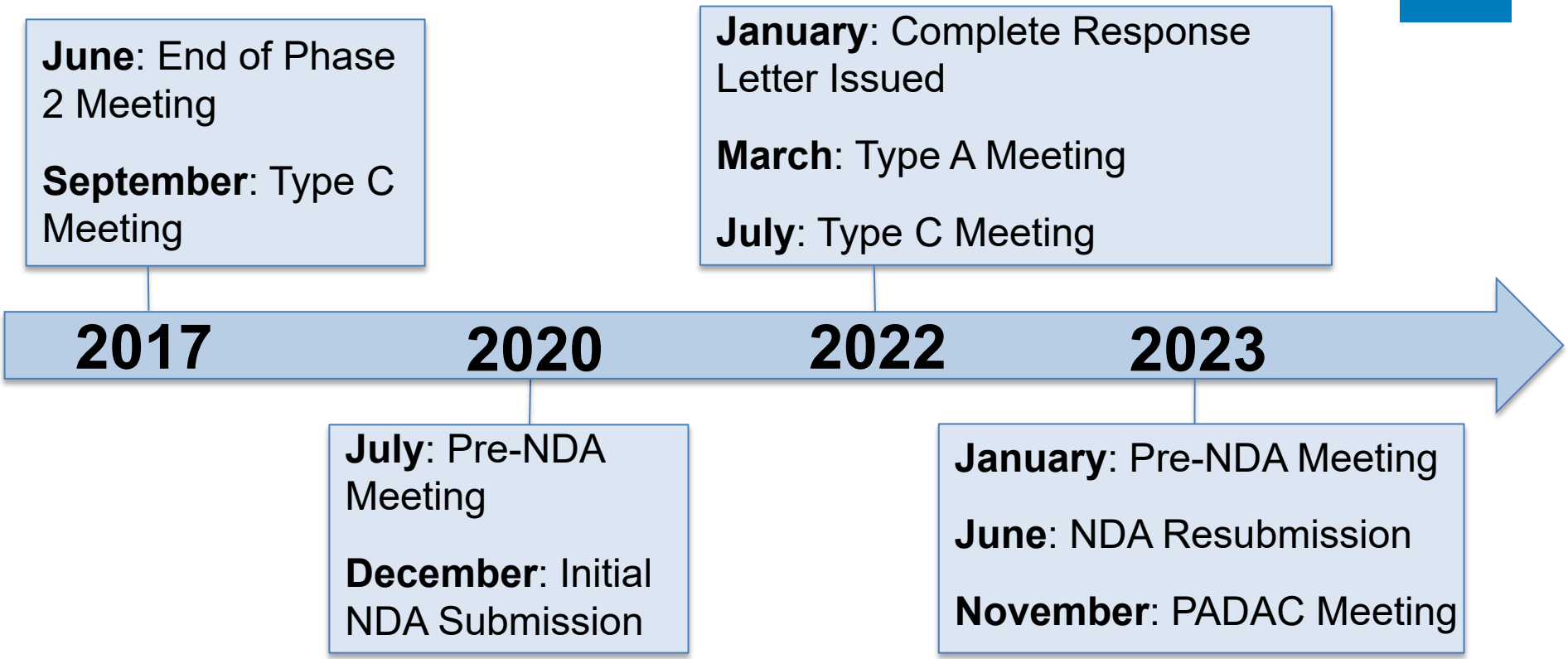
OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

Clinical Development History



Initial NDA and Complete Response

- NDA submitted December 21, 2020
  - Two pivotal trials: P030 and P027

- Complete Response issued January 20, 2022
  - Insufficient validation of cough counting system
  - Additional concerns to be addressed
    - Small reduction in cough frequency of unclear clinical meaningfulness
    - Secondary endpoint results: not statistically persuasive; unclear meaningfulness

Deficiencies in Producing the Unvalidated, Original Cough Counts

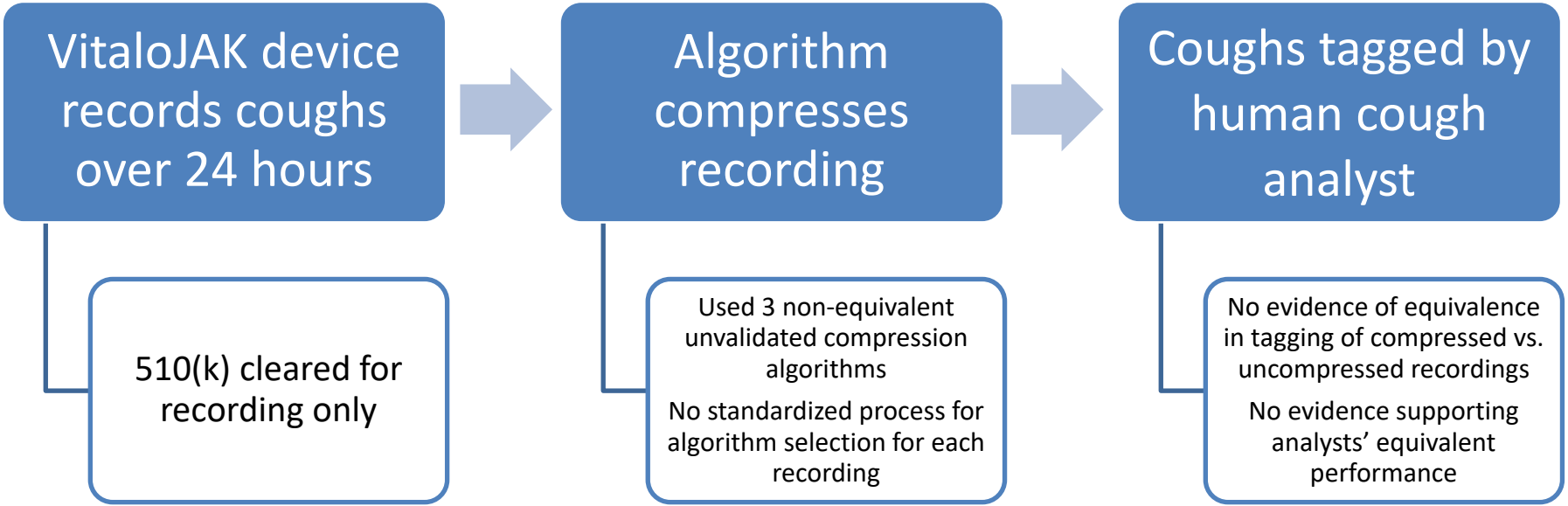


Figure generated by clinical reviewer.

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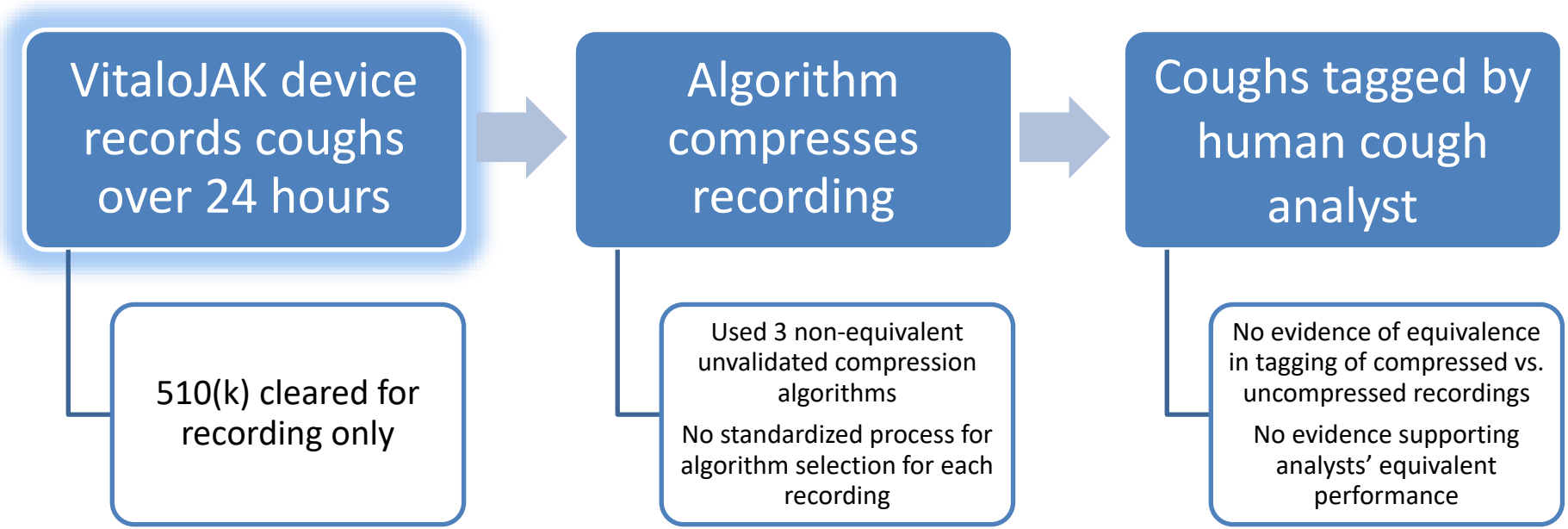
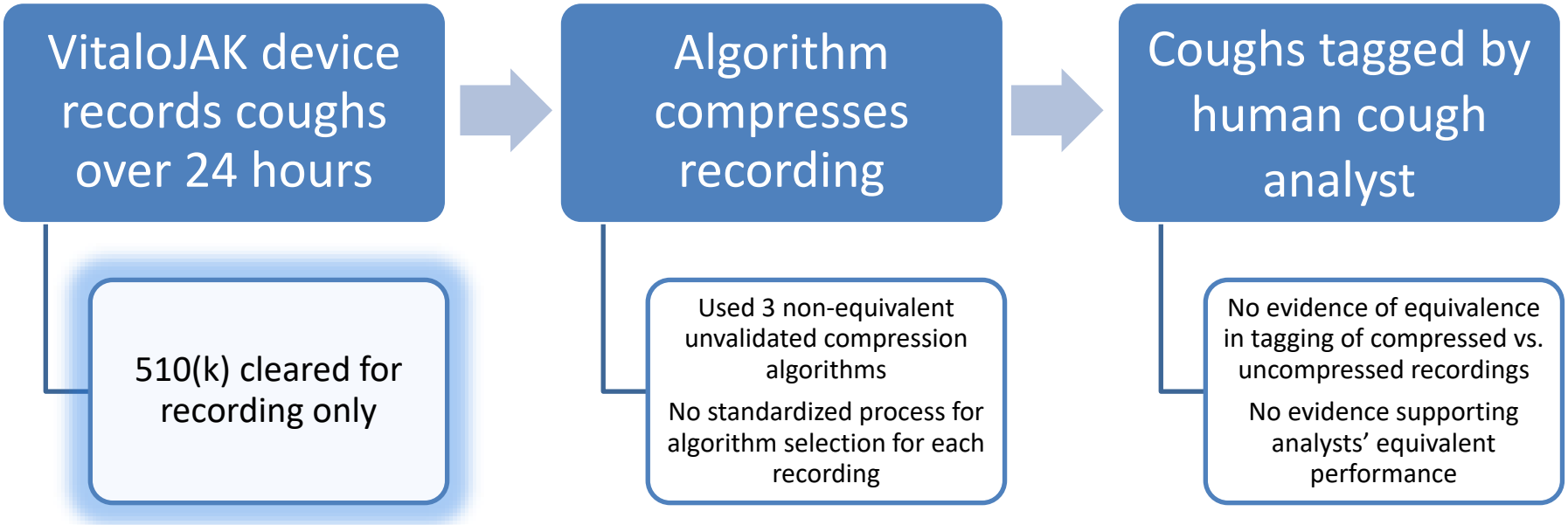


Deficiencies in Producing the Unvalidated, Original Cough Counts



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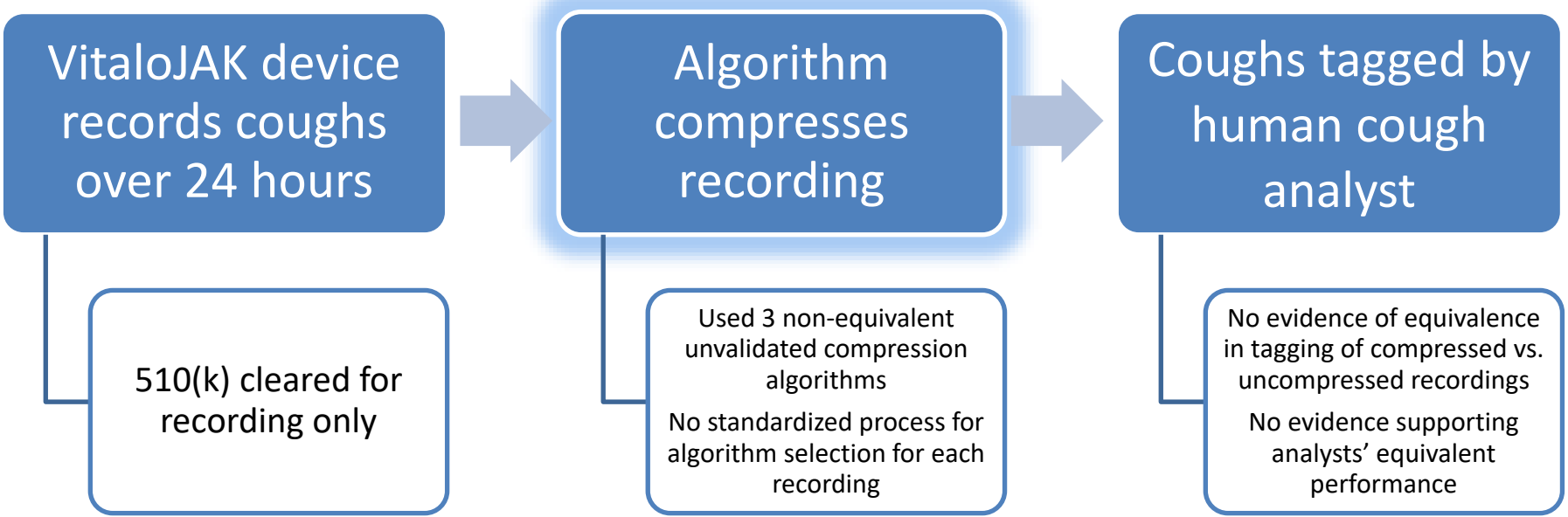

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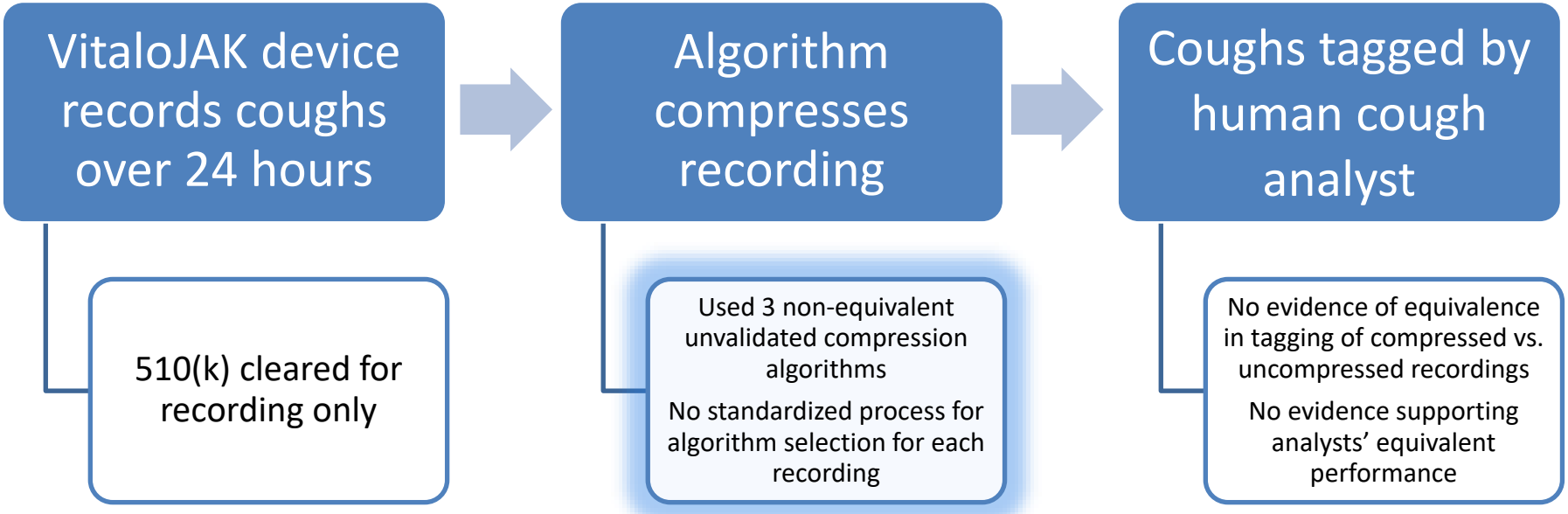

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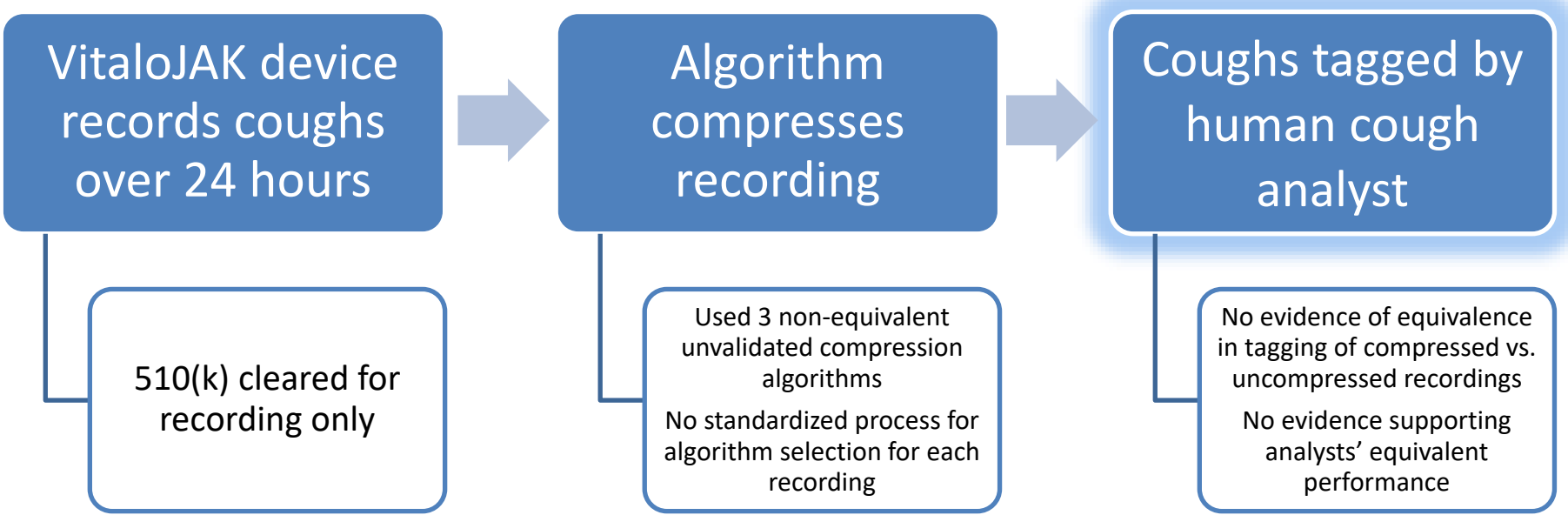

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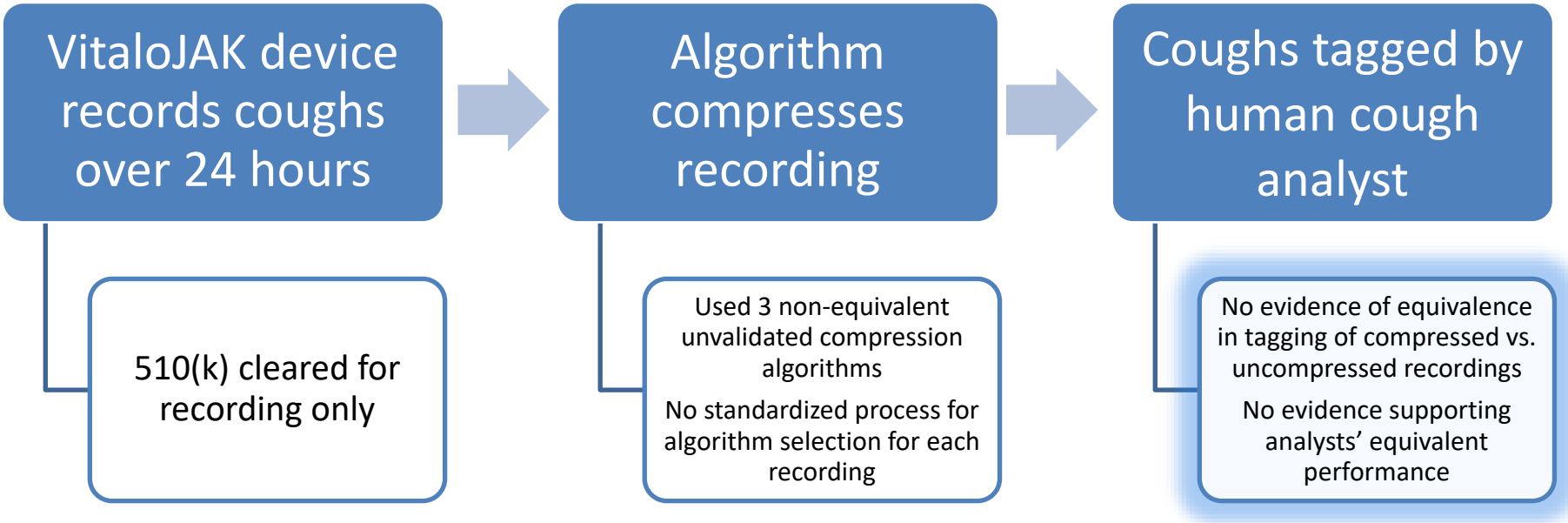
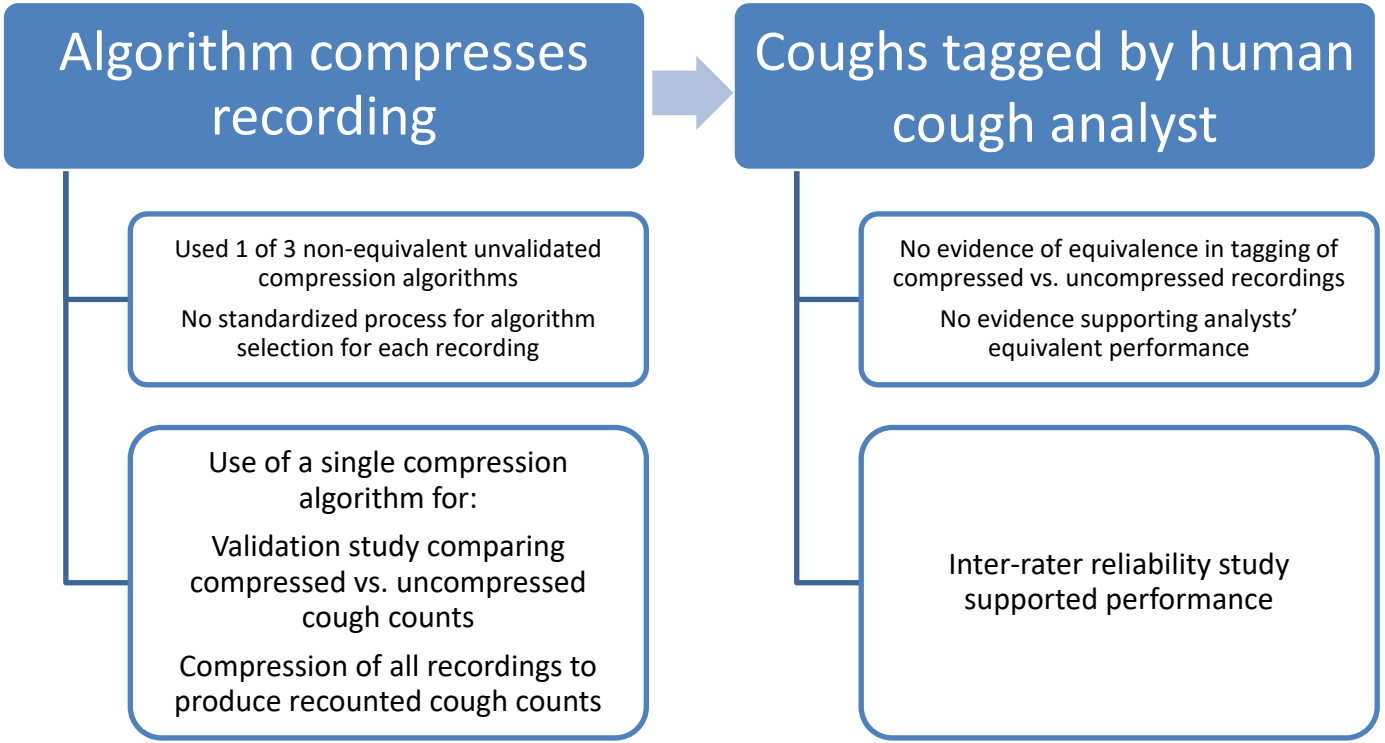


Validated System to Produce Recounted Cough Counts



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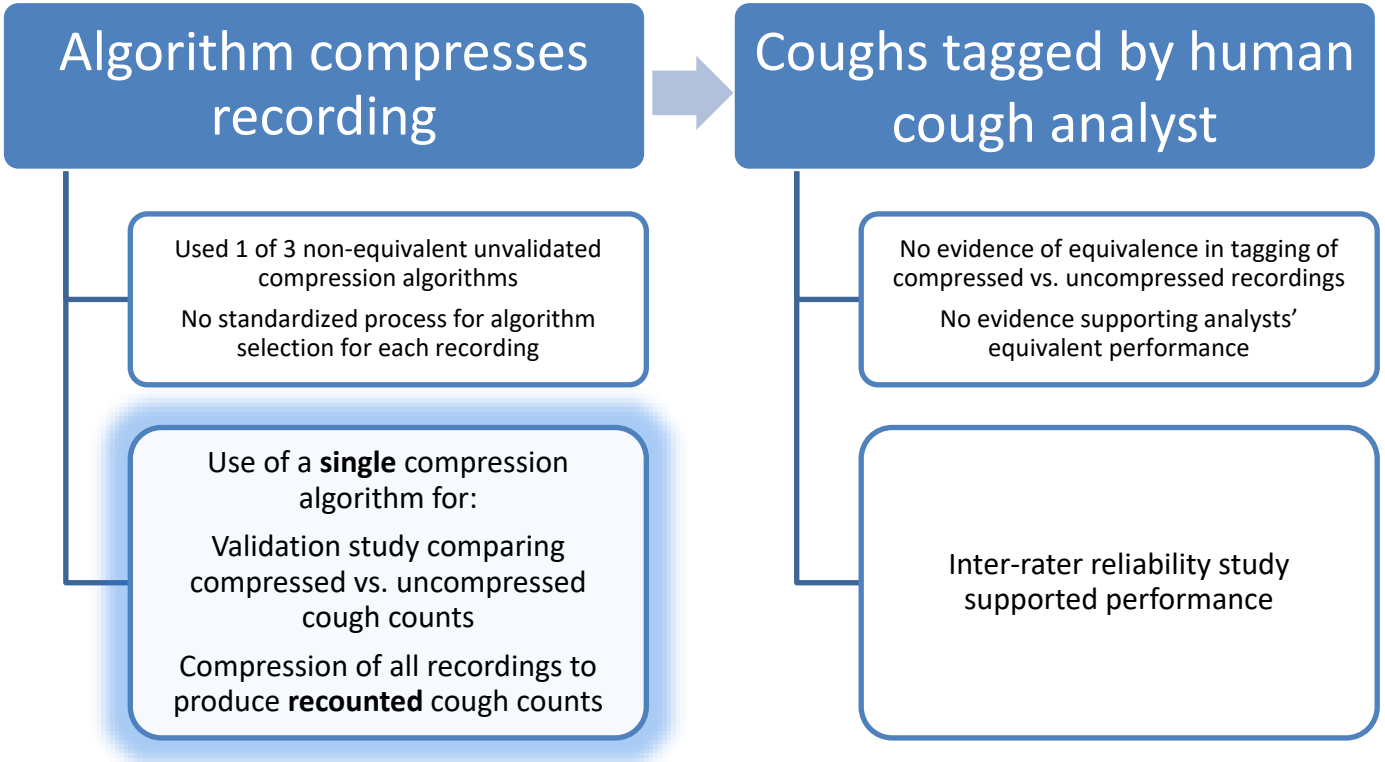

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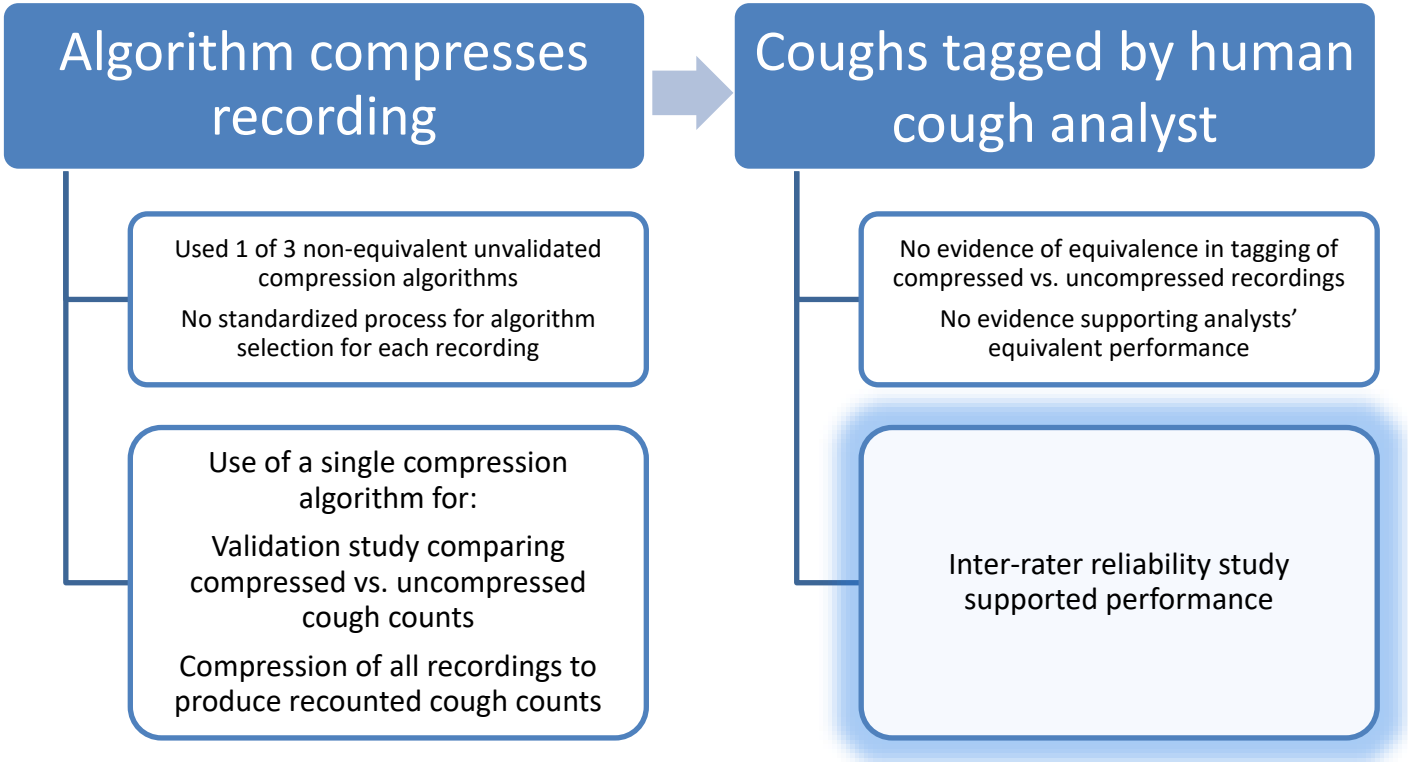

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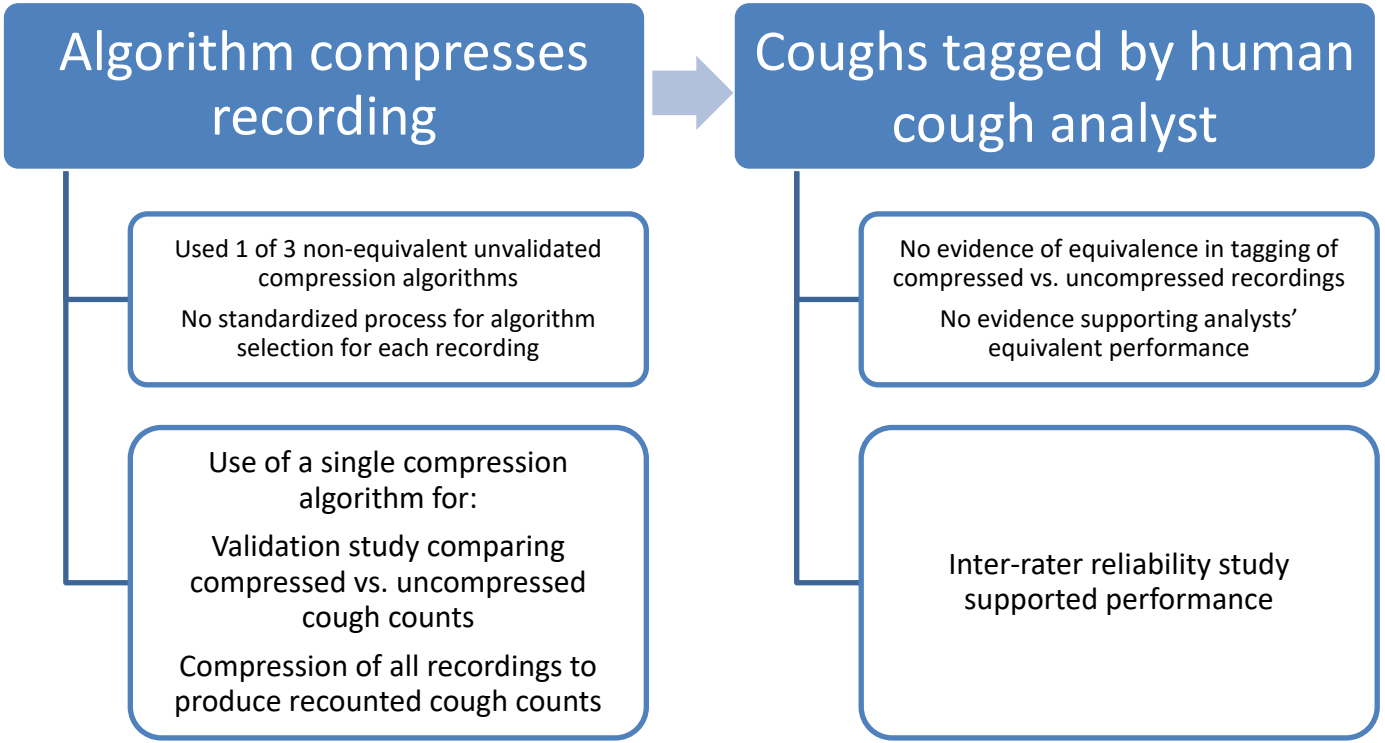

Note: Validation of the VitaloJAK device and compression algorithm used in the gefapixant program is unique to the gefapixant pivotal trials and in no way implies validation beyond the existing 510(k) device clearance.

Clinical Development Program

Trial Identity	Trial Population	Trial Design	Number Treated, Regimen	Primary Endpoint	No. of Sites and Countries
Phase 3 Pivotal Efficacy and Safety Trials					
P030	Adults with RCC or UCC	52-week, R, DB, PC, PG	Total treated: 1314 • Gef 45 mg: 439 • Gef 15 mg: 440 • Placebo: 435	24-hour cough frequency at Week 24	175 sites in 20 countries
P027	Adults with RCC or UCC	52-week, R, DB, PC, PG	Total treated: 730 • Gef 45 mg: 243 • Gef 15 mg: 244 • Placebo: 243	24-hour cough frequency at Week 12	156 sites in 17 countries
Phase 3b Supplementary Efficacy and Safety Trials					
P042	Adult females with stress urinary incontinence and RCC or UCC	12-week, R, DB, PC, PG	Total treated: 375 • Gef 45 mg: 185 • Placebo: 190	Daily episodes of cough-induced stress urinary incontinence at Week 12	90 sites in 12 countries
P043	Adults with recent-onset (<12 months) RCC or UCC	12-week, R, DB, PC, PG	Total treated: 415 • Gef 45 mg: 206 • Placebo: 209	LCQ total score at Week 12	91 sites in 12 countries
Phase 3 Supplementary Safety Trial					
P030 China specific extension	Adults with RCC or UCC	52-week R, DB, PC, PG	Total treated: 160 • Gef 45 mg: 66 • Gef 15 mg: 27 • Placebo: 67	24-hour cough frequency at Week 24	20 sites in China

Source: Clinical reviewer. All treatment doses were given twice daily.
Abbreviations: DB, double-blind; Gef, gefapixant; LCQ, Leicester Cough Questionnaire; PC, placebo-controlled; PG, parallel group; R, randomized; RCC, refractory chronic cough; UCC, unexplained chronic cough

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Pivotal Trial Efficacy Endpoints

- Primary endpoint
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- Secondary endpoints, multiplicity-controlled
  - Awake cough frequency
  - ≥ 1.3-point increase from baseline in LCQ total score (P030 only)
  - ≥ 30% reduction from baseline in 24-hour cough frequency
- Other secondary endpoints
  - ≥ 1.3-point reduction from baseline in mean weekly CSD total score
  - ≥ 2.7-point reduction from baseline in mean weekly CSD total score
  - ≥ 30 mm reduction from baseline in Cough Severity VAS score

Abbreviations: CSD, Cough Severity Diary; VAS, Visual Analog Scale

Evaluating Efficacy via Cough Frequency

- No regulatory precedent for primary endpoint for chronic cough (CC)
- FDA agreed to 24-hour cough frequency as primary efficacy endpoint

- Supporting rationale
  - Objective measure
  - Phase 2 data: 30% relative reduction in geometric mean ratio vs. placebo
- Challenges
  - Frequency is only one aspect of cough
  - No established threshold for meaningful within-patient change

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PRO Endpoints for CC

- Advantages
  - Provide direct evidence of how patients feel
  - Provide insight beyond objective cough frequency
    - Severity, coughing bouts, related symptoms

- Limitations
  - Lack of regulatory experience with PRO selection for CC indication
  - Interpretation is complex and requires supportive evidence
  - No established thresholds for meaningful within-patient change

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Trials Collected a Variety of PRO Endpoints

- LCQ total score
  - The only multiplicity-controlled PRO endpoint (P030)
    - Responder analysis (≥1.3 points)

- Other PRO secondary endpoints were not multiplicity-controlled
  - LCQ total score: additional responder thresholds
  - LCQ domain-level endpoints
  - Cough Severity Diary (CSD)
  - Cough Severity Visual Analog Scale (VAS)

Leicester Cough Questionnaire* (LCQ)

*Basis for the only multiplicity-controlled PRO endpoint, in P030

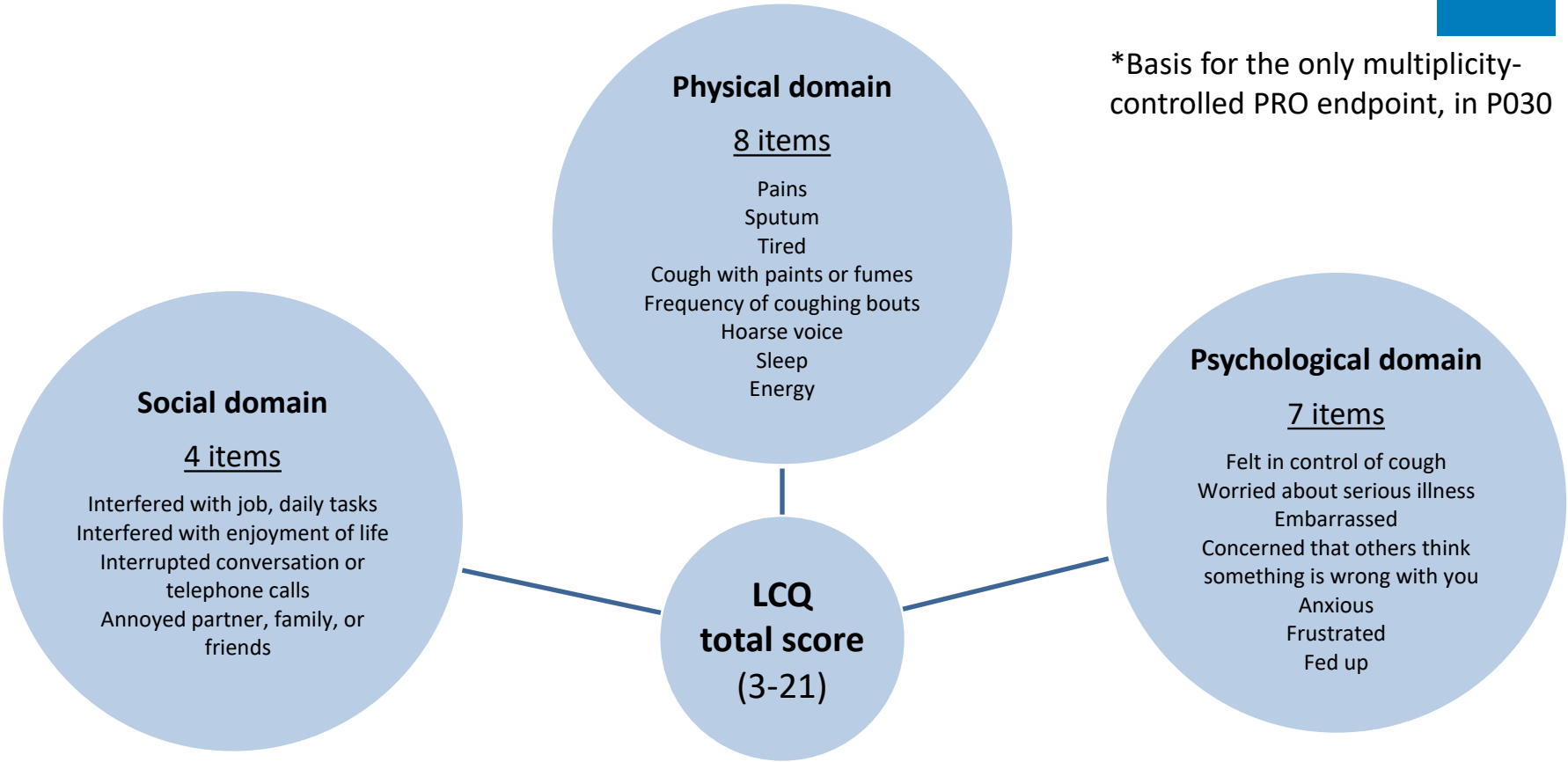


Figure generated by clinical reviewer.

Cough Severity Diary (CSD)

Used in exploratory analyses only

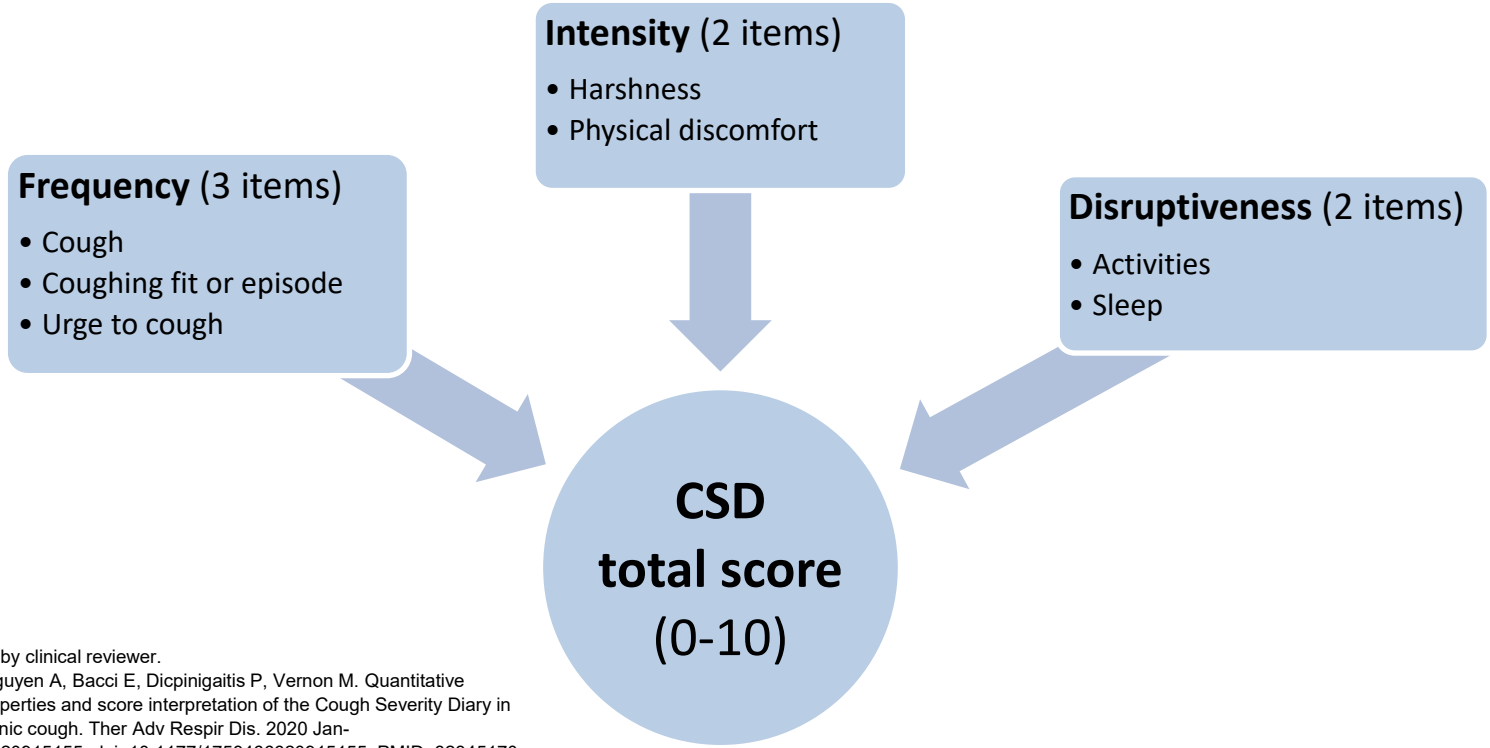
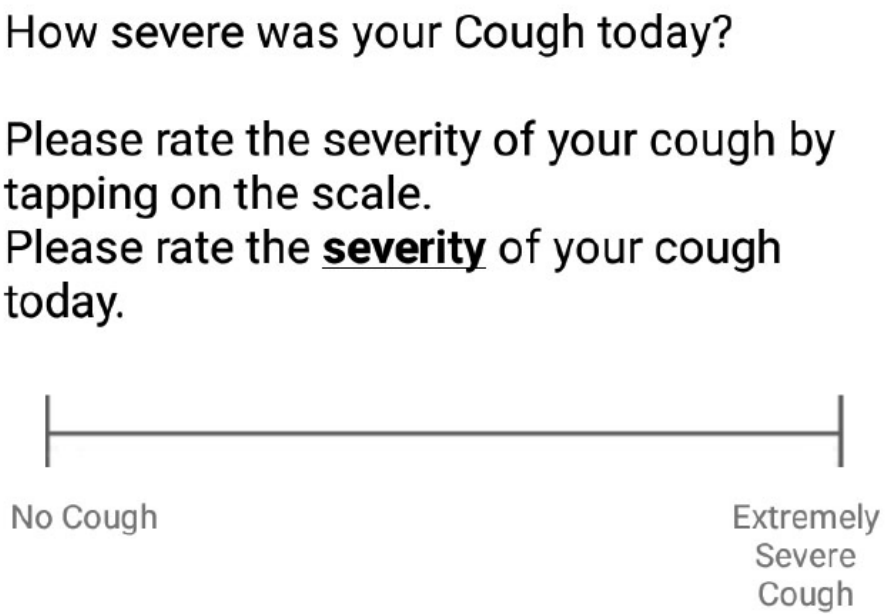


Figure generated by clinical reviewer.
Source: Martin Nguyen A, Bacci E, Dicpinigaitis P, Vernon M. Quantitative measurement properties and score interpretation of the Cough Severity Diary in patients with chronic cough. Ther Adv Respir Dis. 2020 Jan-Dec;14:1753466620915155. doi: 10.1177/1753466620915155. PMID: 32345170; PMCID: PMC7225816.

Cough Severity Visual Analog Scale (VAS)

Used in exploratory analyses only



Source: Appendix 5 and Appendix 6 of the Applicant's response to the August 9, 2023, Information Request (1 of 2).

SAFETY OVERVIEW

Taste Disturbances are Frequent and Non-Severe

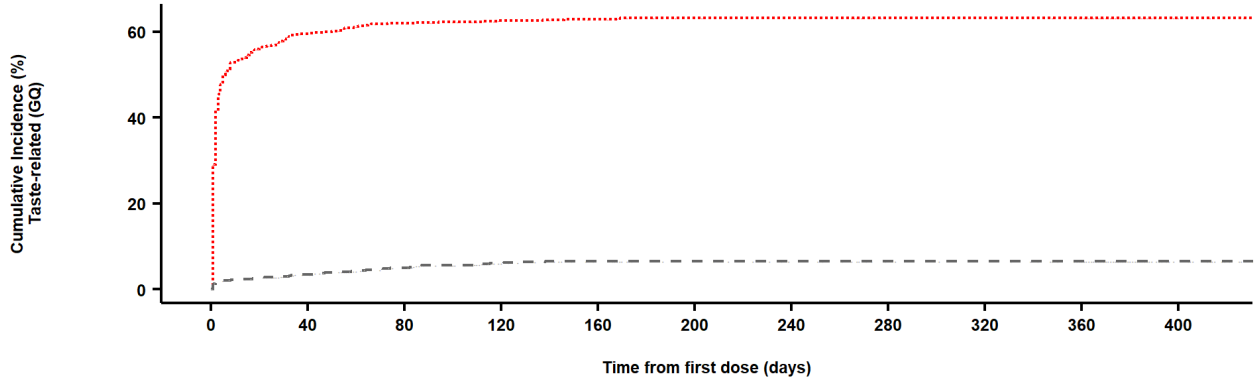
Taste-Related AEs Occurring in ≥1 Subject in Any Treatment Arm, ApAT, Pooled Safety Dataset

Preferred Term Maximum Intensity	Placebo N=675 n (%)	Gefapixant 15 mg N=686 n (%)	Gefapixant 45 mg N=683 n (%)
At least 1 taste-related AE	47 (7.0)	120 (17.5)	447 (65.4)
Mild	41 (6.1)	93 (13.6)	289 (42.3)
Moderate	6 (0.9)	25 (3.6)	141 (20.6)
Severe	0	2 (0.3)	17 (2.5)
Ageusia	6 (0.9)	16 (2.3)	100 (14.6)
Dysgeusia	36 (5.3)	78 (11.4)	281 (41.1)
Hypergeusia	2 (0.3)	2 (0.3)	5 (0.7)
Hypogeusia	4 (0.6)	22 (3.2)	73 (10.7)
Taste disorder	3 (0.4)	10 (1.5)	61 (8.9)

Source: Integrated Summary of Safety Table 5.3.5.3.3-cough: 31; confirmed by clinical reviewer.
Abbreviations: AE, adverse event; APaT, all participants as treated; N, number of subjects in treatment arm; n, number of subjects with adverse event

Time to Onset of Taste-Related Disorders

Safety Population (P027, P030, and P030 China extension)



Number at risk

MK-7264 45 mg BID	748	284	253	231	226	218	217	207	207	203	10
Placebo	741	687	653	610	595	586	579	566	564	553	21

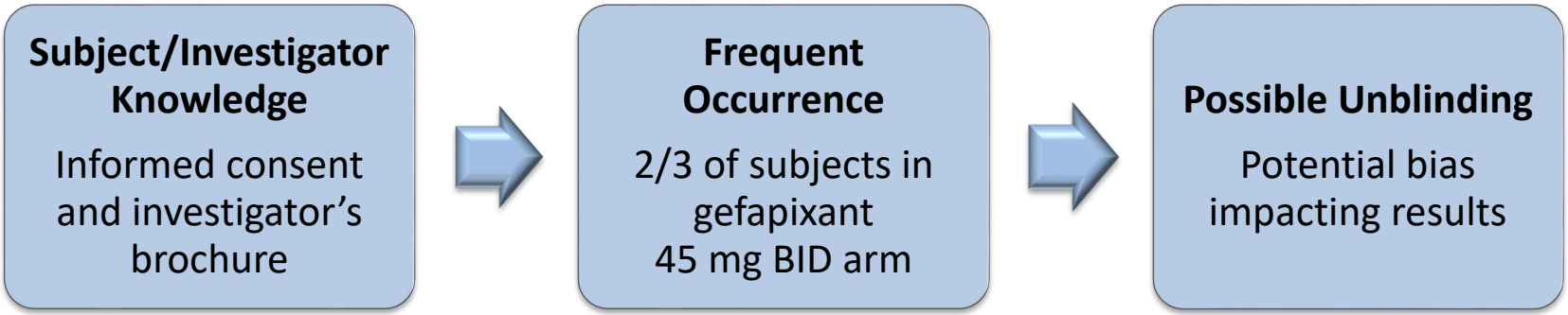
Cumulative Number of Patients with Event

MK-7264 45 mg BID	0	445	464	468	470	473	473	473	473	473	473
Placebo	0	26	37	45	48	48	48	48	48	48	48

MK-7264 45 mg BID Placebo

Source: adae.xpt; Software: R
Abbreviations: BID, twice daily; GQ, grouped query

Taste Disturbances as a Potential Source of Bias



Outline

- Overview of the Clinical Program and Review of Safety
  - Rachel Bean, MD
- **Statistical Review of Efficacy**
  - **Susan Mayo, MS**
- Clinical Considerations
  - Rachel Bean, MD

Pivotal Trial Efficacy Endpoints

Landmark timepoints: P030 (Week 24), P027 (Week 12)
Cough frequency based on recounted data using validated method

- Primary endpoint
  - 24-hour cough frequency
- Secondary endpoints, multiplicity-controlled
  - Awake cough frequency
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- Other secondary endpoints
  - ≥ 1.3-point reduction from baseline in mean weekly CSD total score
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  - ≥ 30 mm reduction from baseline in Cough Severity VAS score

Multiplicity Hierarchy for Primary & Secondary Endpoints

	P030 (all at Week 24)	P027 (all at Week 12)
1	Gefapixant 45 mg is superior to placebo in reducing 24-hour cough frequency	Gefapixant 45 mg is superior to placebo in reducing 24-hour cough frequency
2	Gefapixant 45 mg is superior to placebo in reducing awake cough frequency	Gefapixant 15 mg is superior to placebo in reducing 24-hour cough frequency
3	Gefapixant 45 mg is superior to placebo on the proportion of participants with a ≥1.3-point increase from baseline in LCQ total score	Gefapixant 45 mg is superior to placebo in reducing awake cough frequency
4	Gefapixant 45 mg is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour cough frequency	Gefapixant 45 mg is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour cough frequency
5	Gefapixant 15 mg is superior to placebo in reducing 24-hour cough frequency	Gefapixant 15 mg is superior to placebo in reducing awake cough frequency
6	Gefapixant 15 mg is superior to placebo in reducing awake cough frequency	Gefapixant 15 mg is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour cough frequency
7	Gefapixant 15 mg is superior to placebo on the proportion of participants with a ≥1.3-point increase from baseline in LCQ total score	
8	Gefapixant 15 mg is superior to placebo with respect to the proportion of participants with a ≥30% reduction from baseline in 24-hour cough frequency	

Source: Section 10.8 for Multiplicity in trial protocols for P030 and P027.
Abbreviation: LCQ, Leicester Cough Questionnaire

Subject Disposition

	Trial P030 at Week 24			Trial P027 at Week 12		
	Placebo n (%)	Gefapixant 15mg n (%)	Gefapixant 45mg n (%)	Placebo n (%)	Gefapixant 15mg n (%)	Gefapixant 45mg n (%)
Randomized	436	442	439	244	244	244
Treated (FAS)	435	440	439	243	244	243
Discontinued Treatment	66 (15.2)	82 (18.6)	125 (28.5)	30 (12.3)	28 (11.5)	61 (25.0)
- Adverse Event	21 (4.8)	34 (7.7)	88 (20.1)	7 (2.9)	8 (3.3)	40 (16.4)
- Death	0	1 (0.2)	0	1 (0.4)	0	0
- Lost to follow-up	5 (1.1)	2 (0.4)	3 (0.7)	0	0	0
- Treatment noncompliance	0	0	2 (0.5)	0	0	0
- Other*	5 (1.1)	5 (1.1)	5 (1.1)	1 (0.4)	1 (0.4)	2 (0.5)
- Withdrawal by subject	37 (8.5)	44 (9.9)	30 (6.8)	21 (8.6)	20 (8.2)	21 (8.6)
Discontinued Study	54 (12.4)	74 (16.6)	84 (19.2)	45 (18.4)	44 (18.0)	60 (24.5)

Source: adbase.xpt; FDA statistical analyst. *Physician decision, Pregnancy, Other

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Source: adbase.xpt; FDA statistical analyst. *Physician decision, Pregnancy, Other. Abbreviation: FAS, Full Analysis Set

Demographics and Baseline Characteristics

Characteristic	Trial P030 Placebo N=435	Trial P030 Gefapixant 15 mg N=440	Trial P030 Gefapixant 45 mg N=439	Trial P027 Placebo N=243	Trial P027 Gefapixant 15 mg N=244	Trial P027 Gefapixant 45 mg N=243
Sex (n, %)						
Female	326 (74.9)	329 (74.8)	329 (74.9)	181 (74.5)	181 (74.2)	180 (74.1)
Male	109 (25.1)	111 (25.2)	110 (25.1)	62 (25.5)	63 (25.8)	63 (25.9)
Age (years)						
Mean (SD)	58 (12.6)	58.6 (11.4)	57.8 (12.4)	57.9 (13.1)	59.6 (11.7)	59.4 (13.1)
Median (min, max)	60 (19, 84)	60 (22, 88)	59 (19, 87)	61 (21, 81)	61 (22, 89)	61 (19, 85)
Primary diagnosis (n, %)						
Refractory CC	278 (63.9)	273 (62.0)	279 (63.6)	148 (60.9)	141 (57.8)	139 (57.2)
Unexplained CC	157 (36.1)	167 (38.0)	160 (36.4)	95 (39.1)	103 (42.2)	104 (42.8)
Duration of CC (n, %)						
<10 years	247 (56.8)	231 (52.5)	258 (58.8)	127 (52.3)	130 (53.3)	134 (55.1)
≥10 years	188 (43.2)	209 (47.5)	181 (41.2)	116 (47.7)	114 (46.7)	109 (44.9)
Duration of CC (years)						
Mean (SD)	10.7 (8.8)	11.9 (10.7)	10.9 (9.9)	11.7 (9.9)	11.8 (9.1)	11.2 (9.4)
Median (min, max)	8 (2, 51)	9 (1, 75)	7 (2, 65)	9 (2, 59)	9 (2, 45)	8 (2, 56)
24-Hour cough frequency (n, %)						
Mean (SD)	28.5 (24.6)	28.1 (22.2)	28.6 (29.9)	39.5 (81.1)	28.0 (22.0)	30.2 (39.4)
Median (min, max)	21.3 (0.7, 183.6)	22.1 (1.0, 151.6)	19.9 (0.2, 230.1)	26.1 (0.3, 1053.5)	21.8 (0.8, 132.8)	20.9 (0.2, 399.1)
Q1, Q3	12.4, 37.1	11.4, 39.5	10.9, 37.9	12.9, 45.5	13.2, 37.3	12.2, 36.2
Geometric mean	20.4	20.2	19.4	23.6	20.9	18.9

Source: FDA statistical analyst. Abbreviation: SD, standard deviation

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  - ≥ 30 mm reduction from baseline in Cough Severity VAS score

Primary Endpoint: 24-Hour Cough Frequency

	Trial P030 (Week 24)		Trial P027 (Week 12)	
Statistic	**Placebo**	**Gefapixant 45 mg**	**Placebo**	**Gefapixant 45 mg**
N^	419	409	222	217
Geometric mean at baseline	20.4	19.4	23.6	18.9
Geometric mean at Week 24 or 12	8.7	7.1	10.6	7.4
Geometric mean ratio (95% CI)*	0.43 (0.39, 0.48)	0.37 (0.33, 0.41)	0.47 (0.41, 0.54)	0.39 (0.34, 0.45)
Relative reduction (%) in geometric mean ratio (95% CI) **		-14.6 (-26.0, -1.5)		-17.0 (-31.5, 0.6)
p-value*		0.030		0.057

Source: adeff.xpt; Table 4-2 in CSR Addenda for P030 and P027, validated by statistical analyst.
Geometric means were used because these frequency data were log-transformed.
N^: number of subjects who had baseline and postbaseline values
* Based on the MMRM model for response variable of change from baseline in log-transformed 24-hour cough frequency, adjusted for covariates including treatment, visit, the interaction of treatment by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit
** The estimated relative reduction (relative to placebo) is calculated by 100 (e^{DIFF} -1). DIFF is the treatment difference in change from baseline at Week 24 (P030) or Week 12 (P027) based on the log-transformed data.

Primary Endpoint: 24-Hour Cough Frequency

	Trial P030 (Week 24)		Trial P027 (Week 12)	
Statistic	**Placebo**	**Gefapixant 45 mg**	**Placebo**	**Gefapixant 45 mg**
N^	419	409	222	217
Geometric mean at baseline	20.4	19.4	23.6	18.9
Geometric mean at Week 24 or 12	8.7	7.1	10.6	7.4
Geometric mean ratio (95% CI)*	0.43 (0.39, 0.48)	0.37 (0.33, 0.41)	0.47 (0.41, 0.54)	0.39 (0.34, 0.45)
Relative reduction (%) in geometric mean ratio (95% CI) **		-14.6 (-26.0, -1.5)		-17.0 (-31.5, 0.6)
p-value*		0.030		0.057

Source: adeff.xpt; Table 4-2 in CSR Addenda for P030 and P027, validated by statistical analyst.
Geometric means were used because these frequency data were log-transformed.
N^: number of subjects who had baseline and postbaseline values
* Based on the MMRM model for response variable of change from baseline in log-transformed 24-hour cough frequency, adjusted for covariates including treatment, visit, the interaction of treatment by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit
** The estimated relative reduction (relative to placebo) is calculated by 100 (e^{DIFF} -1). DIFF is the treatment difference in change from baseline at Week 24 (P030) or Week 12 (P027) based on the log-transformed data.

Primary Endpoint: 24-Hour Cough Frequency

	Trial P030 (Week 24)		Trial P027 (Week 12)	
Statistic	**Placebo**	**Gefapixant 45 mg**	**Placebo**	**Gefapixant 45 mg**
N^	419	409	222	217
Geometric mean at baseline	20.4	19.4	23.6	18.9
Geometric mean at Week 24 or 12	8.7	7.1	10.6	7.4
Geometric mean ratio (95% CI)*	0.43 (0.39, 0.48)	0.37 (0.33, 0.41)	0.47 (0.41, 0.54)	0.39 (0.34, 0.45)
Percent reduction from baseline	***57%***	***63%***	***53%***	***61%***
Relative reduction (%) in geometric mean ratio (95% CI) **		-14.6 (-26.0, -1.5)		-17.0 (-31.5, 0.6)
p-value*		0.030		0.057

Source: adeff.xpt; Table 4-2 in CSR Addenda for P030 and P027, validated by statistical analyst.
Geometric means were used because these frequency data were log-transformed.
N^: number of subjects who had baseline and postbaseline values
* Based on the MMRM model for response variable of change from baseline in log-transformed 24-hour cough frequency, adjusted for covariates including treatment, visit, the interaction of treatment by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit
** The estimated relative reduction (relative to placebo) is calculated by 100 (e^{DIFF} -1). DIFF is the treatment difference in change from baseline at Week 24 (P030) or Week 12 (P027) based on the log-transformed data.

Primary and Sensitivity Analyses for Relative Reduction (%) in 24-Hour Cough Frequency

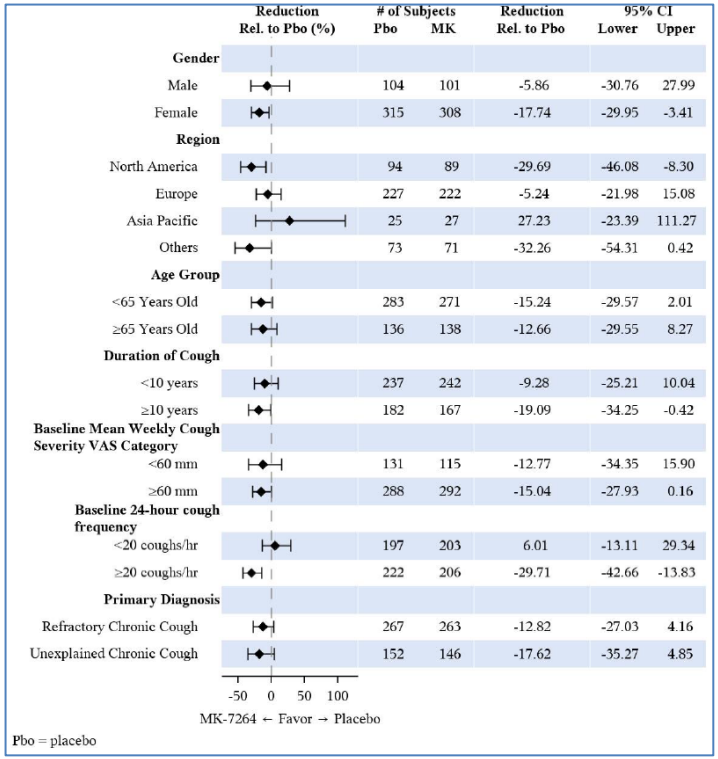
Amount of missing data for primary endpoint: P030, Placebo 15%, 45 mg 21%; P027, Placebo 16%, 45 mg 20%

	Sensitivity Analysis	P030 Gefapixant 45 mg vs. Placebo	P027 Gefapixant 45 mg vs. Placebo
	Primary analysis, original submission	-14.6 (-26.1, -1.4)	-18.5 (-32.9, -0.9)
Resubmission	**Primary analysis, MMRM**	**-14.6 [a] (-26.0, -1.5)**	**-17.0 (-31.5, 0.6)**
Resubmission	J2R – multiple imputation	-12.6 (-24.4, 0.9)	-14.9 (-30.6, 4.4)
Resubmission	J2R – pattern mixture	-12.6 (-22.5, -1.3)	-15.3 (-28.6, 0.5)
Resubmission	MI+ANCOVA [b]	-13.1 (-24.5, -0.1)	-17.1 (-31.2, -0.1)
Resubmission	MI+ANCOVA in subjects with baseline and at least one postbaseline value [c]	-14.5 (-25.8, -1.6)	-17.1 (-31.7, 0.5)
	Primary analysis with 2 placebo outliers at baseline removed	n/a	-16.2 (-30.8, 1.5)

Source: Statistical analyst. J2R Source: 13 October 2023 Information Response. Abbreviations: ANCOVA, analysis of covariance; MI, multiple imputation; n/a, not applicable; J2R, jump to reference. [a] Tipping point analysis supported robustness of this result. [b] Results for Applicant's MI + ANCOVA (not prespecified) are described in the FDA briefing document. [c] Results for modification of Applicant's MI + ANCOVA in subjects with a baseline value and at least one postbaseline value (not prespecified) are described in the FDA briefing document.

24-Hour Cough Frequency by Demographic and Baseline Disease Characteristic Subgroups

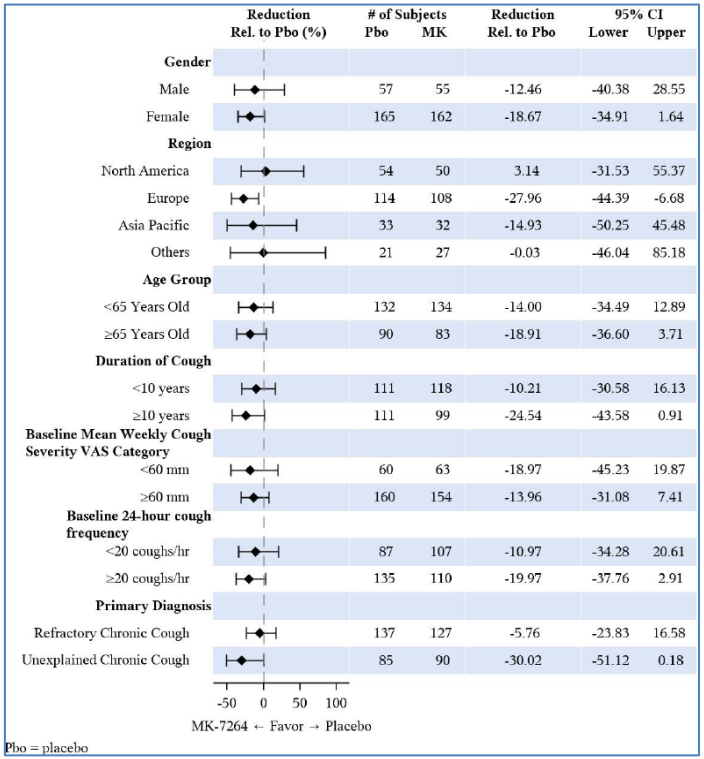
Trial P030 (Week 24)



	Reduction Rel. to Pbo (%)	# of Subjects Pbo	# of Subjects MK	Reduction Rel. to Pbo	95% CI Lower	95% CI Upper
Gender						
Male		104	101	-5.86	-30.76	27.99
Female		315	308	-17.74	-29.95	-3.41
Region						
North America		94	89	-29.69	-46.08	-8.30
Europe		227	222	-5.24	-21.98	15.08
Asia Pacific		25	27	27.23	-23.39	111.27
Others		73	71	-32.26	-54.31	0.42
Age Group						
<65 Years Old		283	271	-15.24	-29.57	2.01
≥65 Years Old		136	138	-12.66	-29.55	8.27
Duration of Cough						
<10 years		237	242	-9.28	-25.21	10.04
≥10 years		182	167	-19.09	-34.25	-0.42
Baseline Mean Weekly Cough Severity VAS Category						
<60 mm		131	115	-12.77	-34.35	15.90
≥60 mm		288	292	-15.04	-27.93	0.16
Baseline 24-hour cough frequency						
<20 coughs/hr		197	203	6.01	-13.11	29.34
≥20 coughs/hr		222	206	-29.71	-42.66	-13.83
Primary Diagnosis						
Refractory Chronic Cough		267	263	-12.82	-27.03	4.16
Unexplained Chronic Cough		152	146	-17.62	-35.27	4.85

Pbo = placebo

Trial P027 (Week 12)



	Reduction Rel. to Pbo (%)	# of Subjects Pbo	# of Subjects MK	Reduction Rel. to Pbo	95% CI Lower	95% CI Upper
Gender						
Male		57	55	-12.46	-40.38	28.55
Female		165	162	-18.67	-34.91	1.64
Region						
North America		54	50	3.14	-31.53	55.37
Europe		114	108	-27.96	-44.39	-6.68
Asia Pacific		33	32	-14.93	-50.25	45.48
Others		21	27	-0.03	-46.04	85.18
Age Group						
<65 Years Old		132	134	-14.00	-34.49	12.89
≥65 Years Old		90	83	-18.91	-36.60	3.71
Duration of Cough						
<10 years		111	118	-10.21	-30.58	16.13
≥10 years		111	99	-24.54	-43.58	0.91
Baseline Mean Weekly Cough Severity VAS Category						
<60 mm		60	63	-18.97	-45.23	19.87
≥60 mm		160	154	-13.96	-31.08	7.41
Baseline 24-hour cough frequency						
<20 coughs/hr		87	107	-10.97	-34.28	20.61
≥20 coughs/hr		135	110	-19.97	-37.76	2.91
Primary Diagnosis						
Refractory Chronic Cough		137	127	-5.76	-23.83	16.58
Unexplained Chronic Cough		85	90	-30.02	-51.12	0.18

Pbo = placebo

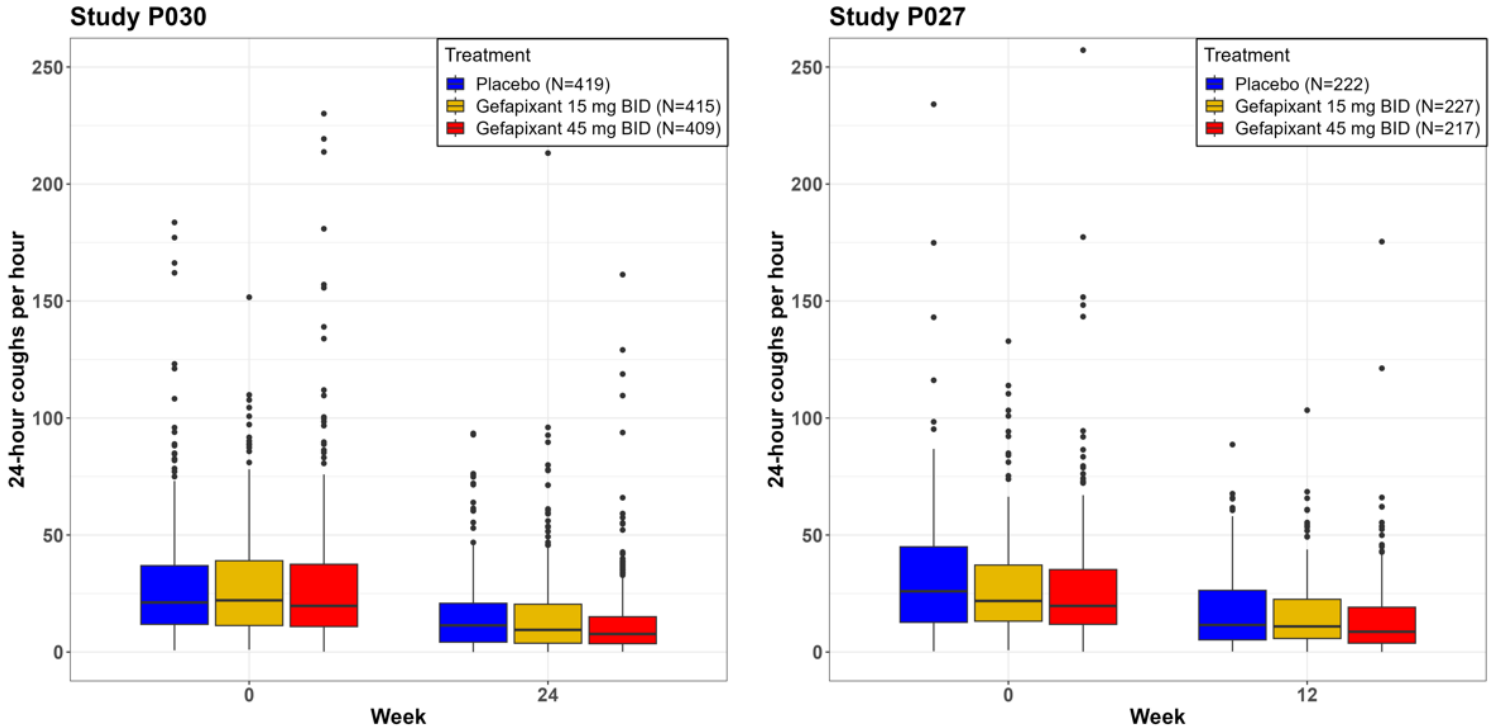
Source: Applicant's response to information request, September 12, 2023, Figures 2-4 and 2-3.
Abbreviations: CI, confidence interval; MK and MK-7264, gefapixant 45 mg; VAS, visual analog scale

Absolute 24-Hour Cough Frequency

	Trial P030 (Week 24)		Trial P027 (Week 12)	
Statistic	**Placebo**	**Gefapixant 45 mg**	**Placebo**	**Gefapixant 45 mg**
N	419	409	222	217
Median cough frequency at baseline (min, max)	21.3 (0.7, 184)	19.9 (0.2, 230)	26.1 (0.3, 1054)	20.9 (0.2, 399)
Median cough frequency at Week 24/12	11.4	7.7	11.6	8.7
Median change from baseline in cough frequency at Week 24/12	-8.7	-9.8	-8.9	-10.5

Source: Statistical analyst

Absolute 24-Hour Cough Frequency

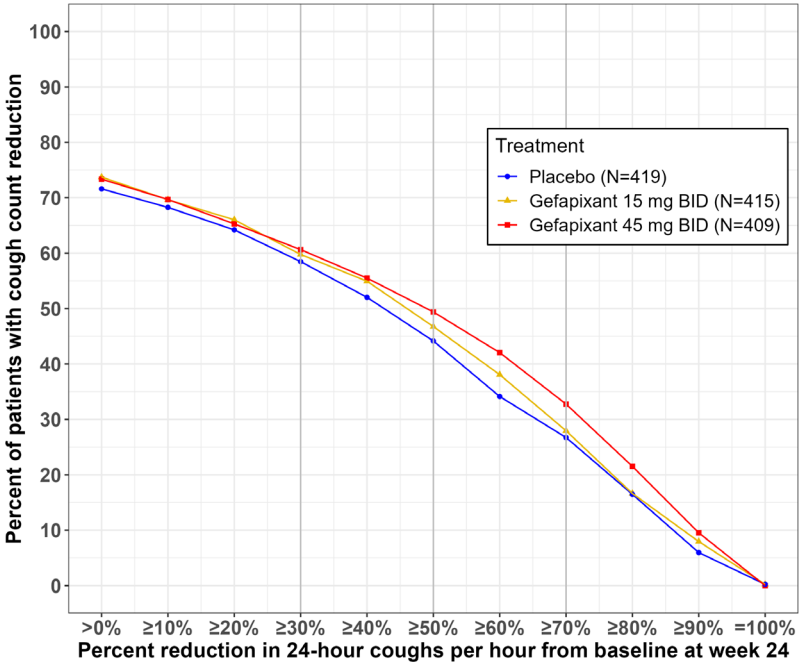


Source: Statistical analyst. For Trial P027, two subjects in the gefapixant 45 mg group at baseline, four subjects in the placebo group at baseline, and two subjects in the placebo group at week 12 had 24-hour cough frequency values greater than 250 and were not included in the figure. These eight subjects had 24-hour cough frequency ranged from 257.2 to 1053.5.

Change from baseline in 24-hour cough frequency	Trial P030 (Week 24)		Trial P027 (Week 12)	
	Placebo	Gefapixant 45 mg	Placebo	Gefapixant 45 mg
Median	-8.7	-9.8	-8.9	-10.5

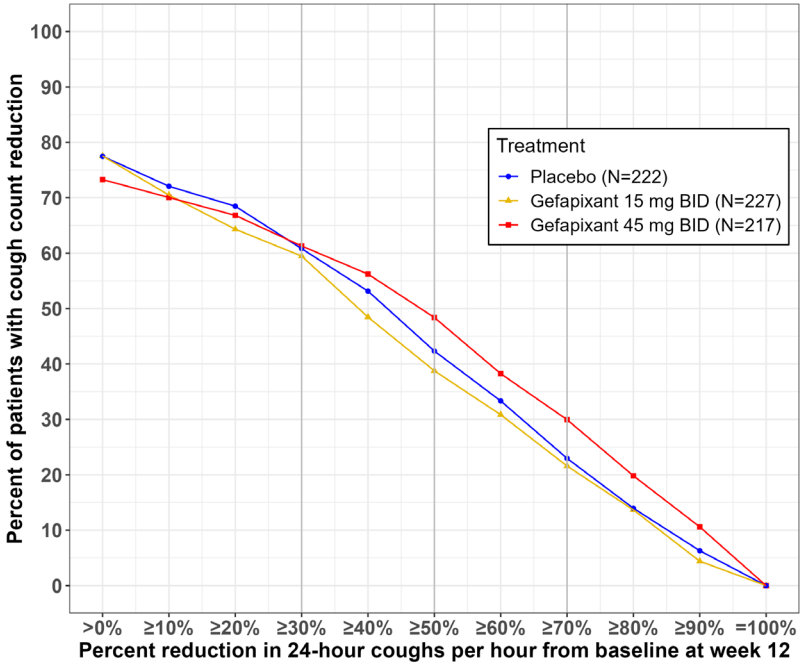
Proportion of Subjects with Percentage Reduction from Baseline in 24-Hour Cough Frequency

Study P030



Total				
409	73%	61%	49%	33%
415	74%	60%	47%	28%
419	72%	58%	44%	27%

Study P027

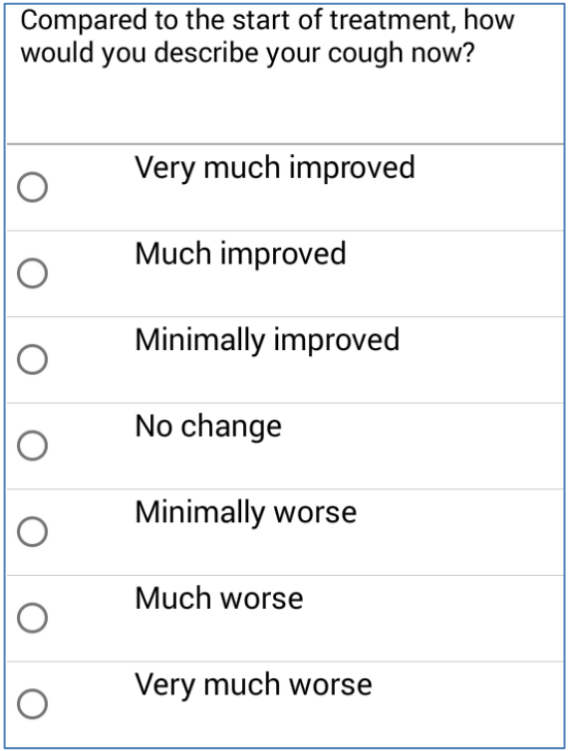


Total				
217	73%	61%	48%	30%
227	78%	60%	39%	22%
222	77%	61%	42%	23%

Source: Statistical analyst

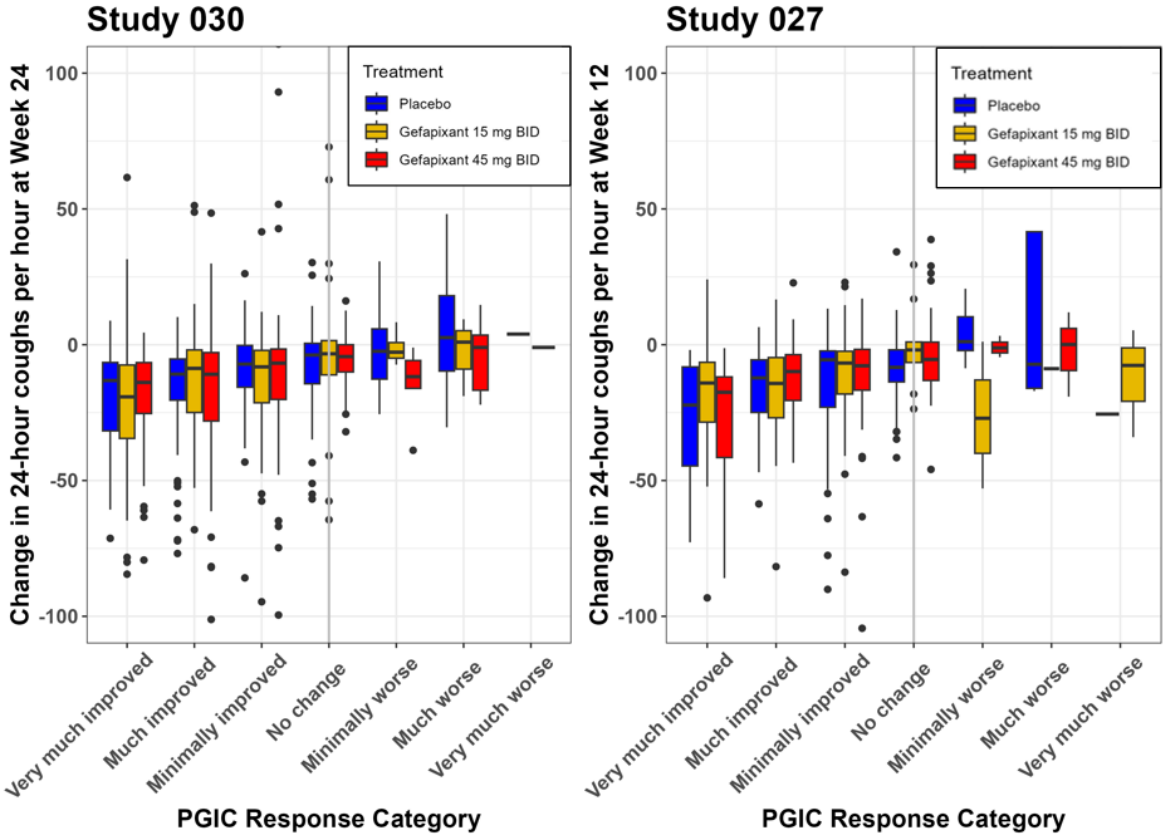
Absolute Change in Cough Frequency and PGIC

- Patient Global Impression of Change (PGIC) used as anchor scale for cough frequency
  - To understand what would be a meaningful amount of change in cough frequency from patients' perspective
  - Exploratory analysis
  - PGIC collected at Weeks 12 and 24 only



Source: Appendix 1 of the Applicant's response to the FDA Information Request dated February 26, 2021

Absolute Change in Cough Frequency and PGIC (Cont.)



Source: Statistical analyst

Absolute Change in Cough Frequency and PGIC (Cont.)

- Exploratory anchor-based analysis findings:
  - Low correlation between absolute change in cough frequency with PGIC score
  - Change in cough frequency occurs nearly independently from patient-reported improvement in chronic cough as captured by PGIC
  - Patients who reported feeling better per the PGIC were not necessarily those patients who were coughing less
- Did not inform meaningfulness of change in cough frequency from patients' perspective

Pivotal Trial Efficacy Endpoints

Landmark timepoints: P030 (Week 24), P027 (Week 12)
Cough frequency based on recounted data using validated method

- Primary endpoint
  - 24-hour cough frequency
- Secondary endpoints, multiplicity-controlled
  - Awake cough frequency
  - ≥ 1.3-point increase from baseline in LCQ total score (P030 only)
  - ≥ 30% reduction from baseline in 24-hour cough frequency
- Other secondary endpoints
  - ≥ 1.3-point reduction from baseline in mean weekly CSD total score
  - ≥ 2.7-point reduction from baseline in mean weekly CSD total score
  - ≥ 30 mm reduction from baseline in Cough Severity VAS score

Multiplicity-Controlled Secondary Endpoints

Variable Statistic	Trial P030 (Week 24) Placebo	 Gefapixant 45 mg	Trial P027 (Week 12) Placebo	 Gefapixant 45 mg
Awake cough frequency per hour				
N [a]	419	409	222	217
Geometric mean at baseline	26.9	25.2	31.4	25.0
Geometric mean at Week 24 or 12	11.3	9.0	13.8	9.6
Geometric mean ratio (95% CI) [bc]	0.43 (0.38, 0.47)	0.36 (0.32, 0.40)	0.46 (0.40, 0.53)	0.39 (0.33, 0.45)
Relative reduction (%) in geometric mean ratio (95% CI) [c]		-15.5 (-27.0, -2.3)		-16.3 (-31.2, 1.9)
p-value		0.023		0.076
≥1.3-point increase from baseline in LCQ total score				
n^d/N^d (%)	245/355 (69)	262/342 (77)		
Odds ratio vs. placebo (95% CI) [e]		1.4 (1.0, 2.0)		
p-value[e]		0.040		
Responder/N (%)[f]	245/415 (59)	262/419 (63)		
Estimated difference (%) (95% CI)[g]		3.3 (-3.3, 9.9)		
≥30% reduction from baseline in 24-hr cough frequency per hour				
n^d/N^d (%)	245/368 (67)	248/347 (72)	135/205 (66)	133/194 (69)
Odds ratio vs. placebo (95% CI) [e]		1.2 (0.9, 1.7)		1.2 (0.8, 1.8)
p-value[e]		0.188		0.435
Responder/N (%)[f]	245/432 (57)	248/434 (57)	135/232 (58)	133/237 (56)
Estimated difference (%) (95% CI)[g]		0.4 (-6.1, 7.0)		-2.2 (-11.2, 6.8)

Source: Tables 4-4 and 4-10 in CSR Addenda, Table 14.2-22 in CSR of Trial P030, and Tables 4-3, 4-4 in CSR Addenda of Trial P027. [a] N=Number of subjects who had baseline and postbaseline values. [b] Based on subjects with nonmissing values at baseline and Week 24. [c] Based on the MMRM model for response variable of change from baseline in log-transformed awake cough frequency, adjusted for covariates including treatment, visit, the interaction of treatment by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit . The estimated relative reduction (relative to placebo) is calculated by 100 (e^{DIFF} -1). DIFF is the treatment difference in change from baseline at Week 24 based on the log-transformed data. [d] N=Number of subjects with available data at Week 24; n=number of responders at Week 24. [e] Based on the logistic regression model with terms of treatment, visit, treatment-by-visit interaction, gender, region, baseline, and baseline-by-visit interaction among subjects who had baseline and post baseline values. [f] N=number of subjects who had baseline values. Subjects with nonmissing baseline data but missing Week 24 data are imputed as nonresponders. [g] Based on the Mietinnen and Nurminen method.

Multiplicity-Controlled Secondary Endpoints

Variable / Statistic	Trial P030 (Week 24)		Trial P027 (Week 12)	
	Placebo	Gefapixant 45 mg	Placebo	Gefapixant 45 mg
Awake cough frequency per hour				
N [a]	419	409	222	217
Geometric mean at baseline	26.9	25.2	31.4	25.0
Geometric mean at Week 24 or 12	11.3	9.0	13.8	9.6
Geometric mean ratio (95% CI) [bc]	0.43 (0.38, 0.47)	0.36 (0.32, 0.40)	0.46 (0.40, 0.53)	0.39 (0.33, 0.45)
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p-value		0.023		0.076
≥1.3-point increase from baseline in LCQ total score				
n^d/N^d (%)	245/355 (69)	262/342 (77)		
Odds ratio vs. placebo (95% CI) [e]		1.4 (1.0, 2.0)		
p-value[e]		0.040		
Responder/N (%)[f]	245/415 (59)	262/419 (63)		
Estimated difference (%) (95% CI)[g]		3.3 (-3.3, 9.9)		
≥30% reduction from baseline in 24-hr cough frequency per hour				
n^d/N^d (%)	245/368 (67)	248/347 (72)	135/205 (66)	133/194 (69)
Odds ratio vs. placebo (95% CI) [e]		1.2 (0.9, 1.7)		1.2 (0.8, 1.8)
p-value[e]		0.188		0.435
Responder/N (%)[f]	245/432 (57)	248/434 (57)	135/232 (58)	133/237 (56)
Estimated difference (%) (95% CI)[g]		0.4 (-6.1, 7.0)		-2.2 (-11.2, 6.8)

Source: Tables 4-4 and 4-10 in CSR Addenda, Table 14.2-22 in CSR of Trial P030, and Tables 4-3, 4-4 in CSR Addenda of Trial P027. [a] N=Number of subjects who had baseline and postbaseline values. [b] Based on subjects with nonmissing values at baseline and Week 24. [c] Based on the MMRM model for response variable of change from baseline in log-transformed awake cough frequency, adjusted for covariates including treatment, visit, the interaction of treatment by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit . The estimated relative reduction (relative to placebo) is calculated by 100 (e^{DIFF} -1). DIFF is the treatment difference in change from baseline at Week 24 based on the log-transformed data. [d] N=Number of subjects with available data at Week 24; n=number of responders at Week 24. [e] Based on the logistic regression model with terms of treatment, visit, treatment-by-visit interaction, gender, region, baseline, and baseline-by-visit interaction among subjects who had baseline and post baseline values. [f] N=number of subjects who had baseline values. Subjects with nonmissing baseline data but missing Week 24 data are imputed as nonresponders. [g] Based on the Mietinnen and Nurminen method.

Multiplicity-Controlled Secondary Endpoints

Variable Statistic	Trial P030 (Week 24) Placebo	 Gefapixant 45 mg	Trial P027 (Week 12) Placebo	 Gefapixant 45 mg
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Geometric mean at Week 24 or 12	11.3	9.0	13.8	9.6
Geometric mean ratio (95% CI) [bc]	0.43 (0.38, 0.47)	0.36 (0.32, 0.40)	0.46 (0.40, 0.53)	0.39 (0.33, 0.45)
Relative reduction (%) in geometric mean ratio (95% CI) [c]		-15.5 (-27.0, -2.3)		-16.3 (-31.2, 1.9)
p-value		0.023		0.076
≥1.3-point increase from baseline in LCQ total score				
n^d/N^d (%)	245/355 (69)	262/342 (77)		
Odds ratio vs. placebo (95% CI) [e]		1.4 (1.0, 2.0)		
p-value[e]		0.040		
Responder/N (%)[f]	245/415 (59)	262/419 (63)		
Estimated difference (%) (95% CI)[g]		3.3 (-3.3, 9.9)		
≥30% reduction from baseline in 24-hr cough frequency per hour				
n^d/N^d (%)	245/368 (67)	248/347 (72)	135/205 (66)	133/194 (69)
Odds ratio vs. placebo (95% CI) [e]		1.2 (0.9, 1.7)		1.2 (0.8, 1.8)
p-value[e]		0.188		0.435
Responder/N (%)[f]	245/432 (57)	248/434 (57)	135/232 (58)	133/237 (56)
Estimated difference (%) (95% CI)[g]		0.4 (-6.1, 7.0)		-2.2 (-11.2, 6.8)

Source: Tables 4-4 and 4-10 in CSR Addenda, Table 14.2-22 in CSR of Trial P030, and Tables 4-3, 4-4 in CSR Addenda of Trial P027. [a] N=Number of subjects who had baseline and postbaseline values. [b] Based on subjects with nonmissing values at baseline and Week 24. [c] Based on the MMRM model for response variable of change from baseline in log-transformed awake cough frequency, adjusted for covariates including treatment, visit, the interaction of treatment by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit . The estimated relative reduction (relative to placebo) is calculated by 100 (e^{DIFF} -1). DIFF is the treatment difference in change from baseline at Week 24 based on the log-transformed data. [d] N=Number of subjects with available data at Week 24; n=number of responders at Week 24. [e] Based on the logistic regression model with terms of treatment, visit, treatment-by-visit interaction, gender, region, baseline, and baseline-by-visit interaction among subjects who had baseline and post baseline values. [f] N=number of subjects who had baseline values. Subjects with nonmissing baseline data but missing Week 24 data are imputed as nonresponders. [g] Based on the Mietinnen and Nurminen method.

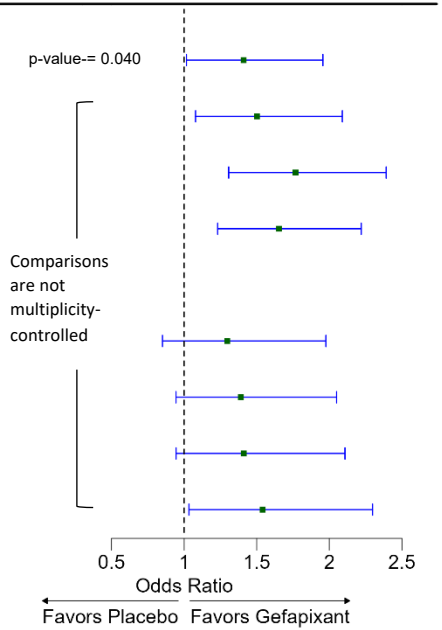
Pivotal Trial Efficacy Endpoints

Landmark timepoints: P030 (Week 24), P027 (Week 12)
Cough frequency based on recounted data using validated method

- Primary endpoint
  - 24-hour cough frequency
- Secondary endpoints, multiplicity-controlled
  - Awake cough frequency
  - ≥ 1.3-point increase from baseline in LCQ total score (P030 only)
  - ≥ 30% reduction from baseline in 24-hour cough frequency
- Other secondary endpoints
  - ≥ 1.3-point reduction from baseline in mean weekly CSD total score
  - ≥ 2.7-point reduction from baseline in mean weekly CSD total score
  - ≥ 30 mm reduction from baseline in Cough Severity VAS score

PRO Secondary Endpoints: Percent Responder Odds Ratios

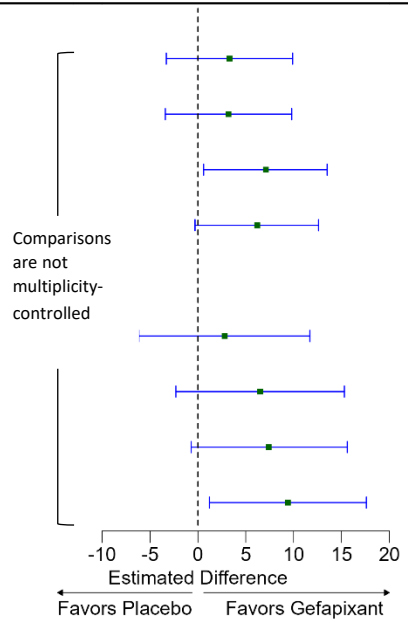
Variable	Gefapixant n/N[a]	Placebo n/N[a]	Percent Responders (%) (Gefapixant v. Placebo)	Odds Ratio v. Placebo (95% CI)
Study P030				
≥1.3 increase in LCQ total score	262/342	245/355	76.6 v 69.0	1.4 (1.0, 2.0)
≥1.3 reduction in mean weekly CSD total score	253/331	237/346	76.4 v 68.5	1.5 (1.1, 2.1)
≥2.7 reduction in mean weekly CSD total score	186/331	154/346	56.2 v 44.5	1.8 (1.3, 2.4)
≥30 mm reduction in Cough Severity VAS score	178/331	150/346	53.8 v 43.4	1.7 (1.2, 2.2)
Study P027				
≥1.3 increase in LCQ total score	134/194	123/196	69.1 v 62.8	1.3 (0.9, 2.0)
≥1.3 reduction in mean weekly CSD total score	129/204	112/211	63.2 v 53.1	1.4 (0.9, 2.1)
≥2.7 reduction in mean weekly CSD total score	84/204	65/211	41.2 v 30.8	1.4 (0.9, 2.1)
≥30 mm reduction in Cough Severity VAS score	87/204	63/211	42.6 v 29.9	1.5 (1.0, 2.3)



Source: statistical analyst, and Tables 14.2-22, 11-5, 11-6, and 11-7 in Trial P030 CSR; Tables 11-7, 11-4, 11-5, and 11-6 in Trial P027 CSR. Gefapixant: gefapixant 45 mg.
Change from baseline at Week 24 (Trial P030)/12 (Trial P027).
Odds ratio is based on the logistic regression model with terms of treatment, visit, treatment-by-visit interaction, gender, region, baseline, and baseline-by-visit interaction among subjects who had baseline and post baseline values.
There was a small discrepancy in odds ratio results for ≥2.7 CSD reduction for Trial P027 compared to the Applicant's result.
n, number of responders at Week 24 for Trial P030 (Week 12 for Trial P027);
N[a], number of subjects with available values at Week 24 for Trial P030 (Week 12 for Trial P027);

PRO Secondary Endpoints: Percent Responder Differences

Variable	Gefapixant n/N[b]	Placebo n/N[b]	Percent Responders (%) (Gefapixant v. Placebo)	Estimated Difference (%) (95% CI)
Study P030				
≥1.3 increase in LCQ total score	262/419	245/415	62.5 v 59.0	3.3 (-3.3, 9.9)
≥1.3 reduction in mean weekly CSD total score	253/437	237/434	57.9 v 54.6	3.2 (-3.4, 9.8)
≥2.7 reduction in mean weekly CSD total score	186/437	154/434	42.6 v 35.5	7.1 (0.6, 13.5)
≥30 mm reduction in Cough Severity VAS score	178/437	150/434	40.7 v 34.6	6.2 (-0.3, 12.6)
Study P027				
≥1.3 increase in LCQ total score	134/236	123/229	56.8 v 53.7	2.8 (-6.2, 11.7)
≥1.3 reduction in mean weekly CSD total score	129/243	112/241	53.1 v 46.5	6.5 (-2.3, 15.3)
≥2.7 reduction in mean weekly CSD total score	84/243	65/241	34.6 v 27.0	7.4 (-0.7, 15.6)
≥30 mm reduction in Cough Severity VAS score	87/243	63/241	35.8 v 26.1	9.4 (1.2, 17.6)



Source: statistical analyst, and Tables 14.2-22, 14.2-35, 14.2-36, and 14.2-43 in Trial P030 CSR; Tables 14.2-52, 14.2-34, 14.2-37, and 14.2-44 in Trial P027 CSR. Gefapixant: gefapixant 45 mg.
Change from baseline at Week 24 (Trial P030)/12 (Trial P027).
Estimated difference is based on the stratified Miettinen and Nurminen method with gender and region.
n, number of responders at Week 24 for Trial P030 (Week 12 for Trial P027);
N[b], number of subjects who had baseline values

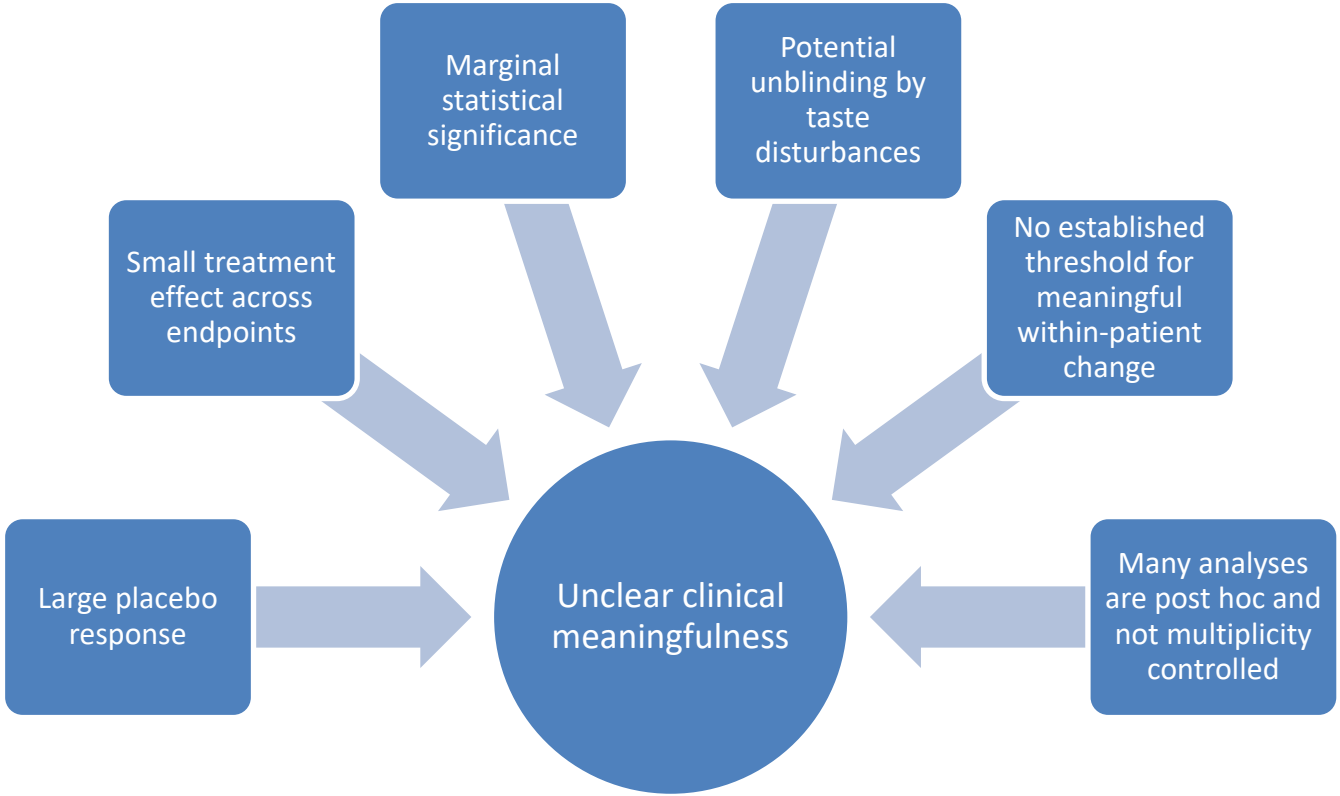
Summary of Efficacy Findings in Pivotal Trials

- High placebo response with little added effect from gefapixant across endpoints
- Marginally statistically significant and small treatment differences in:
  - 24-hour cough frequency
  - Awake cough frequency
  - ≥ 1.3-point increase from baseline in LCQ total score (P030)
- No established threshold for meaningful within-patient change in:
  - Cough frequency
  - PRO endpoints
- Potential bias due to knowledge of taste disturbance
- Clinical interpretation of these findings is required

Outline

- Overview of the Clinical Program and Review of Safety
  - Rachel Bean, MD
- Statistical Review of Efficacy
  - Susan Mayo, MS
- **Clinical Considerations**
  - **Rachel Bean, MD**

Clinical Interpretation of Efficacy is Challenging



Primary Endpoint: 24-Hour Cough Frequency

	Trial P030 (Week 24)		Trial P027 (Week 12)	
Statistic	**Placebo**	**Gefapixant 45 mg**	**Placebo**	**Gefapixant 45 mg**
N	419	409	222	217
Geometric mean at baseline	20.4	19.4	23.6	18.9
Geometric mean at Week 24 or 12	8.7	7.1	10.6	7.4
Geometric mean ratio (95% CI)*	0.43 (0.39, 0.48)	0.37 (0.33, 0.41)	0.47 (0.41, 0.54)	0.39 (0.34, 0.45)
Percent reduction from baseline	*57%*	*63%*	*53%*	*61%*
Relative reduction (%) in geometric mean ratio (95% CI) **		-14.6 (-26.0, -1.5)		-17.0 (-31.5, 0.6)
p-value*		0.030		0.057

Source: adeff.xpt; Table 4-2 in CSR Addenda for P030 and P027, validated by statistical analyst.
Geometric means were used because these frequency data were log-transformed.
* Based on the MMRM model for response variable of change from baseline in log-transformed 24-hour cough frequency, adjusted for covariates including treatment, visit, the interaction of treatment by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit
** The estimated relative reduction (relative to placebo) is calculated by 100 (e^{DIFF} -1). DIFF is the treatment difference in change from baseline at Week 24 (P030) or Week 12 (P027) based on the log-transformed data.

Primary Endpoint: 24-Hour Cough Frequency

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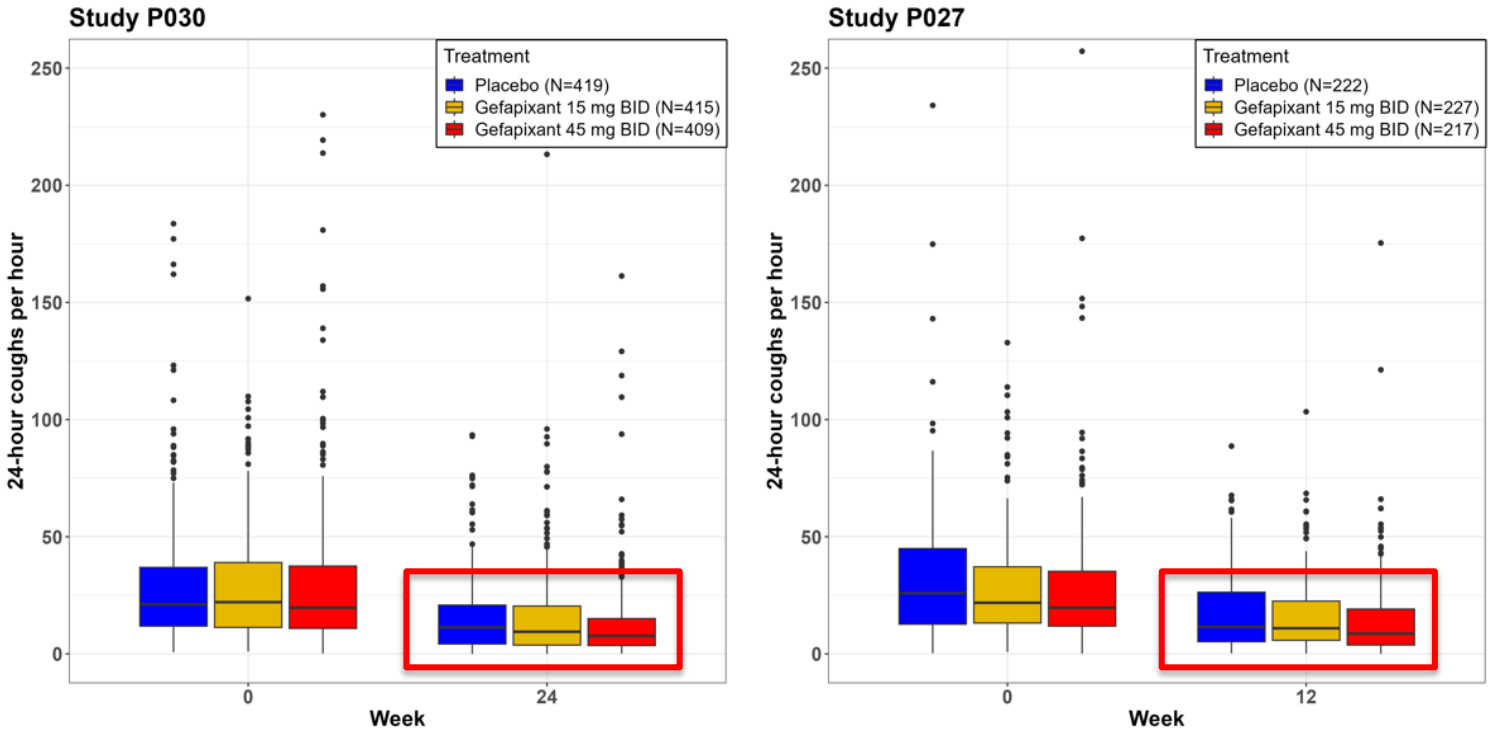
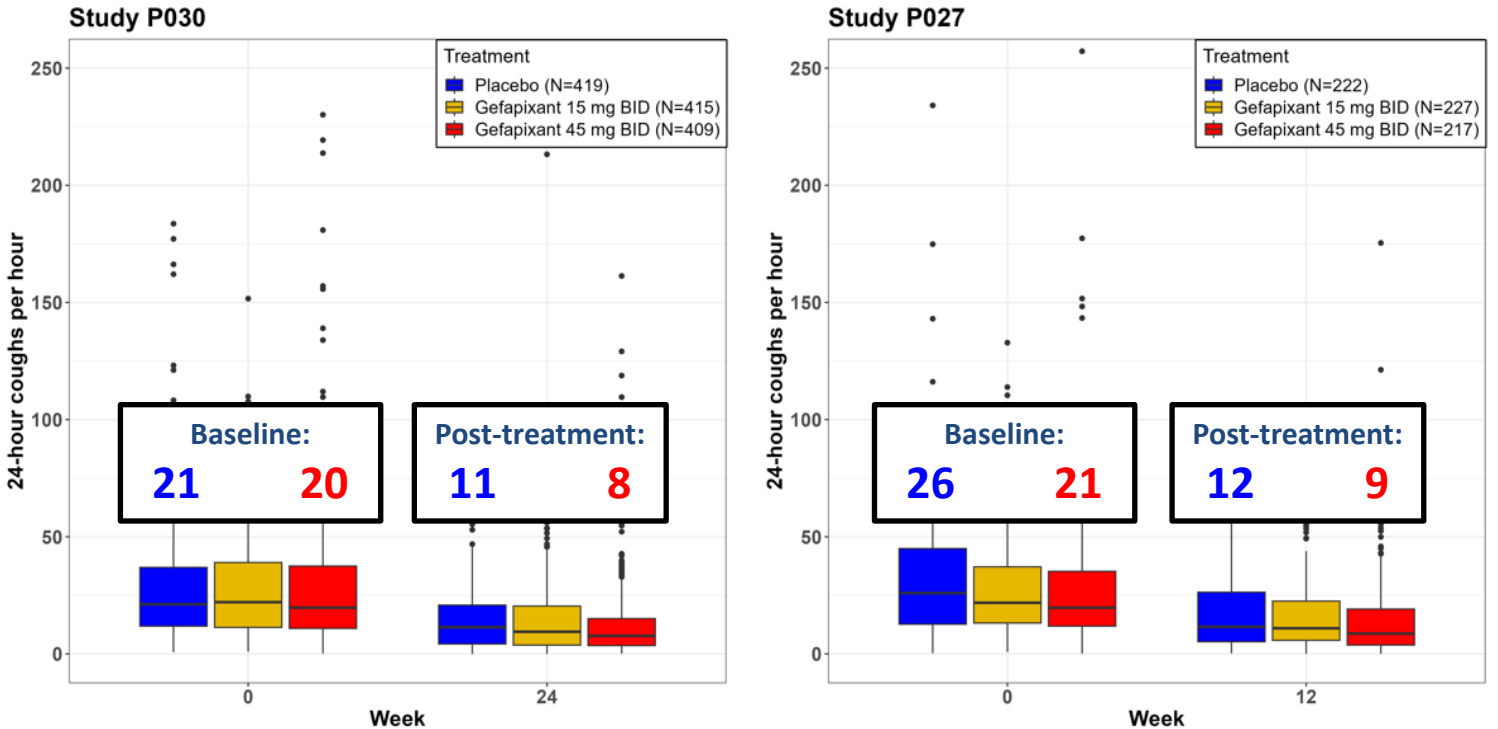
24-Hour Cough Frequency



Source: Statistical analyst. For Trial P027, two subjects in the gefapixant 45 mg group at baseline, four subjects in the placebo group at baseline, and two subjects in the placebo group at week 12 had 24-hour cough frequency values greater than 250 and were not included in the figure. These eight subjects had 24-hour cough frequency ranged from 257.2 to 1053.5.

24-Hour Cough Frequency



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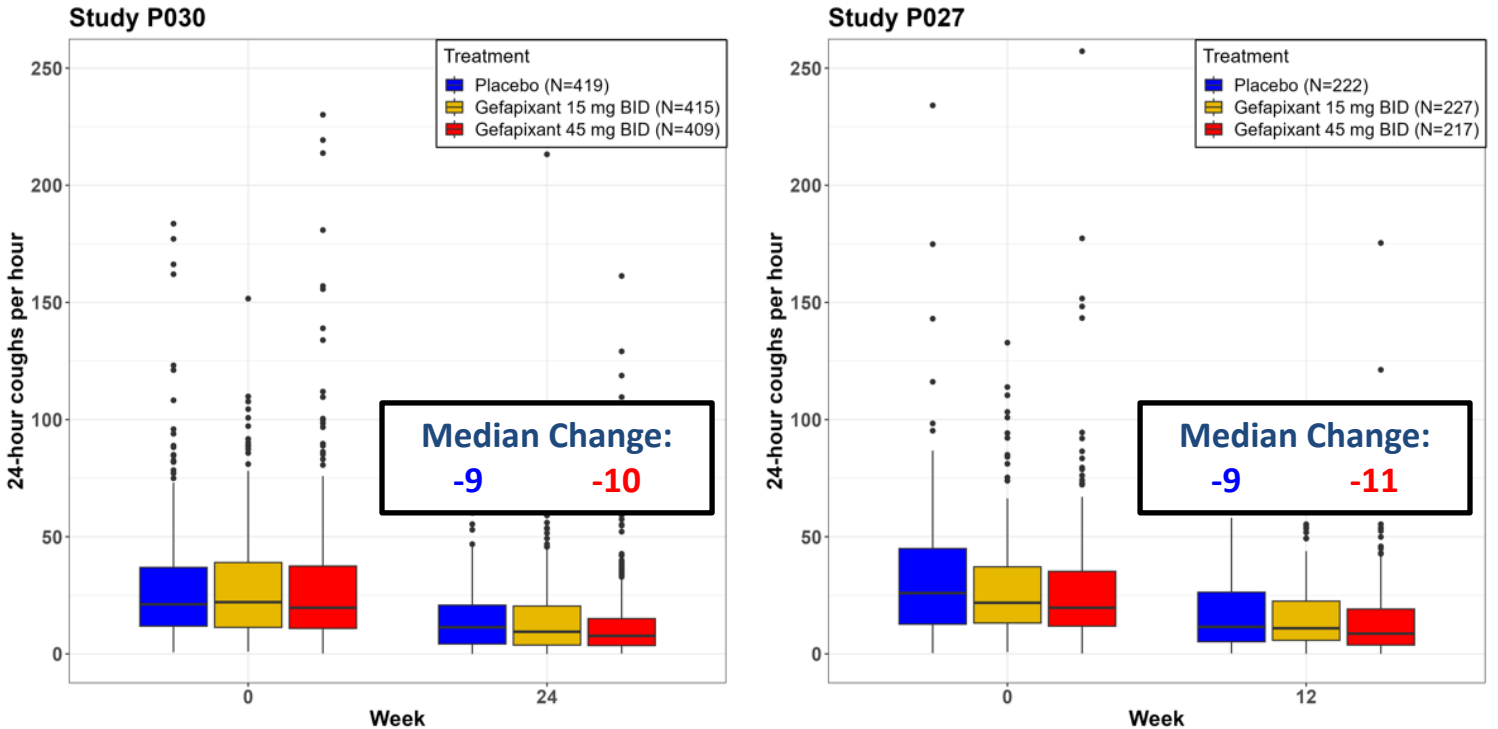
24-Hour Cough Frequency



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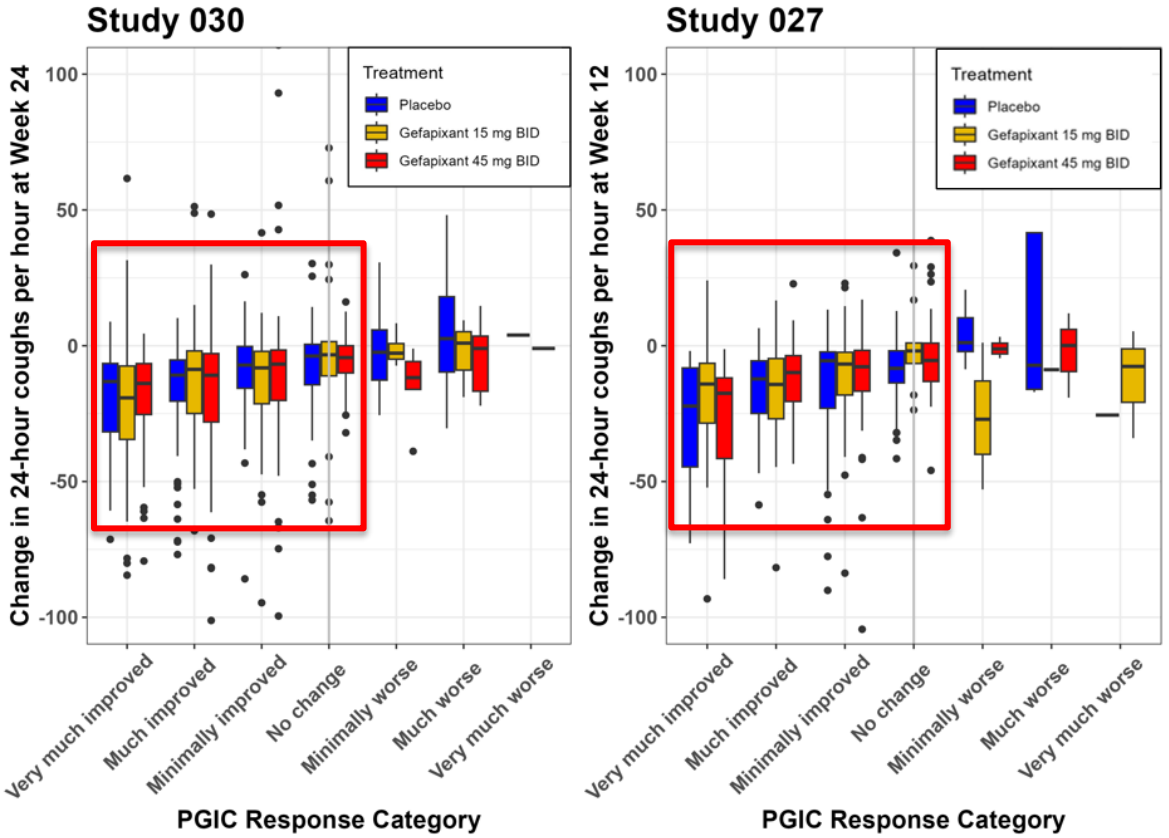
Absolute Change in Cough Frequency and PGIC



Source: Statistical analyst

Multiplicity-Controlled Secondary Endpoints

Variable	Trial P030 (Week 24)		Trial P027 (Week 12)	
Statistic	Placebo	Gefapixant 45 mg	Placebo	Gefapixant 45 mg
Awake cough frequency per hour				
N [a]	419	409	222	217
Geometric mean at baseline	26.9	25.2	31.4	25.0
Geometric mean at Week 24 or 12	11.3	9.0	13.8	9.6
Geometric mean ratio (95% CI) [bc]	0.43 (0.38, 0.47)	0.36 (0.32, 0.40)	0.46 (0.40, 0.53)	0.39 (0.33, 0.45)
Relative reduction (%) in geometric mean ratio (95% CI) [c]		-15.5 (-27.0, -2.3)		-16.3 (-31.2, 1.9)
p-value		0.023		0.076
≥1.3-point increase from baseline in LCQ total score				
n^d/N^d (%)	245/355 (69)	262/342 (77)		
Odds ratio vs. placebo (95% CI) [e]		1.4 (1.0, 2.0)		
p-value[e]		0.040		
Responder/N (%)[f]	245/415 (59)	262/419 (63)		
Estimated difference (%) (95% CI)[g]		3.3 (-3.3, 9.9)		
≥30% reduction from baseline in 24-hr cough frequency per hour				
n^d/N^d (%)	245/368 (67)	248/347 (72)	135/205 (66)	133/194 (69)
Odds ratio vs. placebo (95% CI) [e]		1.2 (0.9, 1.7)		1.2 (0.8, 1.8)
p-value[e]		0.188		0.435
Responder/N (%)[f]	245/432 (57)	248/434 (57)	135/232 (58)	133/237 (56)
Estimated difference (%) (95% CI)[g]		0.4 (-6.1, 7.0)		-2.2 (-11.2, 6.8)

Source: Tables 4-4 and 4-10 in CSR Addenda, Table 14.2-22 in CSR of Trial P030, and Tables 4-3, 4-4 in CSR Addenda of Trial P027. [a] N=Number of subjects who had baseline and postbaseline values. [b] Based on subjects with nonmissing values at baseline and Week 24. [c] Based on the MMRM model for response variable of change from baseline in log-transformed awake cough frequency, adjusted for covariates including treatment, visit, the interaction of treatment by visit, gender, region, the log-transformed baseline value, and the interaction of log-transformed baseline value by visit . The estimated relative reduction (relative to placebo) is calculated by 100 (e^{DIFF} -1). DIFF is the treatment difference in change from baseline at Week 24 based on the log-transformed data. [d] N=Number of subjects with available data at Week 24; n=number of responders at Week 24. [e] Based on the logistic regression model with terms of treatment, visit, treatment-by-visit interaction, gender, region, baseline, and baseline-by-visit interaction among subjects who had baseline and post baseline values. [f] N=number of subjects who had baseline values. Subjects with nonmissing baseline data but missing Week 24 data are imputed as nonresponders. [g] Based on the Mietinnen and Nurminen method.

Multiplicity-Controlled Secondary Endpoints

Variable / Statistic	Trial P030 (Week 24) Placebo	Trial P030 (Week 24) Gefapixant 45 mg	Trial P027 (Week 12) Placebo	Trial P027 (Week 12) Gefapixant 45 mg
Awake cough frequency per hour				
N [a]	419	409	222	217
Geometric mean at baseline	26.9	25.2	31.4	25.0
Geometric mean at Week 24 or 12	11.3	9.0	13.8	9.6
Geometric mean ratio (95% CI) [bc]	0.43 (0.38, 0.47)	0.36 (0.32, 0.40)	0.46 (0.40, 0.53)	0.39 (0.33, 0.45)
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Multiplicity-Controlled Secondary Endpoints

Variable / Statistic	Trial P030 (Week 24) Placebo	Trial P030 (Week 24) Gefapixant 45 mg	Trial P027 (Week 12) Placebo	Trial P027 (Week 12) Gefapixant 45 mg
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N [a]	419	409	222	217
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Geometric mean at Week 24 or 12	11.3	9.0	13.8	9.6
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PRO Secondary Endpoints: Percent Responder Differences

Variable	Gefapixant n/N[b]	Placebo n/N[b]	Percent Responders (%) (Gefapixant v. Placebo)	Estimated Difference (%) (95% CI)
Study P030				
≥1.3 increase in LCQ total score	262/419	245/415	62.5 v 59.0	3.3 (-3.3, 9.9)
≥1.3 reduction in mean weekly CSD total score	253/437	237/434	57.9 v 54.6	3.2 (-3.4, 9.8)
≥2.7 reduction in mean weekly CSD total score	186/437	154/434	42.6 v 35.5	7.1 (0.6, 13.5)
≥30 mm reduction in Cough Severity VAS score	178/437	150/434	40.7 v 34.6	6.2 (-0.3, 12.6)
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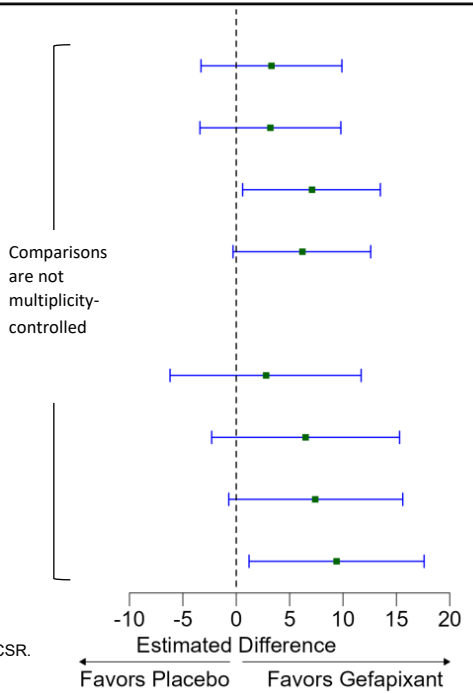

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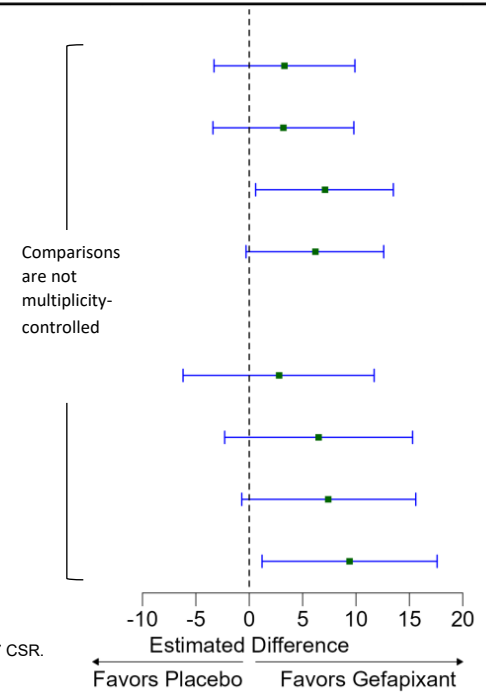

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n, number of responders at Week 24 for Trial P030 (Week 12 for Trial P027);
N[b], number of subjects who had baseline values

Clinical Efficacy Summary

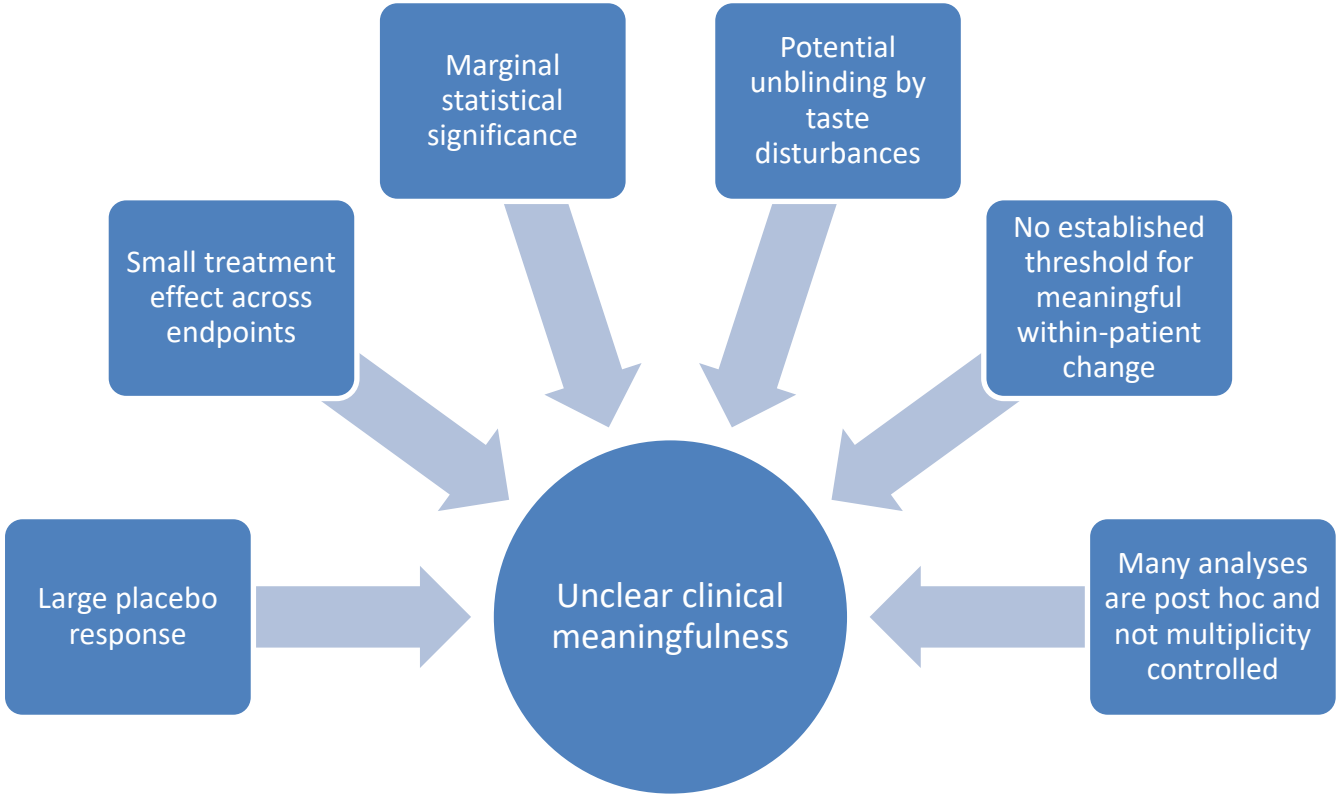
- Patients improved whether on placebo or gefapixant
- Small reduction in cough frequency compared to placebo
  - Marginal statistical significance in 1 of 2 trials
  - Coughing less often did not correlate with feeling better (per PGIC)
  - No identifiable subgroup of “responders”
    - Demographic / baseline disease characteristics
    - Higher percent reductions from baseline
  - Unclear if effect is meaningful or perceptible

Clinical Efficacy Summary

- LCQ results
  - Concerns about content validity of instrument
  - Concerns about ≥ 1.3-point increase to define “responders”
  - Concerns about meaningfulness of the change in total score

- Other PRO endpoints
  - None controlled for multiplicity
  - No evidence to support selected “responder” thresholds
  - Small differences from placebo in “responders” and total scores

Clinical Interpretation of Efficacy is Challenging




FDA
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ADMINISTRATION

FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
Charge to the Committee

NDA 215010: Gefapixant for the Treatment of Refractory or Unexplained Chronic Cough in Adults

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November 17, 2023

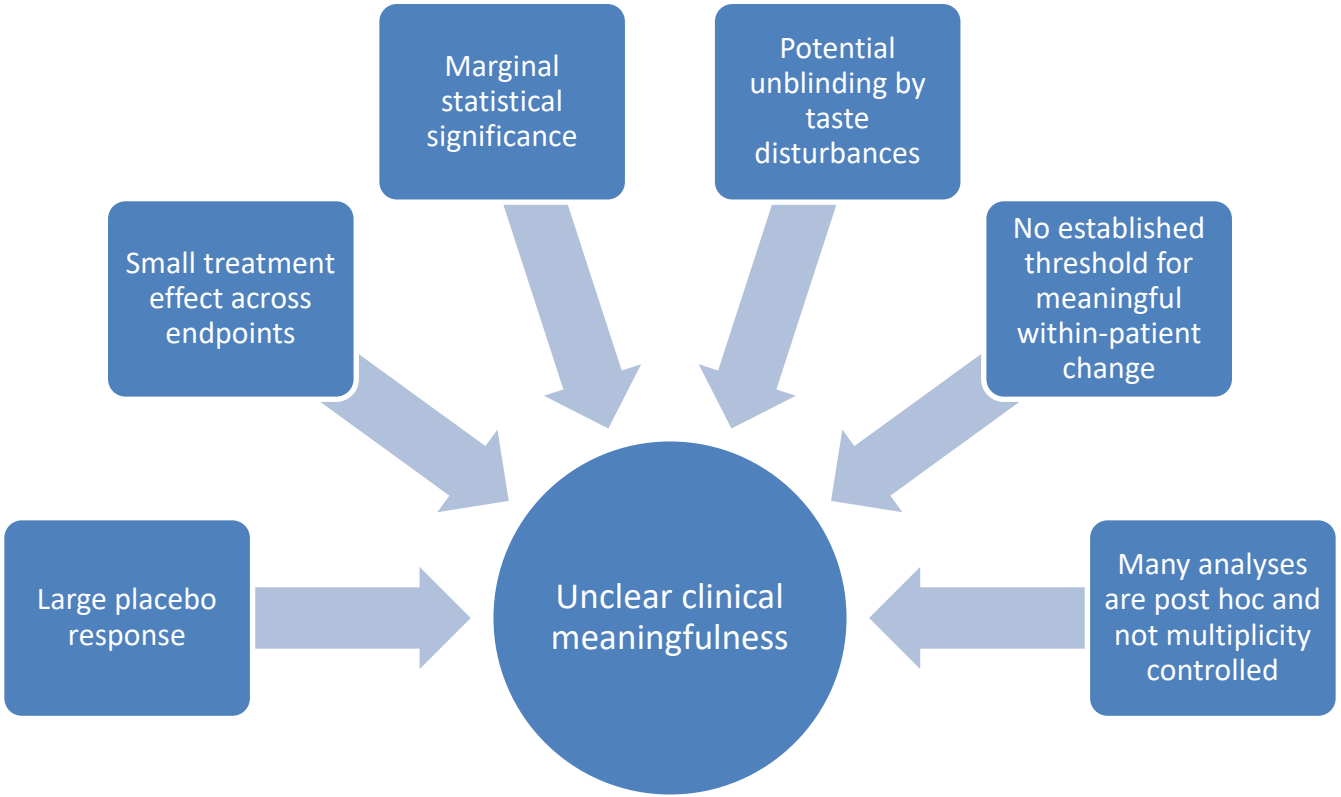
Proposed Use: Gefapixant

- New molecular entity
- Treatment of refractory or unexplained chronic cough
- Common symptomatic condition with no approved therapies
- Novel indication
  - No precedent for study design or efficacy endpoints
  - No experience with interpretation of results

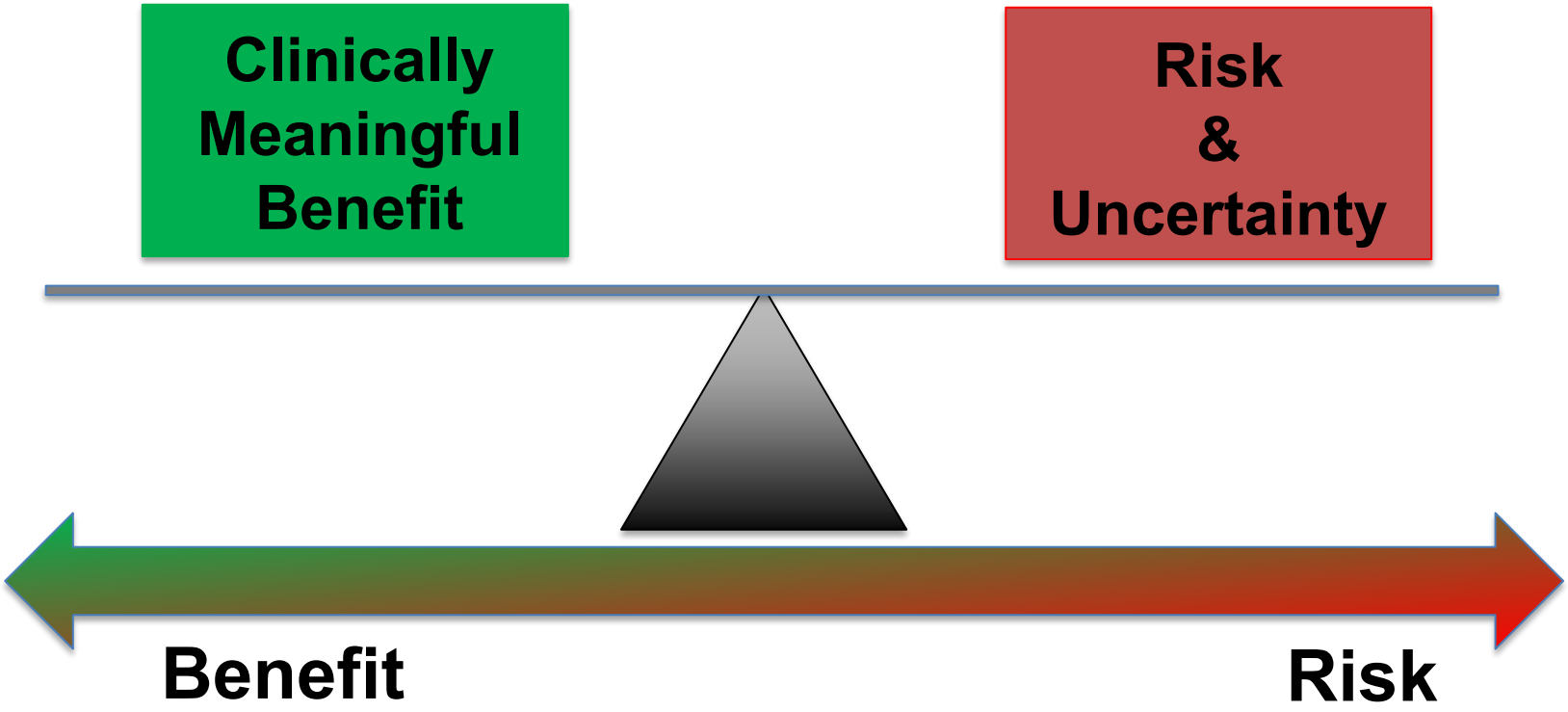
Key Findings in the Gefapixant Program

- Wide variability in baseline cough frequency
- High placebo response
- Small reduction in cough frequency compared to placebo
  - Relative reduction in geometric mean ratio 15-17%
  - Median absolute reduction ~1-2 coughs/hr beyond placebo
  - Statistical significance in 1 of 2 trials using validated recount cough data and prespecified analysis
- Small effect on some PRO endpoints
- Taste disturbances common

Clinical Interpretation of Efficacy is Challenging



Benefit / Risk Framework



Discussion Points

- Discuss the evidence of effectiveness for gefapixant for the treatment of refractory or unexplained chronic cough in adults. Specifically address the following:
  - The small reduction in cough frequency compared to placebo and the clinical meaningfulness of the reduction in cough frequency
  - The observed results from PROs and whether these results provide compelling evidence to inform the clinical meaningfulness of the reduction in cough frequency
  - Potential unblinding of patients due to taste disturbance and its impact on interpretation of cough frequency and PRO results

Discussion Points

- Discuss the overall benefit/risk assessment of gefapixant for the treatment of adults with refractory or unexplained chronic cough, a symptomatic condition.

Voting Question

- Does the evidence demonstrate that gefapixant provides a clinically meaningful benefit to adult patients with refractory or unexplained chronic cough, given the small reduction in cough frequency and results from PROs? Provide a rationale for your vote.
  - If you conclude that there is insufficient evidence of a clinically meaningful benefit, describe the evidence that could be collected to show a benefit that is clinically meaningful.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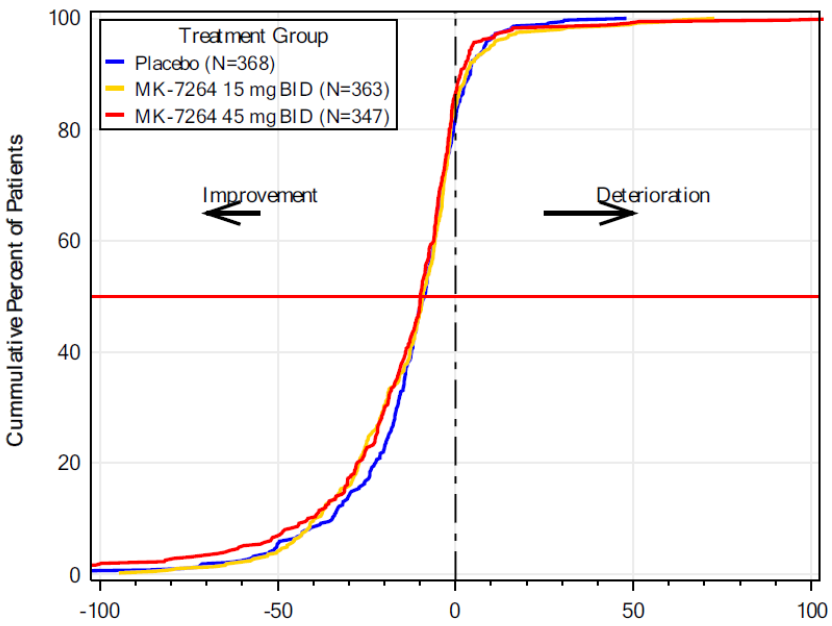
Back-up Slides Shown

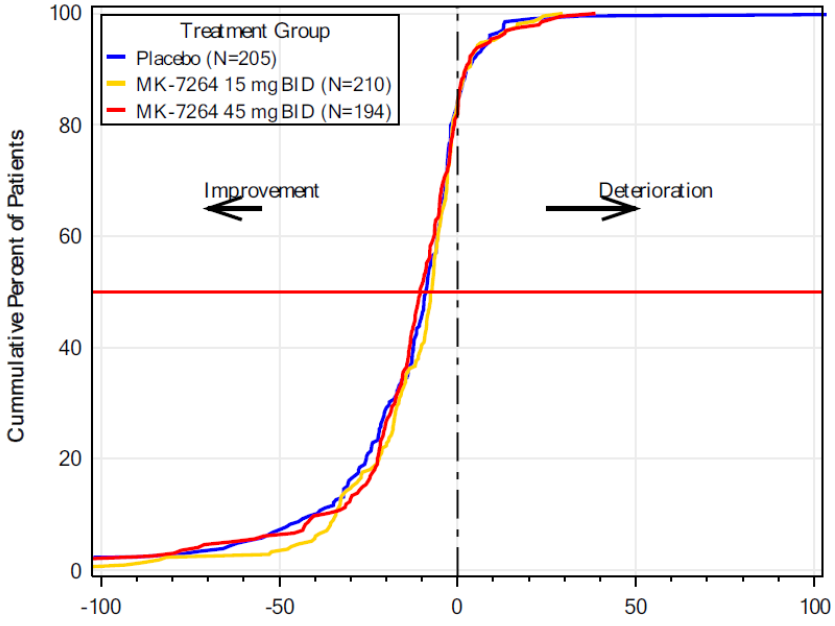
Amount of Missing Data in Cough Frequency

	Trial P030 at Week 24			Trial P027 at Week 12		
	Placebo	Gefapixant 15mg	Gefapixant 45mg	Placebo	Gefapixant 15mg	Gefapixant 45mg
Randomized	436	442	439	244	244	244
Treated (FAS)	435	440	439	243	244	243
Included in primary analysis (baseline and post-baseline cough frequency) among FAS	419	415	409	222	227	217
Excluded from primary analysis for cough frequency but in FAS	16	25	30	21	17	26
Cough frequency available at Week 24 (12)	368	363	347	205	210	194
Amount of missing Data in cough frequency at Week 24 (12)	**15.4%**	**17.5%**	**21.0%**	**15.6%**	**13.9%**	**20.2%**

Source: FDA statistical reviewer

Empirical Cumulative Distribution Function of Absolute Change From Baseline in Cough Frequency, P030 (Week 24) and P027 (Week 12)





Source: Applicant's figure

The cumulative distribution function curves display a continuous view of the change in 24-hour cough frequency from baseline on the x-axis and the cumulative percent of patients reporting up to that level of change at Week 24 (or Week 12) on the y-axis.

24-Hour Cough Frequency by Whether Subjects Experienced Taste Disturbance

Trial P030 (Week 24)	Subjects Experiencing Taste Disturbance			Subjects Not Experiencing Taste Disturbance		
Statistic	Placebo	Gefapixant 15 mg	Gefapixant 45 mg	Placebo	Gefapixant 15 mg	Gefapixant 45 mg
N	38	86	283	381	329	126
Geometric mean at baseline	21.5	22.6	20.4	20.3	19.6	17.2
Geometric mean at week 24	9.0	10.3	7.0	8.7	7.8	7.5
Geometric mean ratio*	0.42	0.46	0.34	0.43	0.40	0.44

Trial P027 (Week 12)	Subjects Experiencing Taste Disturbance			Subjects Not Experiencing Taste Disturbance		
Statistic	Placebo	Gefapixant 15 mg	Gefapixant 45 mg	Placebo	Gefapixant 15 mg	Gefapixant 45 mg
N	10	29	134	212	198	83
Geometric mean at baseline	36.8	21.5	22.1	23.1	20.8	14.7
Geometric mean at Week 24	14.9	11.3	7.5	10.4	10.1	7.2
Geometric mean ratio*	0.41	0.52	0.34	0.45	0.48	0.49

Source: adeff.xpt; statistical analyst.
Geometric means were used because these frequency data were log-transformed.
* Based on subjects with nonmissing values at baseline and Week 24.
Abbreviations: N, number of subjects who had baseline and postbaseline assessments