December 2025

Report

Refractory Chronic Cough (RCC) Therapeutics

PIPELINE ANALYSIS & COMPETITIVE LANDSCAPE 2026–2035

This report was prepared with financial support from **Hyfe Inc.**

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Introduction

Executive Summary

Refractory Chronic Cough (RCC) remains a large, undertreated, and globally unaddressed condition. Despite an estimated 100 million affected worldwide and ~10 million in the U.S[1] , there are no FDA-approved therapies. Current practice relies on off-label medicines with 31–40% adverse event rates, modest efficacy, and limited persistence.The first U.S. approval - expected no earlier than 2026 - will create a new therapeutic category but will enter into a market shaped by high placebo response, demanding regulators, and increasing payer scrutiny.

1. Market Overview

- **Prevalence:** ~450–600M chronic cough; ~100M RCC2[2].
- **Addressable Population:** Diagnostics, referral pathways, and treatment failures narrow global RCC to ~20–30M commercially reachable patients; 2–4M in the U.S.
- **Market Size:** ~$9B in 2024 across the 7 Major Markets (7MM); projected to reach $14–15B by 2035 (CAGR ~6%).
- **Growth Drivers:** aging populations, specialist referral expansion, digital identification tools, and increasing recognition of cough hypersensitivity.

2. Regulatory Reset

Two Complete Response Letters (CRL) for Gefapixant (Jan 2022 and Dec2023) materially raised the evidentiary bar:

- The FDA requires a ≥30% placebo-adjusted reduction in objective 24-hour cough frequency, and clinically meaningful improvements in patient reported outcomes.The high placebo response threatens statistical separation for all mechanisms*.

The U.S. market will likely see one winner, at most two, with meaningful time separation between market entries.

3. Mechanism Performance and Competitive Landscape

Three modalities dominate RCC development:

P2X3 Antagonists. P2X3 remains the most validated mechanism, but only highly selective, taste-sparing agents with ≥30% adjusted efficacy are viable in the U.S.

Kappa/Mu Opioid Modulators (Nalbuphine ER). Highest efficacy potential; regulatory risk tied to opioid-related concerns and need for robust Phase 3 confirmation.

Alternative Mechanisms. Includes TRPM8 agonists, sodium channel blockers, NK-1 antagonists, airway hydration. Intriguing but unproven pathways. Unlikely to deliver first-in-class approval without novel trial designs or biomarker stratification.

Digital Pathways. Meaningful potential both as standalone interventions and in combination with pharmacological drugs. Preliminary data very promising. Trajectory will depend primarily on the pace of adoption of digital therapeutics within health systems.

4. Economic and Access Considerations

Without stronger Health Economics and Outcomes Research (HEOR) evidence, even efficacious therapies may see restricted access or price compression.

*The history of RCC candidate attempt/ failures over the last 15 years strongly suggests that the FDA has a 30% floor for efficacy to consider a drug successful.

1. Global chronic cough prevalence is estimated at 9.6% of adults (Song et al., 2015 meta-analysis), with 5-10% of these patients progressing to refractory or unexplained chronic cough despite guideline directed treatment. However, published estimates vary significantly due to three methodological drivers: (1) self-reported survey data reflecting substantial underdiagnosis and under-coding; (2) definitional inconsistency across studies; and (3) population age differences. No population-based RCC epidemiology data exists for most markets. Therefore 9.6% global prevalence (95% CI 7.6-11.7%) would translate to approximately 632-768M people using current population figures. Our claimed 450-600M range is a very conservative estimate the true figure may be higher.

2. As mentioned in the note above, the range of estimates in publications is very wide. The proportion of UCC/RCC of CC hovers in the literature between 10% to 20-25%. Ortega, Virchowat al. 2025 estimate that 27.9% of CC have RCC (https://pubmed.ncbi.nlm.nih.gov/40661930/)

5. The Digital Inflection Point

Digital therapeutics (DTx) are emerging as central to the RCC treatment model. The field presents two distinct digital opportunities:

5A. Standalone Digital Therapeutics (DTx)

Behavioral cough suppression therapy (BCST) demonstrates 40–88% improvement in RCTs and is guideline-endorsed but bottlenecked by provider scarcity.
Digital delivery via mobile platforms replicates BCST elements:

- Early digital cohorts show ~42% reductions in cough frequency. No drug toxicity; large addressable population, including patients unwilling or unable to take pharmaceuticals.
- Japan-first prescription DTx pathways (e.g., Kyorin × Hyfe) create a regulatory precedent.

Standalone DTx offers a scalable, low-toxicity alternative, and could become the de facto first-line RCC treatment in markets with BCST capacity gaps.

5B. Combination Therapy (Drug + DTx)

Digital augmentation materially strengthens the economics of pharmacologic therapy:

- In RCC, average treatment duration is 6–8 months; digital augmentation increases this by 20–30% (to ~9 months).
- This yields a 20–44% increase in lifetime value (LTV) and a 7–8× ROI for manufacturers due to improved persistence.
- Objective monitoring provides regulators and payers with real-world evidence on durability—currently a major gap in all RCC programs.
- Combination approaches may offer differentiation in a class where efficacy deltas are narrow.

The drug+DTx model is a high-leverage commercial tool and could become a requirement for payers evaluating chronic symptom management therapies.

6. Outlook 2026–2035

Three structural forces will shape the market this decade:

1. Regulatory interpretation of placebo-adjusted efficacy
Only agents demonstrating clear improvement in objective and subjective cough frequency are likely to be approved in the U.S.

2. Durability and HEOR evidence
Therapies demonstrating long-term symptom control with measurable QoL and cost offsets will capture payer support.

3. Digital integration
Objective monitoring and behavioral therapeutics—either standalone or integrated—will expand the market, improve clinical outcomes, and protect persistence-driven revenue.

Bull Case

- High-efficacy agents (e.g., nalbuphine ER) validate in Phase 3.
- Digital therapeutics achieve strong clinical validation and payer acceptance.
- Total RCC market expands to >$15B, with digital contributing a meaningful share.

Bear Case

- Placebo response continues to erode signal detection.
- P2X3 class faces additional setbacks.
- RCC remains largely off-label, with digital filling treatment gaps informally.

The Big Picture

The RCC landscape is at a decisive inflection point. If approved by the FDA, drugs in the pipeline will unlock a substantial and underserved category, but clinical, regulatory, and payer expectations have risen materially following prior failures. Across all mechanisms, placebo-adjusted efficacy, durability, and real-world evidence are now the determinants of success.

Digital therapeutics represent a major, underrecognized source of value creation. They expand access, reduce toxicity, generate real-world data, and improve the economic viability of pharmacologic launches.

In a market defined by high unmet need but high evidentiary burden, the winners will be those who combine validated mechanisms, tolerability, durability, and digital integration into a unified, evidence-driven treatment model.

Thesis

The next decade will be shaped by the convergence of three factors:

1. higher-efficacy P2X3 and non-P2X3 mechanisms,
2. a regulatory reset, and
3. the emergence of digital cough therapeutics as core components of both clinical development and commercial models.

Our central thesis is that therapies capable of demonstrating ≥30% placebo-adjusted efficacy, low discontinuation, durable symptom control, and digital integration will dominate the market and define the first generation of approved RCC treatments.

1. What's Changing

Regulation: The FDA has materially raised the evidentiary bar. Only agents with clear placebo adjusted improvements in 24-hour cough frequency and clinically meaningful PROs are viable. This will compress the field to 1–2 winners.

Mechanistic Validation: The P2X3 class top candidate in the pipeline (camlipixant) shows ~34% placebo-adjusted efficacy with low AE. KOR/MOR agents (e.g., nalbuphine ER) present the highest efficacy signal in RCC and IPF cough (≥40–57% placebo-adjusted) but face class-specific regulatory risk.

Digital therapeutics (DTx) are shifting from adjuncts to core infrastructure. Digital approaches can deliver ~40% cough reduction on their own and extend pharmacologic persistence by 30%, improving lifetime value by ~44%. Digital therapeutics will shape both clinical trial design and post-approval economics.

2. What Most Investors Miss

1. Durability Will Determine Pricing:
Regulators and Health Technology Assessment bodies (HTA) now demand 24–52 week data. Without durability, even efficacious drugs will face price compression or restricted reimbursement.

2. Digital Therapeutics Expand the Market:
Standalone DTx creates an early, scalable treatment modality, while combination therapy meaningfully improves revenue, access, and real-world evidence generation.

3. The Market is Larger Than Modeled:
Using conservative referral and treatment assumptions, the reachable RCC population (~20–30M globally) is substantially underrepresented in published market models.

4. Pricing uncertainty is both a barrier and opportunity.
It is very hard to price a novel therapy when the market size is unknown. Pharma fears walking away from revenue and payers fear budget busting costs. This highlights the need for Real World Data (RWE).

5. First Mover Advantage is Durable:
There is likely to be long period of exclusivity given the temporal dynamics of the drug pipeline. Subesquently, diagnostic friction, specialist bottlenecks, and digital onboarding it is likley that early entrants with integrated digital ecosystems will enjoy persistent lock-in effects.

3. Catalysts (2026–2027)

- Camlipixant Phase 3 readouts (CALM-1/2)
- Nalbuphine ER Phase 3 program initiation and IPF readouts
- Taplucainium Phase 2b results
- DTx regulatory pathway (Kyorin × Hyfe in Japan)
- First real-world HEOR data linking cough reduction to productivity and healthcare utilization

4. Key Risks

- The dynamics of cough and resulting high placebo effect complicates demonstrating placebo adjusted efficacy.
- Regulatory uncertainty following gefapixant's Letters, but potentially interesting opportunities emerging around Prescription Drug Use-Related Software (PDURS)
- Opioid class perception risk for nalbuphine ER
- HTA skepticism absent robust QALY evidence
- Uptake of P2X3 inhibitors likely limited by taste AEs.
- Underdiagnosis and delays in referral reducing near-term uptake

5. Positioning

The most attractive strategic position lies in platforms combining:

- 1. Efficacy ≥30% placebo-adjusted.
- 2. Taste AEs <10%.
- 3. Durability ≥24–52 weeks.
- 4. Digital integration enabling objective monitoring, adherence, and long-term real-world evidence.

Drug candidates meeting these thresholds, paired with digital therapeutics that extend persistence and provide trial-grade, objective endpoints, represent the strongest probability of regulatory approval, payer acceptance, and sustained commercial growth.

Digital therapeutics themselves represent a credible standalone modality, perhaps as the first line therapy, will likely shape both clinical practice and reimbursement frameworks.

Bottom line: RCC is transitioning from an off-label, fragmented category to a defined therapeutic market. The winners will be those that combine validated biology, differentiated tolerability, and digital infrastructure, positioning themselves at the intersection of clinical efficacy, regulatory credibility, and payer-aligned economics.

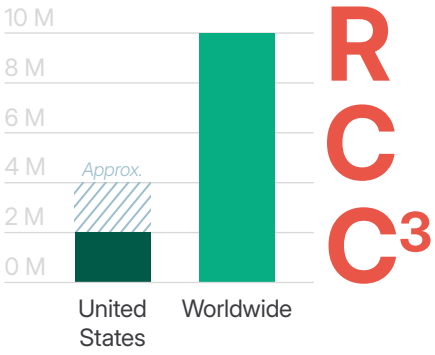
02

Market Landscape

Market Context

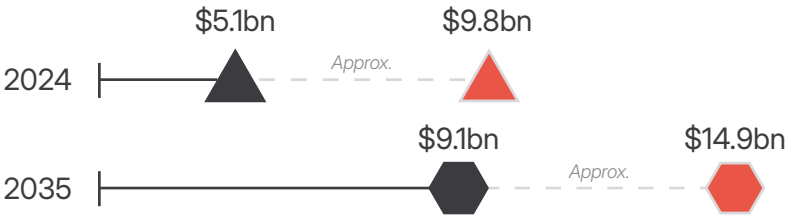
Exhibit 1A MARKET OVERVIEW

1 Patient Population



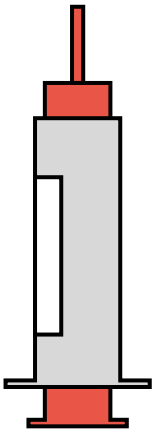
2 Market Size in Billion USD

CAGR: 3.95-8.4%



3 Market Shift

- Merck's Gefapixant was not approved by the FDA in 2023.
- GSK is the current Lead Developer (acquired Bellus Health/ camlipixant for $2 billion in June 2023[6]).
- Camlipixant's Phase 3 results expected in 2025/2026 with a potential of FDA approval in 2026[7].



4 Best-in-Class Efficacy

Trevi's Haduvio (nalbuphine) ER shows

60%

up to cough reduction (43-47% placebo -adjusted) in Phase 2b[8].

5 Digital Health

Prescription digital therapies emerge as a promising player, with up to

41%

possible efficacy and no toxicity[9].

3. "GSK Reaches Agreement to Acquire Late-Stage Biopharmaceutical Company BELLUS Health | GSK," April 18, 2023, https://www.gsk.com/en-gb/media/press-releases/gsk-reaches-agreement-to-acquire-late-stage-biopharmaceutical-company-bellus-health

4. See notes a and 2 above. Additional source: Eli O. Meltzer et al., "Prevalence and Burden of Chronic Cough in the United States,"The Journal of Allergy and Clinical Immunology: In Practice 9, no. 11 (2021): 4037-4044.e2, https://doi.org/10.1016/j.jaip.2021.07.022.

5. "Chronic Cough Market Size to Reach USD 9.1 Billion by 2035," accessed October 18, 2025, https://www.imarcgroup.com/chronic-cough-market-outlook

6. BELLUS HEALTH INC. ANNUAL INFORMATION FORM Fiscal Year Ended December 31, 2022," March 23, 2023, https://www.sec.gov/Archives/edgar/data/1259942/000141057823000342/blu-20221231xex99dd1.html

7. "GSK Delivers Strong 2024 Performance with Further Improvement to Long-Term Growth Outlook | GSK," May 2, 2025, https://www.gsk.com/en-gb/media/press-releases/gsk-delivers-strong-2024-performance-with-further-improvement-to-long-term-growth-outlook/

Exhibit 1B INVESTMENT THESIS

1 Zero approved drugs for RCC

No competition, first-mover captures market.

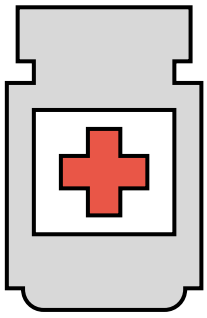
2 Digital therapeutics entrants

Add a scalable, margin-rich revenue layer

3 GSK's $2B acquisition validates opportunity

~$14B+

projected sales contribution through 2035.



4 High unmet needs

31%

of patients fail all current treatments; off-label options show 31–40% AE rates.

Exhibit 1C RISKS

5 Efficacy ceiling / placebo response 30-60% in P2X3 RCTs

Threatens statistical & clinical significance.

6 Economic evidence gap (QALY / CEA)

No cost-utility studies → Limits HTA reimbursement.

7 FDA Approval Uncertainty (post-Gefapixant precedent)

Post-gefapixant CRLs →

>70%

chance bar remains high; risk of US market loss.

8. Trevi Therapeutics Inc, "Trevi Therapeutics Reports First Quarter 2025 Financial Results and Provides Business Updates," accessed October 18, 2025, https://www.prnewswire.com/news-releases/trevi-therapeutics-reports-first-quarter-2025-financial-results-and-provides-business-updates-302450437.html

9. Hyfe to Launch World's First Prescription Digital Therapeutic to Treat Chronic Cough," accessed October 18, 2025, https://www.hyfe.com/news/hyfe-to-launch-worlds-first-prescription-digital-therapeutic-to-treat-chronic-cough

Exhibit 1D KEY SUCCESS FACTORS

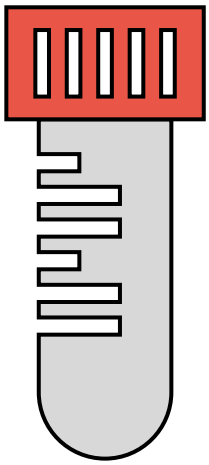
>30%
cough frequency reduction.

24–52
week durability with no evidence of tachyphylaxis.

Taste AEs <10%
Camlipixant 6.5% vs Gefapixant 38–81%

Health-economic proof
reduced specialist use, improved productivity

Exhibit 1E PIPELINE MILESTONES



Company (Asset)	Stage (as of 2025)	
GSK *Camlipixant / BLU-5937*	**Phase 3** CALM-1, CALM-2	
Trevi Therapeutics *Haduvio / Oral Nalbuphine ER*	**Phase 2b** CORAL, IPF cough	**Phase 2a** RIVER, RCC, completed
Kyorin Pharma × Hyfe Inc. *Hyfe DTx*	**Digital Therapeutic** Pre-launch	

Digital Uplift

Integration of digital cough monitoring ("cough companion") increases average treatment duration from 7 to 9.1 months (+30 percent) and expands lifetime value by 44 percent. For every 10,000 treated patients, digital augmentation generates approximately $23 million in incremental net revenue and a 7.7× return on investment.

Unmet Need at a Glance

- Epidemiology of CC, RCC, adult chronic cough percentage.
- Disease burden: QoL impact, healthcare utilization, work productivity and activity impact, anxiety, depression and sleep problems in RCC/CC vs. general population.

~28M

Individuals diagnosed worldwide

~10 million individuals with RCC>1 year

Exhibit 2 EPIDEMIOLOGY[11]

Region	CC (M) / RCC (M)	% of Adults with CC	Comments
Europe	~3M – ~57M	12.7%[1,2]	Higher than global mean due to age structure and climate
China	~2M – ~27.2M	4.1%[3]	National survey of 665.8 M adults[2]
Africa	~3-4M – ~20M	2.3% (95 % CI 0.0–6.7 %)[1]	Lowest reported prevalence; data limited
United States	~0-3M – ~12M	5%[2]	Weighted prevalence 5 %, higher with smoking (7.3 % vs 3.4 %)[1]
Oceania	~0.7-1M – ~4M	18.1% (95 % CI 9.8–27.2 %)[2]	Highest regional prevalence; limited sample size
Japan	~1M – ~4M	4.29%[3]	Web-based nationwide survey[4]

M: Million, CC: Chronic Cough, RCC: Refractory Chronic Cough, CI: Confidence Interval, ~: Approximately

Exhibit 3 BURDEN OF ILLNESS SUMMARY

Outcome	RCC/CC cohort finding	Comparator	Delta Δ / Ratio
Health-related quality of life (HRQoL) (EQ-5D-5L)[12]	**0.80** mean in CC	Matched non-cough controls **0.87**	**0.07**
Cough-specific QoL (Leicester Cough Questionnaire (LCQ) total)[13]	**10.9 ± 4.1** in RCC/UCC	Healthy **20.23** ± **0.85** (scale 3–21)	**9.33**
Mean (SD) **LCQ Score at baseline and after 4 weeks**[14]	**11.7 (± 3.0)** baseline, **14.7 (± 3.6) 4** weeks in CC	—	**3** points improvement
Work productivity and activity impairment (WPAI – total impairment)[15]	**26.48 %** in CC (currently employed)	**18.49 %** in matched non-cough controls	**~8%** higher in CC
Healthcare Resource Utilisation (HRU) (6-mo), **Number of Visits**[15]	**7.71** vs **5.25** HCP visits; **0.21** vs **0.04** ER visits in CC	Matched non-cough controls	**2.46** HCP, **0.17** ER visits
Mean total cost over the 5 years (Pre-diagnosis)[16]	Ca. **$8,000** in RCC/UCC cases	Matched controls **$2,700**	**$5,300** more in RCC/UCC
Mean total costs over 2 years, 12 months prior to and following first specialist clinic consultation[17]	Ca. **$2,200** in per cough patient (RCC/UCC/Other)	—	—
Anxiety / depression (self-reported, 12-month)[15]	**3.9 % / 8.3 %** in CC	**1.5 % / 4.1 %** in controls	**2.4% / 4.2%** higher in CC
Sleep problems (12-month)[15]	**66.2 %** in CC	**48.7 %** in controls	**17.5%** more in CC
Mean number of related visits[13]	**9.3** in RCC	**1.1** in controls	**8.39** ratio

12. Takekazu Kubo et al., "Disease Burden and Quality of Life of Patients with Chronic Cough in Japan: A Population-Based Cross-Sectional Survey," BMJ Open Respiratory Research 8, no. 1 (2021): e000764, https://doi.org/10.1136/bmjresp-2020-000764

13. Reynolds JE, Jetté ME, Wright ML, Sundar KM, Gillespie AI, Slovarp LJ. Normative Values for the Leicester Cough Questionnaire in Healthy Individuals. Annals of Otology, Rhinology & Laryngology. 2023;132(6):705-708. doi:10.1177/00034894221112517

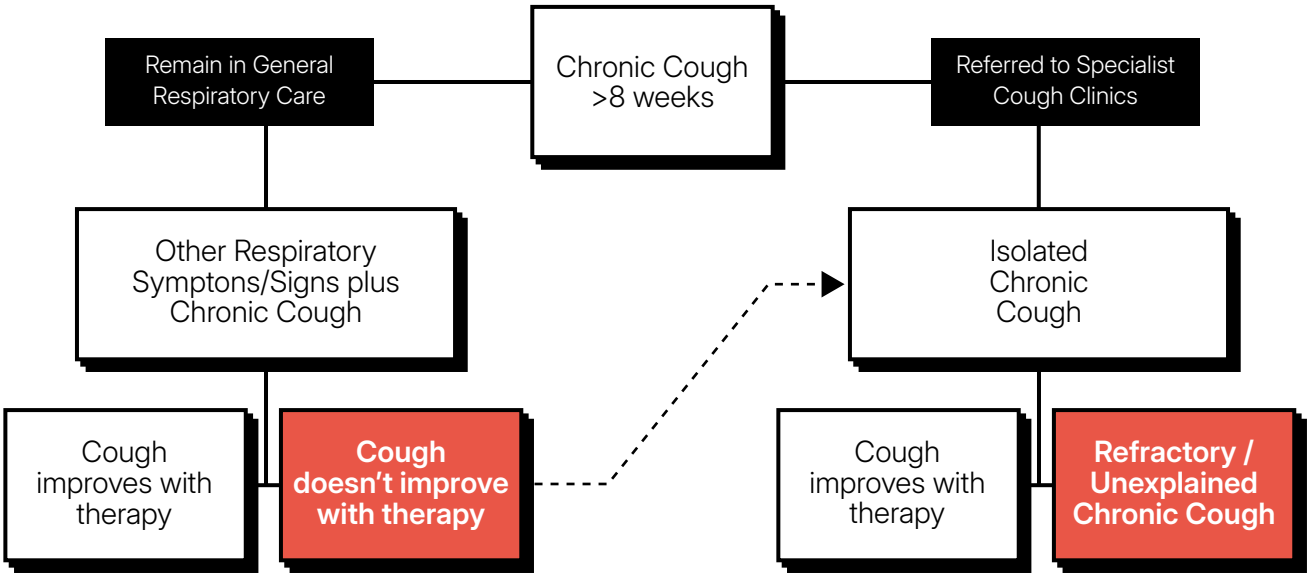
14. Allison Martin Nguyen et al., "Leicester Cough Questionnaire Validation and Clinically Important Thresholds for Change in Refractory or Unexplained Chronic Cough," Therapeutic Advances in Respiratory Disease 16 (May 2022): 17534666221099737, https://doi.org/10.1177/17534666221099737

15. Takekazu Kubo et al., "Disease Burden and Quality of Life of Patients with Chronic Cough in Japan: A Population-Based Cross-Sectional Survey," BMJ Open Respiratory Research 8, no. 1 (2021): e000764, https://doi.org/10.1136/bmjresp-2020-000764

16. Jaclyn A. Smith et al., "An Observational Study to Understand Burden and Cost of Care in Adults Diagnosed with Refractory Chronic Cough (RCC) or Unexplained Chronic Cough (UCC)," Respiratory Research 25, no. 1 (2024): 265, https://doi.org/10.1186/s12931-024-02881-4

Cough Treatments: Who Needs Them?

Exhibit 4A **CLINICAL PROTOCOLS FOR INDIVIDUALS NECESSITATING COUGH THERAPIES[18]**



Current Treatment Landscape

- No drug has been approved by FDA for refractory chronic cough
- RCC care relies on pharmacologic off-label neuromodulators
- Non-pharmacological intervention such as speech or language or behavioral therapy is effective, but underutilized
- Recent years have seen a surge in antitussive development and the first new therapy licensed, though not in the United States or Canada
- A new peripherally acting oral P2X3 receptor antagonist, Gefapixant, now licensed in European Union, United Kingdom, Switzerland, and Japan, is not widely available and not selling well where it is.

17. Peter S. P. Cho et al., "Healthcare Utilization and Costs in Chronic Cough," Current Medical Research and Opinion 38, no. 7 (2022): 1251-17, https://doi.org/10.1080/03007995.2022.2065142

18. COPD: chronic obstructive pulmonary disease, IPF: idiopathic pulmonary fibrosis

Historic Pipeline Failures

Over the last 13 years, 15 different candidates, across 9 different mechanisms were abandoned, failed to generate evidence or were rejected by the FDA.

Mechanisms

- NaV1.7
- TNF-α
- TRPV1
- TRPA1
- α7 nAChR
- NK1
- TRPV4
- Mast cell stabilizer
- P2X3

Failed Candidates

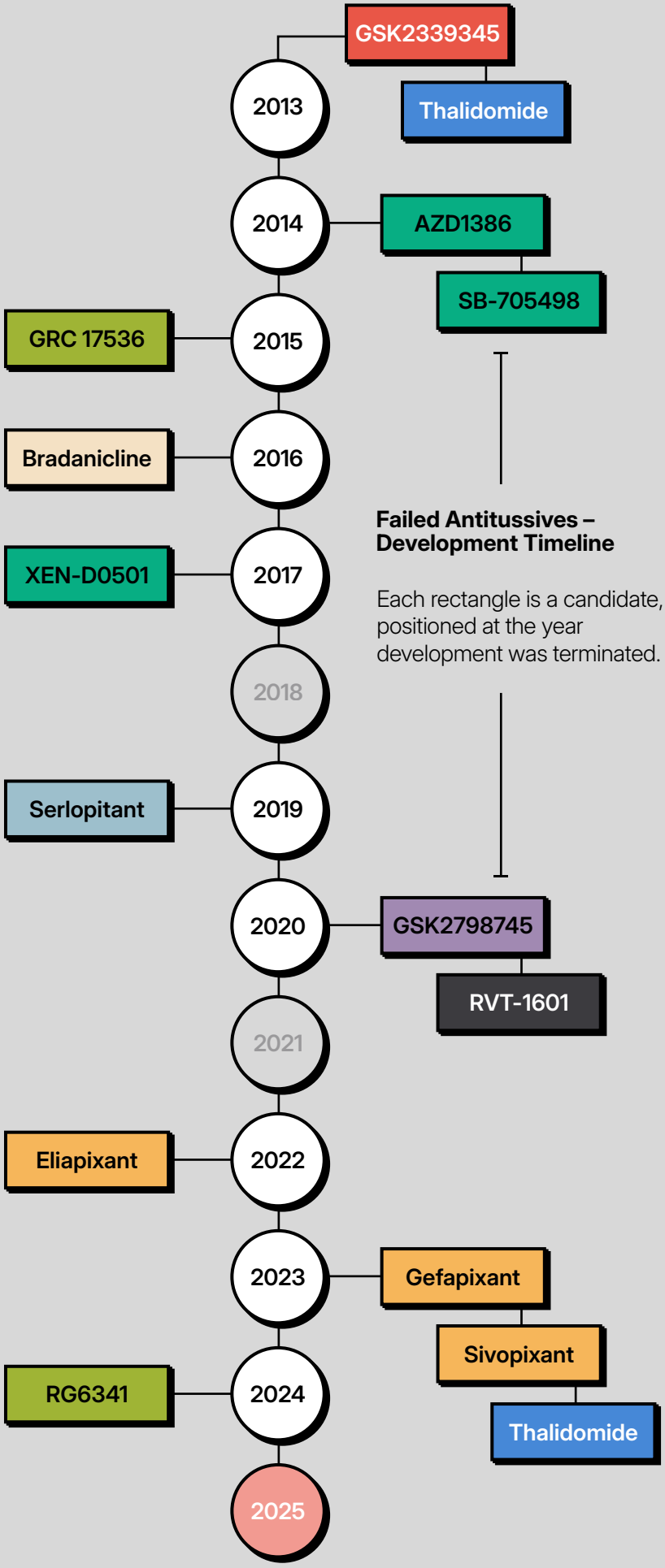
15

Mechanisms Tested

9

Years

13



Failed Antitussives – Development Timeline

Each rectangle is a candidate, positioned at the year development was terminated.

Exhibit 4B STEPWISE APPROACH TO THE DIAGNOSIS AND MANAGEMENT OF CHRONIC COUGH[19, 20]

ACE – Angiotensin-Converting Enzyme; ARB – Angiotensin Receptor Blocker; BAL – Broncho Alveolar Lavage; BDR – Bronchodilator Reversibility; CRS – Chronic Rhinosinusitis; CXR – Chest X-Ray; COPD – Chronic Obstructive Pulmonary Disease; CQLQ – Cough Quality Of Life Questionnaire; GERD – Gastroesophageal Reflux Disease; H_2 – Histamine; ICS – Inhaled Corticosteroids; ILO – Inducible Laryngeal Obstruction; LCQ – Leicester Cough Questionnaire; LTRA – Leukotriene Receptor Antagonist; LABA – Long-Acting β_2-Agonist; LAMA – Long-Acting Muscarinic Antagonist; MTD – Muscle Tension Dysphonia; NAEB – Non-Asthmatic Eosinophilic Bronchitis; PPI – Proton Pump Inhibitor; VAS – Visual Analogue Scale

PRIMARY CARE

Step 1

INITIAL EVALUATION

- **Check:** Cough history, cardio-respiratory, GI, nasal symptoms, ACE-I use, smoking.
- **Test:** Chest X-ray, spirometry., CBC.
- **Urgent referral**: Hemoptysis, weight loss, fever, abnormal chest X-ray.

Step 2

TREATABLE TRAIT (Therapeutic Trials)

- **Asthma/EB:** ICS ± LABA ± LTRA (6–8 weeks)
- **COPD:** LAMA (6–8 weeks)
- **CRS:** Anti-histamine ± nasal steroid, anticholinergic, decongestants (6–8 weeks)
- **Smoking cessation:** ACE-I to ARB antagonist or alternate.
- **GERD:** PPI, ± H2 antagonist, ± prokinetic agents.

PRIMARY CARE

- If Persistent Cough

Step 3

SECONDARY/ TERTIARY CARE

CHECK OR CONFIRM DIAGNOSIS

- **Asthma:** MCT/BCT, BDR, FeNO or sputum eosinophils (if available).
- **NAEB:** Sputum, bronchoscopy, biopsy or BAL
- **CRS:** Naso-Endoscopy ± CT sinus
- **Reflux:** pH impedance ± manometry
- **ILO or MRD:** Laryngoscopy. Optimize adherence, inhaler technique, and exposure control

OBJECTIVE MONITORING

- **Use across:** Step 2 → Step 3 → RCC/UCC to verify response and guide escalation
- **Digital measures:** cough frequency (events/hr), bout duration, diurnal pattern, triggers
- **PROs:** daily VAS (0–100), weekly LCQ (3–21)
- **Responder:** ≥30% reduction in cough counts or LCQ +1.3.
- **Non-responder:** <30% improvement → stop/switch
- **Dashboard alerts:** 2-week (ICS/anti-LKT) and 1-week (morphine) checkpoints

ASSESS SEVERITY OR IMPACT (QoL)

- **Cough severity:** 0-1 Numerical scale, VAS (0-100 mm)
- **Impact on QoL:** LCQ, CQLQ

- **Treat**
  Based on confirm diagnosis

RESPONSE ASSESSMENT

Improves with therapy

NO IMPROVEMENT

Confirm adherence
Consider overlap syndromes

Refractory Chronic Cough **RCC**

Unexplained Chronic Cough **UCC**

SECONDARY/ TERTIARY CARE

TREATMENT

- **Non-pharmacologic:** Cough control therapy, speech/physiotherapy, education or counselling (4–8 weeks).
- **Pharmacologic:** Morphine SR 5–10 mg twice daily, strong recommendation (1–2 weeks), Gabapentin/Pregabalin (8–12 weeks)or Amitriptyline (8–12 weeks) → conditional, monitor for side effects → If no benefit: titrate or rotate agent, consider clinical trial (P2X3 antagonist).

Exhibit 5 TREATMENT OR THERAPY FOR RCC

Treatment	Therapy / Drug	Evidence	Usage Status
Non-pharmacologic	Speech, Language & Physiotherapy[18, 21]	RCTs show improvement in QoL and reductions in cough frequency; benefits maintained post treatment	Guideline-endorsed first-line
Off-label neuromodulator	Gabapentin[18,19]	RCT: LCQ improvement; small studies show symptom reduction	Off-label
	Pregabalin[18,19]	RCT (often with BCST): QoL/severity improvement; limited objective frequency effect	Off-label
Off-label opioid	Morphine (slow-release, low dose)[18,19]	RCTs/clinical studies show LCQ and frequency improvement (responders)	Off-label; ERS supports; CHEST not
Tricyclic	Amitriptyline[18,19]	Small studies suggest symptom/QoL benefit; limited evidence	Off-label (limited evidence)
P2X3 antagonist	Gefapixant[18,19]	Phase 3: ↓ 24-h cough frequency vs placebo; LCQ ↑; meta-analysis: frequency ↓ ~18%, LCQ +~1.0; taste AEs common	Licensed (EU/UK/CH/JP); not FDA-approved
	Camlipixant (BLU-5937)[19]	Phase 2b: additional cough frequency reduction over placebo; low taste AEs; Phase 3 ongoing	Phase 3
κ-opioid receptor agonist / μ-opioid receptor antagonist	Nalbuphine ER (IPF cough focus)[19]	IPF cough: ~50% cough frequency reduction vs placebo with PRO gains	IPF studies; RCC trials ongoing
Sensory counter-irritant	TRPM8 agonist (AX-8)[19]	RCT: significant reduction over 4 h in subgroup with throat irritation; not over 8 h overall	Investigational

RCT: Randomized Controlled Trial, QoL: Quality of Life, IPF: idiopathic pulmonary fibrosis

19. Alyn H Morice et al., "ERS Guidelines on the Diagnosis and Treatment of Chronic Cough in Adults and Children," The European Respiratory Journal 55, no. 1 (2019): 1901136, https://doi.org/10.1183/13993003.01136-2019.

20. I. Satia et al., "Chronic cough: Investigations, management, current and future treatments," Can. J. Respir. Crit. Care Sleep Med., vol. 5, no. 6, pp. 404–416, Nov. 2021, doi: 10.1080/24745332.2021.1979904.

21. Anju T. Peters et al., "Therapeutic and Mechanistic Advances in Chronic Cough," Annals of Allergy, Asthma & Immunology 134, no. 6 (2025): 639–48, https://doi.org/10.1016/j.anai.2024.12.021

Regulatory Reset (U.S./EU/JP)

- FDA precedent and evidentiary bar
- 2020–2027 milestones and readouts
- EU/UK/Japan regulatory status

Exhibit 6 **REGULATORY TIMELINE & READOUTS**

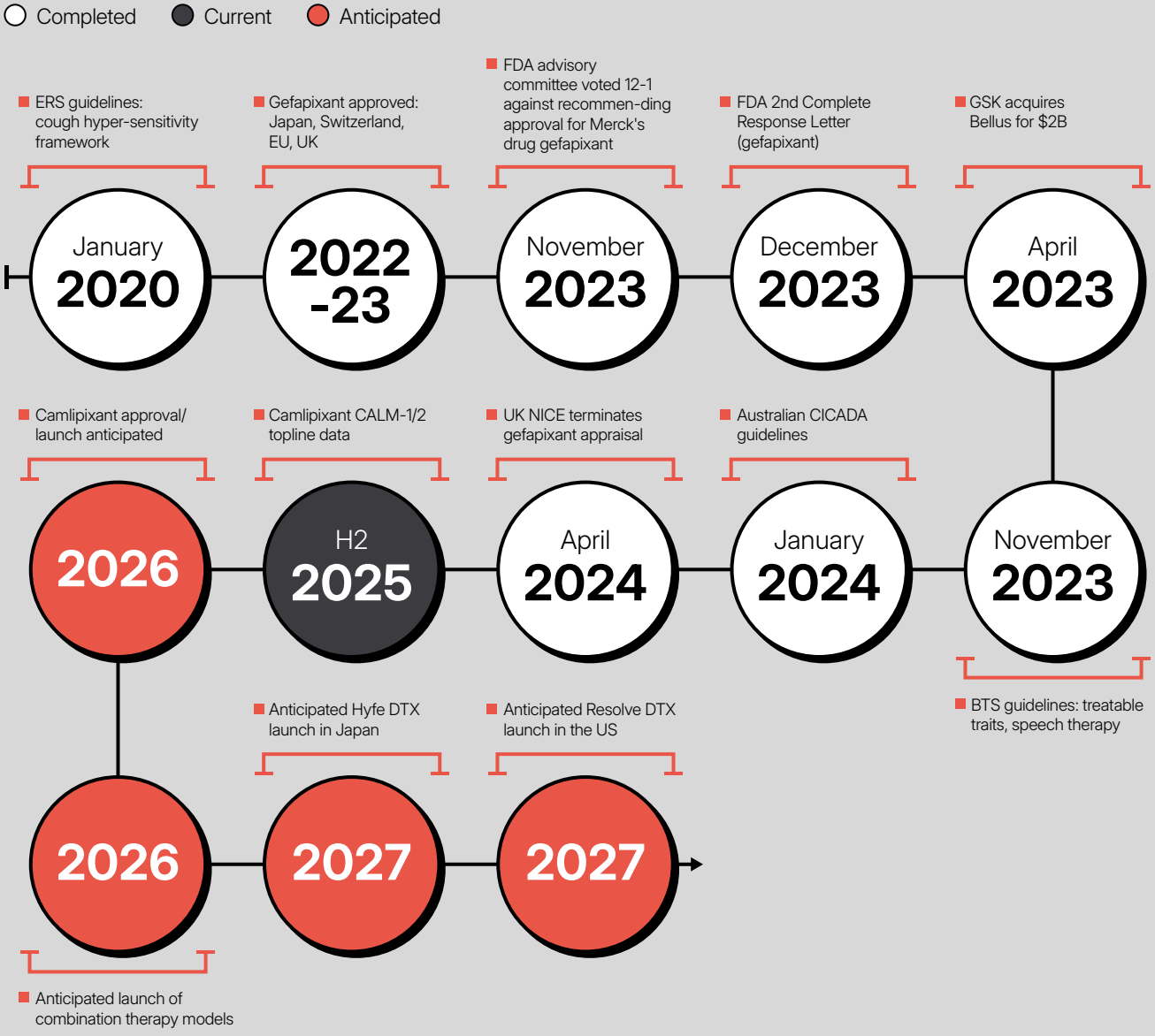


Exhibit 7 **REGULATORY STATUS BY REGION**

Drug & Status	Regions			
Gefapixant *Drug Status: Limited*	**US (FDA)** Rejected 2 times	**EU (EMA)** Accepted Sept. 2023	**Japan (PMDA)** Accepted Jan. 2022	**China (NMPA)** Rejected
Camlipixant *Drug Status: Pipeline*	**US (FDA)** Phase 3	**EU (EMA)** Phase 3	**Japan (PMDA)** Phase 3	**China (NMPA)** -
Nalbuphine ER *Drug Status: Pipeline*	**US (FDA)** Phase 2 → 3	**EU (EMA)** Phase 2	**Japan (PMDA)** -	**China (NMPA)** -
Taplucainium *Drug Status: Pipeline*	**US (FDA)** Phase 2b	**EU (EMA)** Phase 2b	**Japan (PMDA)** -	**China (NMPA)** -
HS-10383 *Drug Status: Pipeline*	**US (FDA)** -	**EU (EMA)** -	**Japan (PMDA)** -	**China (NMPA)** Phase 2
Hyfe DTx *Drug Status: Pipeline*	**US (FDA)** -	**EU (EMA)** -	**Japan (PMDA)** Pre-clinical	**China (NMPA)** -
Cough Pro *Drug Status: At Scale*	**US (FDA)** OTC	**EU (EMA)** OTC	**Japan (PMDA)** OTC	**China (NMPA)** OTC

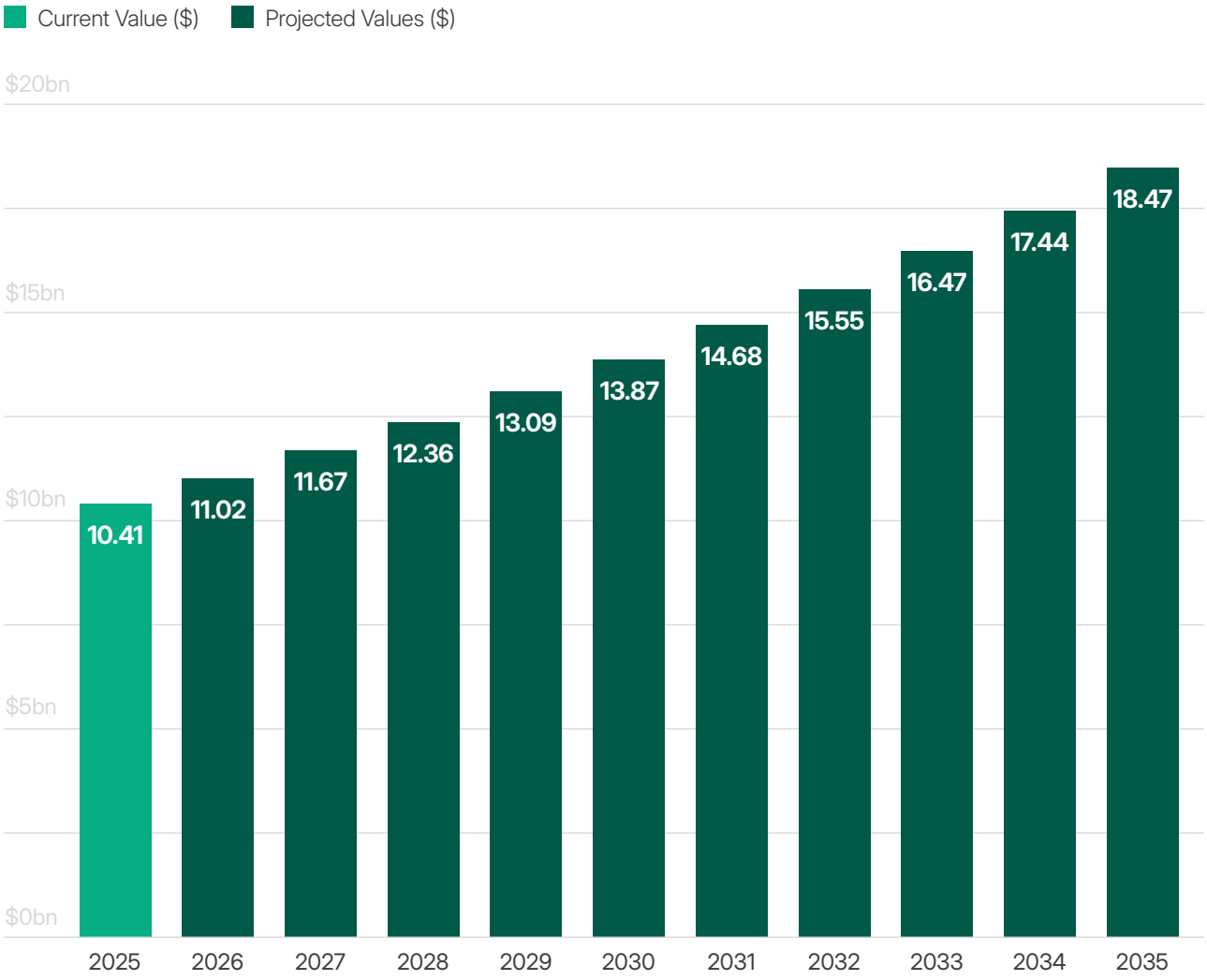
03

Market Outlook & Growth Dynamics

Market Size Forecast to 2035

- RCC treatment market size
- Compound Annual Growth Rate (CAGR) 2025→2035.
- Patient population, market value, and market key players.

Exhibit 8 **RCC TREATMENT MARKET SIZE IN BILLION USD FROM 2025-2035**[22,23]



22. "Chronic Refractory Cough Treatment Market Size & Forecast 2025," accessed October 22, 2025, https://www.futuremarketinsights.com/reports/chronic-refractory-cough-treatment-market

23. GSK reaches agreement to acquire late-stage biopharmaceutical company BELLUS Health | GSK.". Accessed: Oct. 16, 2025. [Online]. Available: https://www.gsk.com/en-gb/media/press-releases/gsk-reaches-agreement-to-acquire-late-stage-biopharmaceutical-company-bellus-health/

Exhibit 9 **COMPOUND ANNUAL GROWTH RATE (CAGR) FROM 2025 TO 2035, BY REGION[20]**

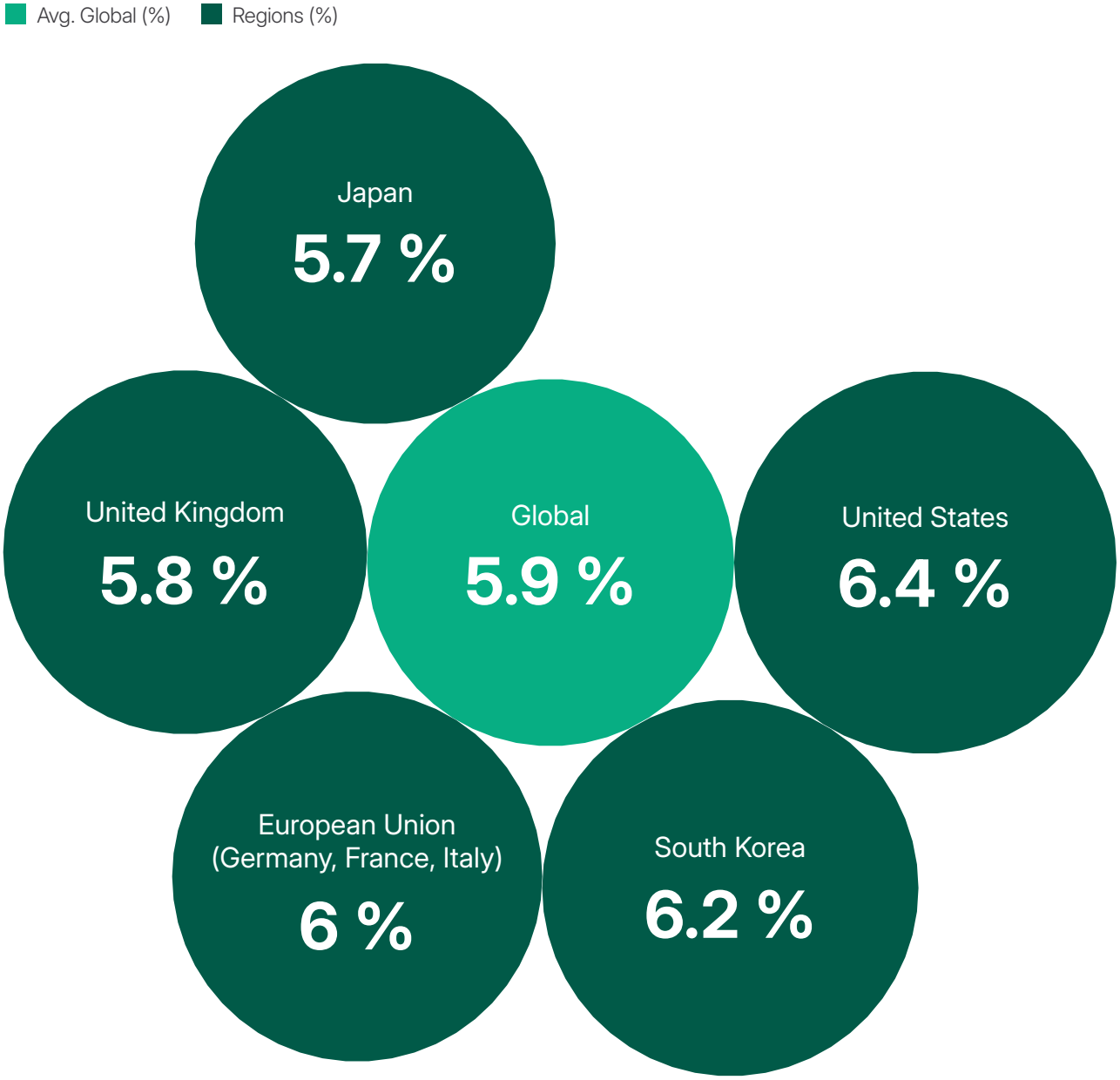
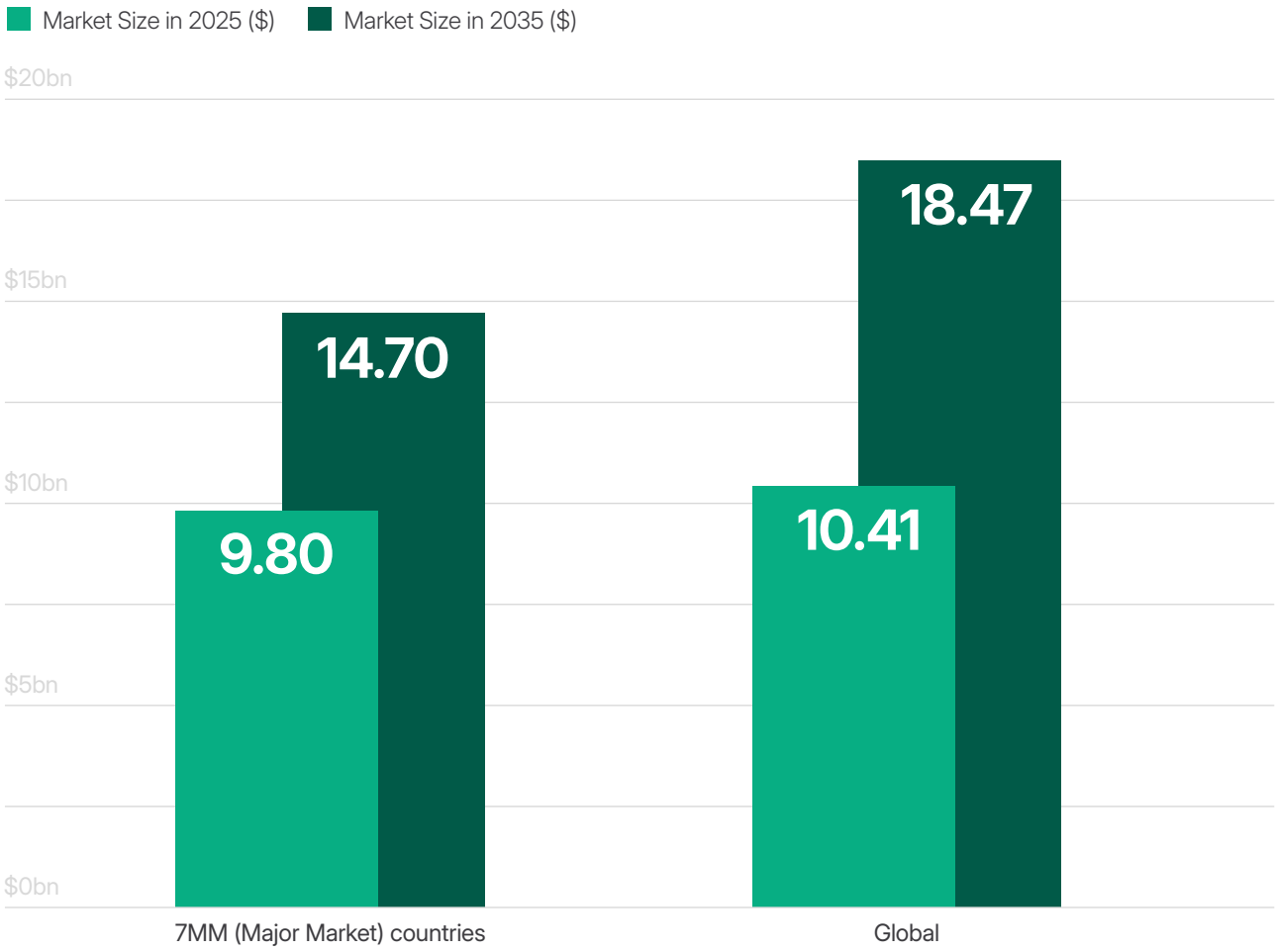


Exhibit 10 PATIENT POPULATION[24,25]

Global CC **80-120 M**	United States[17]/ Europe with RCC **6 M**	RCC cough clinic patients[18] **42 %**
Global RCC **10-12.9 M**	7MM (Major Market) countries **12 M Cases**	

Exhibit 11 MARKET VALUE IN BILLION USD



24. DelveInsight Business Research LLP, "Chronic Refractory Cough Market Still Unexplored, with Pharma Companies Eyeing First-Mover Advantage in the US | DelveInsight," accessed October 23, 2025, https://www.prnewswire.com/newsreleases/chronic-refractory-cough-market-still-unexplored-with-pharma-companies-eyeing-first-mover-advantage-in-the-us-delveinsight-302309439.html

25. See note 1 and 2 on large discrepancies in literature. Additional Source: E. O. Meltzer et al., "Prevalence and Burden of Chronic Cough in the United States," J. Allergy Clin. Immunol. Pract., vol. 9, E. O. Meltzer et al., no. 11, pp. 4037-4044.e2, Nov. 2021, doi: 10.1016/j.jaip.2021.07.022

Investment Response

- Modalities: P2X3, KOR/MOR, TRPM-8, inhaled anesthetic-like, DTx
- Competitive positioning; partnering opportunities

Exhibit 12 GLOBAL MOLECULE INVENTORY OVERVIEW

Inventory Information

GSK
Camlipixant[28]

Efficacy (Phase 2/3)
Phase 2b: 34.4% reduction (50mg BID), 34.2% reduction (200mg BID)< vs placebo (p<0.005).

Taste AE
Dysgeusia 4.8-6.5%.

Timeline/ Status
CALM-1 Phase 3 data readout H2 2025; CALM-2 data readout H2 2026; CALM-1/2 regulatory submission planned H2 2026 (US/EU/JP).

ROA, Dosage
Oral, 50-200mg BID

Hyfe Inc./ Kyorin Pharmaceuticals
Prescription Digital Therapeutics (DTx) (Japan)[30]

Efficacy (Phase 2/3)
Pivotal Trials 2026, Digital.

Taste AE
NA

Timeline/ Status
Japan: 2027/ 2028

ROA, Dosage
Not applicable (NA)

Hyfe Inc.
CoughPro[31]

Efficacy (Phase 2/3)
Early three cases: visible reduction in cough frequency; >50% reduction in one user; robust RCTs pending.

Taste AE
NA

Timeline/ Status
Mid-2024 feature launch; ongoing pilots; larger controlled studies planned 2025; Japan, expanding.

ROA, Dosage
NA

Merck
Gefapixant[27]

Efficacy (Phase 2/3)
Phase 3 (COUGH-1 & COUGH-2): placebo-adjusted reduction in 24-h cough frequency 18.5% at week 12 (COUGH-1) and 14.6% at week 24 (COUGH-2). In COUGH-2, LCQ responders (≥1.3-point increase): 76.8% vs 70.1% on placebo (≈ +6.7% absolute; OR 1.41). Cough-severity VAS responders (≥30 mm improvement): 53.3% vs 40.9% (≈+12.4% absolute; OR 1.65).

Taste AE
COUGH-1/2: 59.3-68.9%, of patients vs 4–8% on placebo. Discontinuation due to AEs (mostly taste disturbance): 21.4–22.5% on 45 mg BID vs 5.3-5.7% on placebo.

Timeline/ Status
FDA rejected 2x (Jan 2022), Approved: Japan, EU, UK, UK NICE: terminated / no recommendation (30 Apr 2024).

ROA, Dosage
Oral. 45mg Two times in a day (BID)

26. "Chronic Refractory Cough Market Size 2025-2035," accessed October 23, 2025, https://www.imarcgroup.com/chronic-refractory-cough-market.

27. Lorcan P. McGarvey et al., "Efficacy and Safety of Gefapixant, a P2X3 Receptor Antagonist, in Refractory Chronic Cough and Unexplained Chronic Cough (COUGH-1 and COUGH-2): Results from Two Double-Blind, Randomised, Parallel-Group, Placebo-Controlled, Phase 3 Trials,"The Lancet 399, no. 10328 (2022): 909-23, https://doi.org/10.1016/S0140-6736(21)02348-5

NeRRe Therapeutics

Orvepitant[32]

Efficacy (Phase 2/3)

Phase 2 (VOLCANO-2): Significant patient-reported cough burden improvement in cough hypersensitivity; ongoing Phase 2 in IPF chronic cough (NCT05185089).

Taste AE

Well-tolerated; no major taste AEs reported.

Timeline/ Status

Phase 2 (IPF chronic cough) ongoing (2025); not yet approved; proof-of-concept in cough hypersensitivity.

ROA, Dosage

Oral, 10, 20 or 30mg once daily (OD)

Sensory Cloud

Sensory Cloud airway hydration mist[33]

Efficacy (Phase 2/3)

No formal Phase 2/3 trials for cough; multiple peer-reviewed studies show improved airway hydration and particle clearance.

Taste AE

No taste AEs; drug-free, natural salts formula.

Timeline/ Status

Marketed direct-to-consumer (2023–2025); available online; ongoing research and scale-up.

ROA, Dosage

Breathe the mist deeply through nose 3 times a day

Shionogi

Sivopixant (S-600918)[29]

Efficacy (Phase 2/3)

Phase 2a (406 pts: Primary endpoint (24hr cough) not met, 300mg: VAS improvement (p=0.0433), LCQ (p=0.0227).

Taste AE

Dose-related taste disturbance: 2.0% (50 mg), 13.6% (150 mg), 33.0% (300 mg) vs 2.9% placebo; all mild–moderate and reversible.

Timeline/ Status

No Phase 3 announced, high placebo response, discontinued.

ROA, Dosage

Oral, 50 mg, 150 mg, and 300 mg once daily (OD)

Competitive Positioning Insights

- **Camlipixant:** First-mover advantage if 2026 launch, best-in-class profile
- **Camlipixant's** superior efficacy (~34% vs gefapixant's ~14-19%) with dramatically reduced taste AE (~5-7% vs 50-81%) addresses FDA's efficacy bar and commercial tolerability concerns. GSK's $50B+ sales projection validates confidence
- **Trevi's Haduvio (Nalbuphine) ER:** Highest efficacy (60% reduction), dual indication (IPF + RCC), undervalued at ~$200-300M market cap, Phase 3 initiation 2026
- **Next-Generation Digital Companions:** no toxicity, personalized regimens, combination therapies, biomarker-selected populations
- **DTx** poses a very interesting alternative to pharmaceutical molecules - potentially achieving higher efficacy with no toxicity. Promising opportunity for combination therapies (molecule plus digital component) that could drive efficacy up as well as revenue through increased retention and adherence

28. Jaclyn A. Smith et al., "Camlipixant in Refractory Chronic Cough: A Phase 2b, Randomized, Placebo-Controlled Trial (SOOTHE)," American Journal of Respiratory and Critical Care Medicine 211, no. 6 (2025): 1038-48, https://doi.org/10.1164/rccm.202409-1752OC

29. Lorcan McGarvey et al., "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 2b Trial of P2X3 Receptor Antagonist Sivopixant for Refractory or Unexplained Chronic Cough," Lung 201, no. 1 (2023): 25-35, https://doi.org/10.1007/s00408-022-00592-5

30. Peter V. Dicpinigaitis et al., "Efficacy and Safety of Eliapixant in Refractory Chronic Cough: The Randomized, Placebo-Controlled Phase 2b PAGANINI Study," Lung, June 1, 2023, 1-12, https://doi.org/10.1007/s00408-023-00621-x, "Hyfe to Launch World's First Prescription Digital Therapeutic to Treat Chronic Cough," accessed October 23, 2025, https://www.hyfe.com/news/hyfe-to-launch-worlds-first-prescription-digital-therapeutic-to-treat-chronic-cough

Exhibit 13 COMPETITIVE LANDSCAPE

Asset	Category	Company	MOA	Status/ Phase	Key Data (Efficacy)	Key Data (AEs)	Timeline/ Milestone
Gefapixant (Lyfnua®)	Approved Drug	Merck	P2X3 antagonist (10–15x selectivity)	Approved: JP, CH, EU, UK; FDA rejected (2x)	18.5% ↓ (12wk), 14.6% ↓ (24wk), abs. diff. 1–2 coughs/hr (N=2,044)	Taste: 50-81%, (dysgeusia 21%, ageusia 6.5%); D/C: 14%	Launched 2022–23 JP/EU/UK; UK NICE terminated, US FDA rejected (Jan/Dec 2023)
Camlipixant (BLU-5937)	Phase 3	GSK	P2X3 antagonist (960–1500x selectivity)	Phase 3 (CALM-1/2) ongoing	34.4% ↓ (50mg BID), 34.2% ↓ (200mg BID) vs placebo (Phase 2b SOOTHE)	Taste: 6.5% (mild, 0 D/C)	Results H2 2024/2025; submission/launch 2026–27; EPS accretive 2027
Nalbuphine ER (Haduvio™)	Phase 2/3	Trevi Therapeu-tics	Kappa opioid agonist / Mu antagonist (KAMA)	Phase 2b/2a (CORAL, RIVER); Phase 3 planned	IPF: 60.2% ↓ (108mg BID), placebo-adj. 43.3%; RCC: 67% ↓ baseline, 57% placebo-adj.	Serious non-fatal AEs: 1.6% vs 10% placebo, nausea, constipation, sedation and, may become habit-forming	Phase 3 start H1 2026, NDA 2026–27; first with efficacy in IPF & RCC
Taplucainium (NOC-110)	Phase 2	Nocion Therapeutics	Charged sodium channel blocker	Phase 2b (ASPIRE) enrolling	First patient Nov 2024; results 2025–26	Not reported	Inhaled; novel non-P2X3; $122M funding
AX-8	Phase 2	Axalbion	TRPM8 agonist, oral disintegrating tablet	Phase 2 (Parts 1–2) 2022–2025	44% ↓ at 2 hours (Part 1); rapid benefit (≤ 15min); refined Part 2 in progress	Not reported	Targets throat discomfort VAS ≥50mm
HS-10383	Phase 2	Jiangsu Hansoh	Selective P2X3 antagonist	Phase 2 ongoing (China), Phase 1 MAD 2024	Half-life 35–48h; no taste AEs in Phase 1	No taste AEs	China-first strategy; domestic focus
Orvepitant (ORV-PF-01)	Phase 2	NeRRe Therapeutics	NK-1 antagonist (brain-penetrant)	Phase 2b (VOLCANO-2): endpoint missed; IPF P2	PROs improved (LCQ +1.6, p=0.009); primary missed (large placebo); IPF cough ongoing	Well tolerated	Funding £20M Series B2; KaNDy sold to Bayer $425M upfront

↓: reduction in cough frequency or severity, OTC: Over-the-counter (consumer), Rx: Prescription, HV = Healthy Volunteers, DTx = Digital Therapeutic, N/A = Not applicable/not reported

31. "Exploring Cough Reduction Through Digital Content-Case Studies from CoughPro's Cough Management Features," accessed October 24, 2025, https://www.hyfe.com/white-papers/cough-reduction-through-digital-content-case-studies-coughpro-cough-management

32. Pipeline-NeRRe Therapeutics, n.d., accessed October 24, 2025, https://www.nerretherapeutics.com/pipeline/

33. "Science," FEND, accessed October 24, 2025, https://www.hellofend.com/pages/science

↓: reduction in cough frequency or severity, OTC: Over-the-counter (consumer), Rx: Prescription, HV = Healthy Volunteers, DTx = Digital Therapeutic, N/A = Not applicable/not reported

Eliapixant (BAY 1817080)	Discontinued/ Failed Drug	Bayer	P2X3 antagonist (high selectivity)	Discontinued (Feb 2022)	27% ↓, but drug-induced liver injury (1 pt, 150mg); high selectivity, but DILI	Liver injury; others	Failed; DILI safety
Sivopixant (S-600918)	Discontinued/ Failed Drug	Shionogi	P2X3 antagonist	Phase 2b failed	60.4% placebo response; signal overwhelmed	Mild-moderate reversible	No phase 3 announced
Filapixant (BAY1902607)	Discontinued/ Failed Drug	Bayer	P2X3 antagonist	Discontinued ~2020	89% taste AEs despite high selectivity	Taste AEs	Failed; PK fluctuations, taste
Hyfe Cough DTx (Japan)	Digital Therapeutic (Rx)	Hyfe/Kyorin	Prescription digital therapeutic (AI+BCST)	In development; Japan first	BCST: 41% ↓ cough, 88% success vs 14% placebo (behavioral); pilot in progress	N/A	Only prescription DTx for chronic cough; launches 2026/27 JP
CoughPro (consumer DTx)	Digital Therapeutic (OTC)	Hyfe Inc.	Consumer DTx, AI+BCST, iOS/Android	Subscription, live in UK/Canada/EU	Case studies: >50% ↓ in some users, dramatic cough frequency reduction, robust RCTs pending	N/A (digital)	Consumer version available in App store. Prescription version Pre-clinical in Japan
Sensory Cloud (hypertonic divalent cations)	Consumer Device	FEND/Sensory Cloud	Airway hydration mist: Ca^{2+}, Mg^{2+}, hypertonic	Marketed (consumer device)	Peer-reviewed: improved airway hydration, reduced PM2.5/PM10/PM 0.1 particle absorption	None reported; 100% natural	Drug-free; 3x/day use; improves mucosal defense; no RCT in RCC
VNS (Vagus Nerve Stimulation)	Neuromo-dulation Device	Multiple	Implanted neuro-stimulator, modulates vagus nerve	FDA-approved for epilepsy/depression; investigational for cough	No RCT efficacy in cough; high device cost ($25–35K); investigational only	Surgical risks, device-related AEs	Not approved for cough; investigational/off-label use; implant required
TENS (Transcutaneous Electrical Nerve Stimulation)	Neuromo-dulation Device	Multiple	Non-invasive electrical stimulation (skin)	FDA-cleared for pain (not cough); pilot cough studies	Pilot: tolerability/feasibility in cough, but no established efficacy	Skin irritation, discomfort	Off-label for cough; consumer units $30–$200; more research needed
taVNS (Trans-cutaneous Auricular VNS)	Neuromo-dulation Device	Multiple	Non-invasive ear-based vagus nerve stimulation	Research stage	Effects bidirectional: can worsen or improve cough depending on parameters	Local irritation, variable response	Research only; not approved for cough; parameter optimization required
tDCS (Transcranial Direct Current Stimulation)	Neuromodulation Device	Multiple	Non-invasive brain stimulation (scalp electrodes)	Healthy volunteer data only	Increased cough threshold in HVs; no patient RCTs yet	Mild headache, tingling, skin redness	Needs patient trials; investigational only

Three Boxes for Commercial Success

- Efficacy >30% (placebo-adjusted)
- AEs related to taste <10%
- Durability 24–52 weeks without tachyphylaxis

FIRST-IN-CLASS TREATMENT

Feature	Camlipixant
Efficacy	**>30%** cough reduction in clinical trials for patients with refractory chronic cough. This was shown in the Phase 2b SOOTHE trial for the 50 mg and 200 mg twice-daily doses.
Adverse Events (AEs)	**<10%** of patients experienced taste alteration (dysgeusia), and it was usually mild to moderate. No cases of complete taste loss (ageusia) were reported in the Phase 2b SOOTHE trial.[28]
Durability	No evidence of tachyphylaxis (decreased effectiveness over time) has been reported in clinical data. Phase 3 trials (CALM-1 and CALM-2) are ongoing to confirm long-term efficacy and safety over **24 to 52 weeks.**

04

Commercial, Economic & Access Landscape

Where Revenue Tailwinds Are Strongest (Mechanisms)

- P2X3, KOR/MOR, inhaled, DTx mechanism
- Selected assets and placebo-adjusted efficacy

Exhibit 14 MECHANISM BENCHMARKING

Mechanism	Adj. Efficacy (%)	Key AEs (Discont. %)	Durability Evidence	Comments
P2X3 antagonists (Gefapixant, Camlipixant)	**16 – 34 %** cough reduction	Taste AEs **38 – 81 %** (Gefapixant), **6.5 %** (camlipixant)	12 – 24 weeks data only	FDA rejections highlight need > 1–2 coughs/hour reduction; NICE cost-effectiveness concerns.
KOR/MOR agonists (Nalbuphine ER)	**~60 %** reduction (Phase 2)	Nausea, constipation, somnolence (**~10 %**)	Durable benefit in IPF and RCC studies	Trevi CORAL and Phase 3 planned 2026.
Inhaled Na^+ channel blockers (Taplucainium)	Ongoing Phase 2b	Mild AEs reported so far (< **5 %**)	Early stage	Nocion Therapeutics $122 M funding (2024 Series B).
Digital Therapeutics (Hyfe DTx)	**40 %** cough frequency reduction	None reported	Real-world pilot and clinical validation underway	KYORIN partnership (Japan), first prescription DTx expected 2026 – 27.
BCST (Behavioral Cough Suppression Therapy / Speech Therapy)	**41 – 88 %** symptom improvement across RCTs and meta-analyses	None drug-related (mild voice fatigue in < **5 %**)	Proven durability ≥ 3 months post-intervention in RCTs	BCST validated behavioral modality; forms the basis for DTx models.

Exhibit 15 SELECTED TREATMENT EFFICACY

Treatment	Cough Reduction	Responder Rate	Taste AEs	Discontinuation
Nalbuphine ER 108mg	**60.2%** (43% adj.)	**65% (≥50%)**	Minimal	Low
Gefapixant 45mg	**18.5-14.6%** (adj.)	Not reported	**58-69%**	**13.9-15%**
Camlipixant	**34.4-34.2%** (adj.)	Not reported	**6.5%**	**0%**
Digital BCST (Such as Hyfe x Kyorin)[35]	**41% reduction** (preliminary study)	**80%** reported QoL improvement	None	Minimal
Gabapentin (Off-label neuromodulator)	**~31%** reduction	**67% (≥50%)**	**31%** nausea	**~10%**

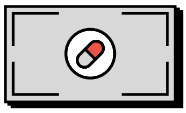
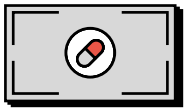
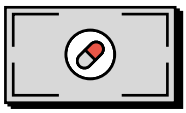
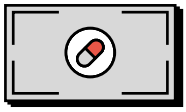
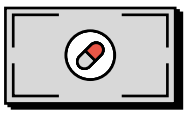
34. "Jaclyn A. Smith et al., "Camlipixant in Refractory Chronic Cough: A Phase 2b, Randomized, Placebo-Controlled Trial (SOOTHE)," American Journal of Respiratory and Critical Care Medicine 211, no. 6 (n.d.): 1038–48, https://doi.org/10.1164/rccm.202409-1752OC

35. New Clinical Trial Evidence Validates Effectiveness of Hyfe's Digital Chronic Cough Platform - https://www.hyfe.com/news/new-clinical-trial-evidence-validates-effectiveness-of-hyfes-digital-chronic-cough-platform

Corporate Financial Flexibility

- Cash runway, leverage, ability to fund launches and PSPs

Exhibit 16 **OPERATOR BALANCE SHEET SNAPSHOT**

Company & Cash ($M)	Debt ($M)	Runway (Qtrs)	Comments
 **GSK** (Camlipixant) **$3,620M**	**$21,280**	>8 (~2 years)	Based on Q2 2025 financials: net debt ≈ $17.35 B; debt-to-equity 1.08; stable credit rating (May 2025)[36]. $2 B acquisition of Bellus (2023) supports Camlipixant launch and PSP funding.
 **Trevi Therapeutics** (Nalbuphine ER) **$203.9M**	**$0.89**	~8 (~4.8 years; runway into 2029)	As of Q2 2025 report (June 30, 2025): $203.9 M in cash and equivalents, supported by a $115 M public offering. Annual burn ≈ $43 M. Debt negligible (<$1 M)[37]. Haduvio (oral nalbuphine ER) is advancing to Phase 3 for RCC/IPF; FDA meeting planned Q4 2025.
 **Nocion Therapeutics** (Taplucainium) **$122M**	**No debt disclosed**	6–8	$62 M Series B (Mar 2024); Phase 2b fully funded through 2026[38].
 **NeRRe Therapeutics** (Orvepitant) **$26.6M**	**Not disclosed**	Uncertain or estimated ≤ 4 quarters	Privately held; $84.4M rose since 2012 from investors[39]. Last funding of £20 M in Series B2 (July 2021) supported Phase 2 Orvepitant (IPF cough)[40]. Likely requires new capital or partner to advance Phase 3.
 **Hyfe Inc.** (Digital Therapeutics) Confidential early-stage funding	**Not disclosed**	–	Early-stage US based privately held company[41]. Japan-first launch via Kyorin (2025); collaboration-based funding model.

36. Christopher Kawala et al., "Gefapixant, a P2X3 Receptor Antagonist, for the Treatment of Refractory or Unexplained Chronic Cough: A Randomized, Double-Blind, Controlled, Parallel-Group, Phase 2b Trial: Discussions from a Twitter Journal Club @respandsleepjc (#rsjc)," Canadian Journal of Respiratory, Critical Care, and Sleep Medicine 5, no. 1 (2021): 72–74, https://doi.org/10.1080/24745332.2020.1777598 "Glaxosmithkline | GSK - Debt," accessed October 26, 2025, https://tradingeconomics.com/gsk:us:debt

37. "Trevi Therapeutics Reports Second Quarter 2025 Financial Results and Provides Business Updates - Aug 7, 2025," accessed October 26, 2025, https://ir.trevitherapeutics.com/investors/; "Trevi Therapeutics (TRVI) Statistics & Valuation," StockAnalysis, accessed October 26, 2025, https://stockanalysis.com/stocks/trvi/statistics/

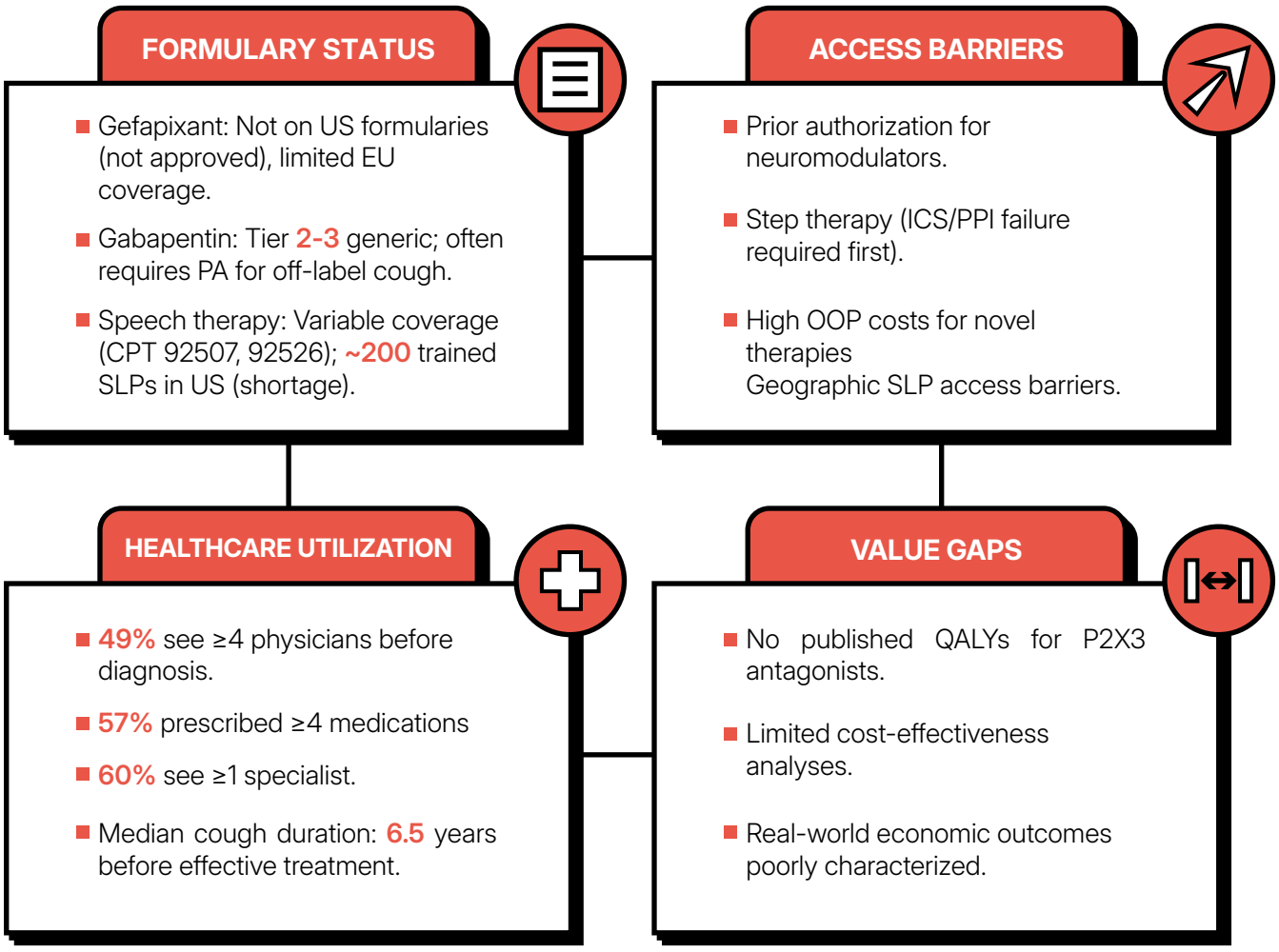
38. Workbox, "Nocion Therapeutics Announces $62 Million Series B Financing to Advance Lead Program in Cough into Later Stage Developmen," Nocion Therapeutics, March 3, 2024, https://www.nociontx.com/nocion-therapeutics-announces-62-million-series-b-financing-to-advance-lead-program-in-cough-into-later-stage-development/

39. "NeRRe Therapeutics 2025 Company Profile: Valuation, Funding & Investors | PitchBook," accessed October 27, 2025, https://pitchbook.com/profiles/company/55807-84

Payer/HTA Heat map (US/EU/JP)

- U.S. PA/step therapy expectations; EU/UK/Japan price corridors.

Exhibit 17 **PAYER PERSPECTIVES**



40. "NeRRe Therapeutics Raises £20 Million," Forbion, accessed October 27, 2025, https://forbion.com/news-insights/news/nerre-therapeutics-raises-20-million-in-a-series-b2-financing-round/

41. ""Hyfe Stock Price, Funding, Valuation, Revenue & Financial Statements," accessed October 27, 2025, https://www.cbinsights.com/company/hyfe/financials

42. "Lyfnua to Get 7.7% Price Cut in November, Retevmo Analysis Results Reported: CEA," PHARMA JAPAN, accessed October 27, 2025, https://pj.jiho.jp/article/249435

43. Peter S. P. Cho et al., "Healthcare Utilization and Costs in Chronic Cough," Current Medical Research and Opinion 38, no. 7 (2022): 1251–57, https://doi.org/10.1080/03007995.2022.2065142

44. Vishal Bali et al., "Understanding the Economic Burden of Chronic Cough: A Systematic Literature Review," BMC Pulmonary Medicine 23, no. 1 (2023): 416, https://doi.org/10.1186/s12890-023-02709-9

45. Lorcan P. McGarvey et al., "A Real World Study of Cough Burden and Quality of Life of UK Patients Who Have Undergone Evaluation for Chronic Cough," Current Medical Research and Opinion 39, no. 12 (2023): 1717–28, https://doi.org/10.1080/03007995.2023.2284371

Exhibit 18 PRICING & ACCESS HEAT MAP

Region	**United States**
Expected Price ($/mo)	NA (no approved drug)*
Coverage Tier	NA
Key Restrictions	Prior authorization and step therapy required for off-label neuromodulators (e.g., gabapentin, amitriptyline). Must fail ICS/PPI therapy first.
Comments	No FDA-approved RCC therapy. Gefapixant received a 2nd CRL (Dec 2023). Future drugs will face high bar for efficacy (**>16–19%** benefit threshold) and adherence to cough hypersensitivity framework. Expected specialty-tier pricing with PA.
Region	**United Kingdom**
Expected Price ($/mo)	NA (no NHS price)*
Coverage Tier	NA
Key Restrictions	-
Comments	NICE appraisal (TA969) was terminated (Apr 2024); manufacturer withdrew submission. No NHS coverage or reimbursement pathway currently exists.
Region	**European Union**
Expected Price ($/mo)	Country-specific (EMA-approved)
Coverage Tier	Mid-tier (subject to national HTA)
Key Restrictions	Label-restricted to RCC/UCC indication, taste AE profile may trigger prescribing caution.
Comments	EMA approved Lyfnua (Sept 2023); reimbursement varies by member state (e.g., AMNOG in Germany, HAS/ASMR in France, AIFA in Italy). Cost-effectiveness scrutiny expected due to modest incremental benefit.
Region	**Japan**
Expected Price ($/mo)	≈ **¥11,250–¥12,190**/ mo (≈ US **$75–85**, FX = **145**)
Coverage Tier	NHI-listed (national reimbursement)
Key Restrictions	Restricted to RCC/UCC label per MHLW listing
Comments	Gefapixant (Lyfnua) reimbursed under Japan's national insurance. Initial NHI price: **¥203.2**/tab (45 mg BID ≈ ¥12,190/mo). CEA-based price cut: **7.7%** (Aug 2023)[42] → ~**¥11,250**/mo. ICER: **¥17.6** million/QALY

*There are no published US/UK/EU list prices for RCC drugs because no US/UK approval exists and EU prices are negotiated country-by-country. Where exact national list prices are available (Japan), it is provided

Health-Economics Lens

- Direct costs, excess utilization, productivity; dossier evidence plan[66,67]

Exhibit 19 HEALTH-ECONOMICS AND OUTCOMES RESEARCH (HEOR) EVIDENCE PLAN

Claim	Evidence Type	Metric / Endpoint
RCC drives higher healthcare utilization & costs vs non-CC	Retrospective obs., claims & SLR	Outpatient/ED/hospitalizations; total medical costs; correlation with cough severity[43,44]
RCC causes material productivity loss	Cross-sectional	WPAI absenteeism, presenteeism45, overall work & activity impairment (%)[46]
Cough-specific QoL improves with effective therapy	Instrument validation & MCID	LCQ Total 1.3-2.3 & domain scores47, MCID 1.3 points[48]
Objective cough frequency is a registrational endpoint	RCTs (COUGH-1 & 2)[49], regulatory docs. [50]	24-h cough frequency at Week 12, Week 24
Japan HTA: ICER ~¥17.6M/QALY → 7.7% price cut	Cost-effectiveness evaluation[51]	Δ Cost ¥107,160; ΔQALY 0.006; post-CEA price –7.7%
Taste AEs (dysgeusia) limit persistence or adherence	Meta-analysis & EPAR safety	Dysgeusia or ageusia rates, discontinuation due to AEs[52,53]
EU access depends on national HTA despite EMA OK	Regulatory/HTA landscape[51]	Member-state appraisal outcomes (AMNOG/HAS/AIFA)
UK: no NHS price/access (appraisal terminated)	HTA decision	Terminated TA; no recommendation[54]
US: no approved RCC drugs; high payer bar	Regulatory & payer policy	AdCom 12–1 against, CRL55. PA/step edits likely if approved
Dossier mapping of LCQ → EQ-5D to model utilities	Method plan (to develop)	Mapping algorithm, anchor-based MCID, from one metric (LCQ) to another (EQ-5D)[56]

46. Raffaele Antonelli Incalzi et al., "Prevalence, Clinical Characteristics, and Disease Burden of Chronic Cough in Italy: A Cross-Sectional Study," BMC Pulmonary Medicine 24, no. 1 (2024): 288, https://doi.org/10.1186/s12890-024-03095-6

EU/UK/Japan Reimbursement

- NICE/PMDA signals; EU pricing pressures; DiGA-like routes.

Exhibit 20 **REIMBURSEMENT SUMMARY BY MARKET**

Market	**United States**
Status	No approved RCC drug yet
ICER/HTA Notes	Payers expect QALY/RWE, prior-auth. standard
Price Corridor	**$10–20K/yr** modeled*
Next Step	Align dossier to payer evidence needs; prepare PA/step protocols
Market	**United Kingdom**
Status	NICE appraisal terminated (no NHS coverage)
ICER/HTA Notes	Cost-effectiveness concern flagged
Price Corridor	Within EU corridor (post-negotiation)
Next Step	Re-engage with HTA after stronger QALY evidence/RWE
Market	**European Union**
Status	Gefapixant approved (limited reimbursement in places)
ICER/HTA Notes	Single-payer negotiation, risk-sharing
Price Corridor	**~$5–12K/yr** post-negotiation*
Next Step	Country-by-country HTA; commit to post-marketing studies
Market	**Japan**
Status	Gefapixant reimbursed; national insurance
ICER/HTA Notes	ICER **~¥17.6M/QALY**; **7.7%** price cut (Aug 2023)
Price Corridor	**¥1–2M/yr**
Next Step	Maintain RWD; manage adherence (taste) to support value case

*The US/EU prices above are modeled placeholders for scenario planning (not official list prices). There are no published US/EU list prices for RCC drugs because no FDA approval exists.

47. Antonelli Incalzi et al., "Prevalence, Clinical Characteristics, and Disease Burden of Chronic Cough in Italy."

48. A. A. Raj et al., "Clinical Cough IV:What Is the Minimal Important Difference for the Leicester Cough Questionnaire?," in Pharmacology and Therapeutics of Cough, ed. Kian Fan Chung and John Widdicombe (Springer, 2009), https://doi.org/10.1007/978-3-540-79842-2_16

05

Pipeline, Strategy & Scenarios

Pipeline Scorecard & 2025–2027 Milestones

- Key readouts and regulatory paths for leading assets

Exhibit 21 **COMPANY PIPELINES**

Company (Asset)	Stage (as of 2025)	Next Milestone / Notes
GSK (Camlipixant / BLU-5937)	**Phase 3** (CALM-1, CALM-2)	Topline results H2 2024–2025; regulatory submissions 2026; expected launch 2026–2027; "scale opportunity" > £2B potential
Trevi Therapeutics (Haduvio / Oral Nalbuphine ER)	**Phase 2b** (CORAL, IPF cough); Phase 2a (RIVER, RCC) completed	CORAL topline Q2 2025; Phase 3 initiation H1 2026; NDA target 2026–2027; RCC Phase 2a showed 67% cough reduction.
Nocion Therapeutics (Taplucainium Bromide / NTX-1175)	**Phase 2b** (ASPIRE) enrolling	First patient dosed Nov 2024; topline 2025–2026; $122M total raised to fund through readout (Series B, $62-70M, Mar 2024).
Axalbion (AX-8)	**Phase 2** (Part 2) enrolling	Enrollment Aug 2024–H2 2025; 40 mg TID in refined RCC population; results expected 2025–2026.
NeRRe Therapeutics (Orvepitant)	**Phase 2** (IPF chronic cough)	Funded by £20M Series B2 (2021); exploring partnership for Phase 3; leadership previously sold KaNDy to Bayer ($425M+).
Hyfe Inc. (CoughPro)	**Commercial OTC wellness product**	Consumer-grade digital cough tracker incorporating BCST techniques; available worldwide as wellness product
Kyorin Pharmaceutical × Hyfe Inc (HyfeDTX)	**Digital Therapeutic** (pre-launch)	Japan-first launch planned 2027; reimbursement expected under NHI collaboration.

Hansoh Pharma (HS-10383)	**Phase 2** (China-first)	Once-daily oral P2X3 antagonist with no taste AEs in Phase 1; ongoing Phase 2 in 2025.
Shionogi & Co. (Sivopixant / S-1207)	**Discontinued post-Phase 2b**	Terminated following Phase 2b failure (2023); no ongoing chronic cough studies.
Bayer AG (Eliapixant / Filapixant)	**Discontinued**	Both programs halted; no active RCC pipeline since 2023.

The Placebo Problem

- High placebo response; objective frequency endpoints are critical.

Placebo Effect Challenge

60-85% placebo response rate (Gefapixant, Sivopixant, Orvepitant) complicates clinical development:

- Gefapixant Ph3: 60-82% placebo pts achieved ≥1.3-point LCQ improvement.
- Placebo reduced awake cough 54.8%, VAS improved 24.2mm.
- Only 6.9% absolute difference vs active in responder rates.
- Requires >30% cough reduction for meaningful clinical benefit perception.

The Retention Multiplier (Adherence Economics & LTV)

- DTx-driven duration improvements; LTV/ROI framework.

The Problem

Non-retention cost pharma $650B annually (2016 estimate, likely >$800B today). 30% of prescriptions never filled, 50% of chronic therapy patients discontinue within 12 months. For RCC specifically, current neuromodulators show no sustained benefit post-discontinuation—patients stop therapy, symptoms return, value lost.

The Opportunity

Improving average therapy duration by 20% generates growth equivalent to adding thousands of new patients at <10% acquisition cost. In chronic cough (avg. 6-8 month treatment duration), extending to 9.6 months via digital retention tools = 20% LTV increase with marginal investment.

Exhibit 22 **PROVEN RETENTION STRATEGIES:** Benchmark Data

Intervention	Results	Cost Structure	Scalability
Patient Support Programs (AbbVie Humira Complete PSP)	**29% higher adherence** **22% lower discontinuation** **51% standard care stopped** **35% with support** (12mo)	■ High-touch: nurse ambassadors, call centers. ■ ~$500-1,500/patient/year	Limited; labor-intensive
Connected Digital Sensors (Resmed/Propeller inhalers)	**58% increase controller medication adherence** **78% reduction rescue inhaler use**	■ Smart devices + app platform. ■ ~$150-300/patient/year	High; hardware + software
Gamification/Incentives (HealthPrize platform)	**54% increase prescription fill rates** **39% reduction refill gap** (diabetes)	■ Rewards program + engagement platform. ■ ~$100-250/patient/year	Very high; pure software
Patient Education/Journey Mapping	**20% adherence increase** (chronic conditions) **Improved satisfaction scores**	■ Digital content + targeted messaging. ■ ~$50-100/patient/year	Very high; content distribution

RCC-Specific Retention Economics

Baseline Assumptions

- Avg. RCC treatment duration: **6-8** months (current neuromodulators).
- Monthly Rx cost: **$900-1,200** (novel P2X3 antagonists estimated **$10-15K** annual).
- Patient acquisition cost: **$2,000-5,000** (detailing, DTC, PSP enrollment).
- Current discontinuation: **20-30%** within **3** months, **50%**+ by **12** months.

50. "Lyfnua | European Medicines Agency (EMA)," July 17, 2023, https://www.ema.europa.eu/en/medicines/human/EPAR/lyfnua

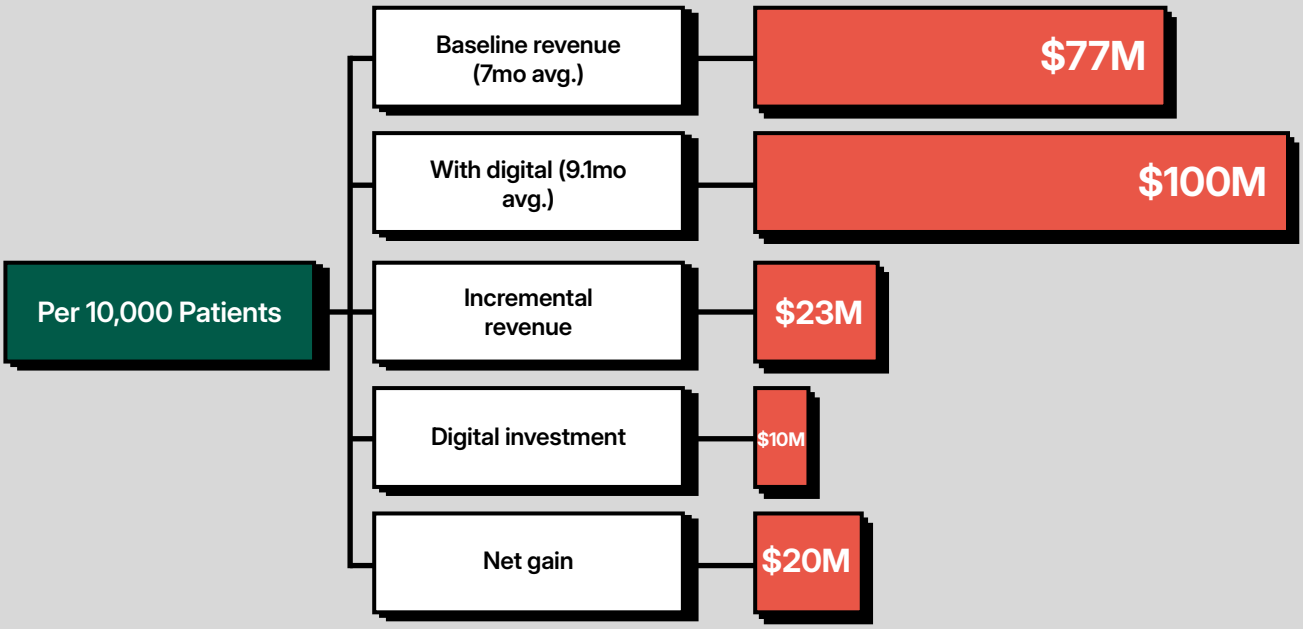
51. "[Cost-Effectiveness Evaluation," accessed October 27, 2025, https://database.inahta.org/article/30940

52. Elena Kum et al., "Efficacy and Tolerability of Gefapixant for Treatment of Refractory or Unexplained Chronic Cough," JAMA 330, no. 14 (2023): 1359–69, https://doi.org/10.1001/jama.2023.18035

53. "Lyfnua | European Medicines Agency (EMA)," July 17, 2023, https://www.ema.europa.eu/en/medicines/human/EPAR/lyfnua

Exhibit 23 DIGITAL THERAPEUTIC VALUE PROPOSITION

Scenario	Baseline (no digital)	With Digital Therapeutic	Incremental Value
Avg. duration	7 months	9.1 months (+30%)	+2.1 months
Revenue/patient	$7,700	$10,010	+$2,310 (+30%)
Discontinuation (12mo)	55%	38.5% (-30% relative)	16.5pp improvement
LTV (3-year)	$15,400	$22,110	+$6,710 (+44%)
Digital platform cost	$0	$300/patient/year	ROI: 7.7:1



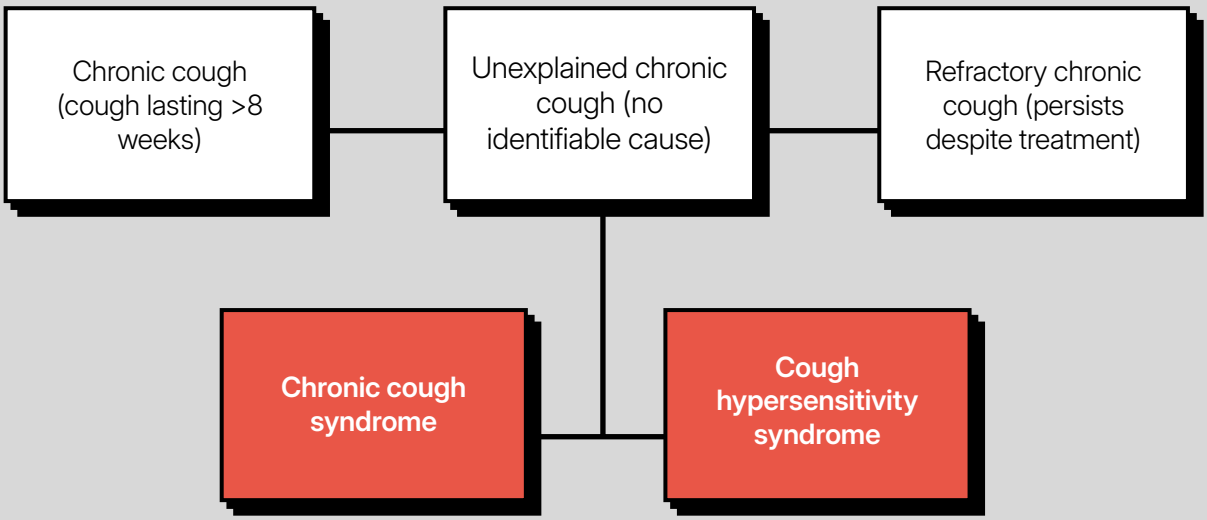
Equivalent to adding 2,990 new patients without acquisition costs.

54. "Overview | Gefapixant for Treating Refractory or Unexplained Chronic Cough (Terminated Appraisal) | Guidance | NICE," NICE, April 30, 2024, https://www.nice.org.uk/guidance/ta969

55. Robert Barrie, "FDA Rejects MSD's Gefapixant for Chronic Cough," Pharmaceutical Technology, December 21, 2023, https://www.pharmaceutical-technology.com/news/fda-rejects-msds-gefapixant-for-chronic-cough/

56. Andrew Trigg et al., "Psychometric Validation of the Severity of Chronic Cough Diary, Leicester Cough Questionnaire, and a Cough Severity Visual Analogue Scale in Patients with Refractory Chronic Cough," Journal of Patient-Reported Outcomes 9, no. 1 (2025): 65, https://doi.org/10.1186/s41687-025-00888-z.56.

Color Box: The Lost Coughers
The Nomenclature Trap



Each term applies different diagnostic criteria, treatment pathways, and specialist referral patterns. A patient might be diagnosed with "chronic cough" by their primary care physician, "unexplained chronic cough" by a pulmonologist after negative tests, and never reach the "refractory" designation that would qualify them for specialist care or clinical trials—despite coughing continuously for years.

The result: Different standards apply to different patients, not based on symptom severity, but on which doctor they see and which terminology that doctor prefers.

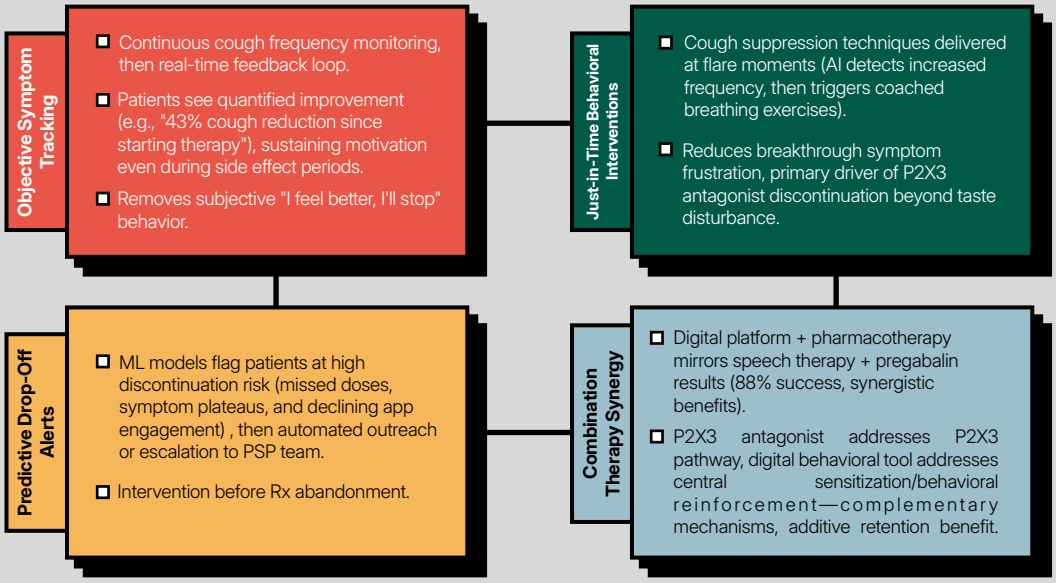
The Cost of Invisibility

Without disease status, chronic cough lacks:

- **Clinical legitimacy:** Primary care physicians often dismiss persistent cough as a symptom to treat, not a condition to diagnose
- **Specialist pathways:** No clear referral criteria or designated specialists (pulmonology? ENT? gastroenterology?)
- **Treatment guidelines:** Fragmented, inconsistent protocols across different medical specialties
- **Patient community:** No one identifies as "a chronic cougher", then the condition remains shameful and isolating
- **Research funding:** Without ICD code clarity and disease recognition, clinical trials struggle to define endpoints and recruit patients
- **Reimbursement pathways:** Payers question the medical necessity of treatments for a "symptom" rather than a "disease".

Next-Generation Retention Tools for Chronic Cough

AI-Powered, Sensor-Based Platforms (e.g., CoughPro, Dtx) offer RCC-specific advantages:



Commercial Model

- Pharma sponsors/subsidizes digital platform access for patients on therapy.
- Cost: **$200-400**/patient/year (vs **$2,000-5,000** acquisition cost).
- **25-35%** improvement in **12**-month persistence rates.
- Payback period: **2-3** months of extended therapy.

Pharma Launch Scenario (Digital-Enhanced)

- **200K** patients Year 1 (base case)
- Without digital: 7-month avg. duration → **$1.4B** revenue
- With digital: **9.1**-month avg. duration → **$1.82B** revenue
- Incremental: **+$420M** (**+30%**)
- Digital investment: **~$60M**
- Net: **+$360M** Year 1 (6:1 ROI)

Payer Value Proposition

- Reduced specialist visits (fewer symptom relapses from non-adherence).
- Lower rescue medication use (maintenance therapy continuity).
- Improved productivity (sustained cough control vs episodic treatment).
- Health economic data demonstrates cost-effectiveness (UK NICE requirement).

Strategic Positioning

For Novel RCC Assets

- **Integrated Digital Strategy = Competitive Advantage:** Next-gen launches require bundled digital therapeutic demonstrating adherence improvement + cost offset.
- **Differentiation Beyond Molecule:** If efficacy/tolerability similar with competitors/ generics, digital ecosystem becomes tie-breaker. "Best-in-class molecule + best-in-class retention platform."
- **Real-World Evidence Generation:** Digital platforms capture objective efficacy data (24-hour cough frequency), adherence patterns, and patient-reported outcomes—feeds post-marketing studies, label expansion, guideline inclusion.
- **Prescription Defense:** Once patients engage with digital platform (app downloaded, device paired), switching costs increase dramatically. Behavioral lock-in protects share vs me-too P2X3s.

First-Mover Advantage Calculation

- 2-month head start on competitors → 200K patient platform engagement.
- Switching cost: patients lose accumulated data, learned behavioral techniques, community connections.
- Estimated retention advantage: 15-20pp vs late-following competitors.
- Translates to 30-40K patient volume protection = $330-440M annual revenue shiel.

Investment Implication

Digital therapeutic partnerships should be evaluated as core value drivers, not marketing add-ons. For RCC assets in development, allocating $10-20M to digital strategy (platform development, RCT validation, payer dossier) delivers 5-10x ROI through LTV extension, potentially worth $50-200M in exit valuation

57. 11 Min Read, "BELLUS Health Announces Positive Topline Results from Its Phase 2b SOOTHE Trial of BLU-5937 for the Treatment of Refractory Chronic Cough," BioSpace, December 13, 2021, https://www.biospace.com/bellus-health-announces-positive-topline-results-from-its-phase-2b-soothe-trial-of-blu-5937-for-the-treatment-of-refractory-chronic-cough

58. Bellus Health Inc. - a GSK company, A Phase 3, 24-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Efficacy and Safety Study With Open-Label Extension of BLU-5937 in Adult Participants With Refractory Chronic Cough Including Unexplained Chronic Cough (CALM-2), Clinical trial registration no. NCT05600777 (clinicaltrials.gov, 2025), https://clinicaltrials.gov/study/NCT05600777

59. "Sec.Gov/Archives/Edgar/Data/1259942/000115752323000470/A53365640ex99_1.Htm," accessed October 28, 2025, https://www.sec.gov/Archives/edgar/data/1259942/000115752323000470/a53365640ex99_1.htm

60. Trevi Therapeutics Inc, "Trevi Therapeutics Announces Positive Topline Results from the Phase 2a RIVER Trial of Haduvio in Patients with Refractory Chronic Cough," accessed October 28, 2025, https://www.prnewswire.com/news-releases/trevi-therapeutics-announces-positive-topline-results-from-the-phase-2a-river-trial-of-haduvio-in-patients-with-refractory-chronic-cough-302396487.html

61. "Trevi Therapeutics Announces Positive Topline Results from the Phase 2b CORAL Trial of Haduvio in Patients with Idiopathic Pulmonary Fibrosis Chronic Cough - Jun 2, 2025," accessed October 28, 2025, https://ir.trevitherapeutics.com/investors/

Case Study — Camlipixant

- Efficacy, taste AEs, durability, launch math.

Exhibit 24 CAMLIPIXANT KEY DATA

Metric	Result	Comparator	Adj. Effect	Comments
24-h cough frequency (SOOTHE Phase 2b)	↓ **28–32%** at **50–200** mg BID (Day 28)	Placebo	Placebo-adjusted improvement at active doses	Phase 2b SOOTHE reported statistically significant and clinically meaningful reductions; AE profile similar to placebo overall[4]
Taste AEs (SOOTHE Phase 2b)	**4.8–6.5%** (no ageusia; no discontinuations due to taste)	Placebo **~0%**	—	Markedly lower taste disturbance vs first-gen P2X3 (e.g., gefapixant)[32, 57]
Durability signal	Effect observed through Day 28 in Phase 2b; Phase 3 designed for **24–52** wks	—	—	CALM-1 (52 wks) & CALM-2 (24 wks) are the confirmatory durability studies[58]
Phase 3 status & timing	CALM-1 topline H2 2024; CALM-2 2025 (company disclosures)	—	—	GSK/Bellus disclosures and filings note timelines and validation work[4,59]

Case Study — Nalbuphine ER (Haduvio)

- RCC/IPF read-through, program plan.

Exhibit 25 NALBUPHINE ER KEY DATA

Metric	Result	Comparator	Adj. Effect
RCC Phase 2a (RIVER), **primary endpoint**[60]	**57%** placebo-adjusted reduction in 24-h cough frequency, **p<0.0001**	Placebo	**–57%**
IPF chronic cough Phase 2b (CORAL), **primary endpoint**[61]	Met across doses; best dose **–43.3%** placebo-adjusted	Placebo	**–43.3%** (108 mg BID)
Program next steps[62,63]	FDA meeting Q4 2025 to align Phase 3 in IPF cough, broader ILD program planned	—	—

62. "Trevi Therapeutics Reports Second Quarter 2025 Financial Results and Provides Business Updates - Aug 7, 2025," accessed October 28, 2025, https://ir.trevitherapeutics.com/investors/.

63. "Positive Topline Results from Phase 2b Trial of Haduvio in Patients with IPF Chronic Cough (CORAL)," June 2, 2025, https://filecache.investorroom.com/mr5ir_trevi_ir/188/06%2002%2025%20Trevi%20Therapeutics%20CORAL%20TLD%20Presentation%20vF.pdf

64. "New Clinical Trial Evidence Validates Effectiveness of Hyfe's Digital Chronic Cough Platform," accessed October 28, 2025, https://www.hyfe.com/news/new-clinical-trial-evidence-validates-effectiveness-of-hyfes-digital-chronic-cough-platform

Case Study — Hyfe DTx (Japan-first)

- Digital efficacy, combo value, and ROI

Exhibit 26 DTX VALUE STACK

Component	Value Driver	Metric	Evidence	Comments
Digital efficacy (BCST-based)	Symptom reduction without drug AEs	**~42%** avg. reduction in cough frequency (4 wks.); QoL ↑ (LCQ)	Hyfe PoC cohort (N=10 RCC): **–41.8%** frequency, **–41.5%** bouts.	Early cohorts; pragmatic validation ongoing[64,65]
Japan market entry	National pathway with pharma partner	Milestone/royalty structure, 2027 target	Kyorin × Hyfe collaboration announcement & PDF	Japan-first Rx-DTx commercialization under NHI pathway[28,66]
Combination value (Drug + DTx)	Adherence & persistence; PRO/QoL lift	Higher LCQ gain; fewer discontinuations	Rationale from payer/HTA norms + DTx analytics	Basis for outcomes-based contracts once a drug is approved. (Inference informed by payer practice)
Access & coding (U.S.)	Reimbursable digital care	RTM CPT 98975/98978 utilization	U.S. RTM coding for DTx	Supports medical-benefit coverage; variable by plan. (General policy context)
ROI for payers	Reduced HCRU & productivity loss	Target: **≥ 20%** ER/clinic visit reduction by 12–18 mo	DTx analytics + future claims RWE	Forms basis for BIA and employer pilots. (Program target; validate with RWE)
Scale vs SLP scarcity	Addresses access bottleneck	**~200** SLPs trained in BCST in U.S.	Hyfe DTx page — BCST capacity gap	Digital delivery expands access beyond limited specialists[67]

Partnering & M&A (Who Buys / Who Builds)

- Strategic fit and deal comps; bundling opportunities.

M&A Transactions

GSK Acquisition of Bellus Health (Camlipixant)

- Deal Value: **$2.0** billion (**$14.75**/share).
- Date: April 2023 announcement, June 2023 close.
- Premium: **103%** over closing price.
- Bellus Cash: **$337M** acquired.
- Net Consideration: **~$1.7B**.
- Rationale: Camlipixant Phase 3, expected 2026 launch, EPS accretive 2027.

Deal Multiples

- Evaluate Pharma 2028 forecast: **$574M** revenue.
- NPV: **$1B+.**
- Morningstar: **>$500M** peak sales.
- Motley Fool: **$1.2B** peak US sales.

Risk Matrix & Mitigants

- Regulatory, placebo, reimbursement, execution, mitigations.

65. Kennedy Ferruggia Editor Assistant and Laurie Slovarp CCC-SLP PhD, "CHEST 2025: Improving Access to Chronic Cough Treatment Through a Digital Therapeutic Solution | Pharmacy Times," October 28, 2025,

Exhibit 27 RISK REGISTER

Risk	Evidence Supporting Likelihood	Impact Rationale	Likelihood	Impact	Mitigations
Efficacy ceiling / placebo response	Placebo response **30–60 %** across all P2X3 RCTs (SOOTHE, COUGH-1/2, RIVER). High probability to reappear	Direct threat to statistical and clinical significance → regulatory rejection possible.	**High (4–5)**	**High (4–5)**	Optimize trial design (enrichment + digital cough monitoring); emphasize LCQ **≥ 1.3** gain for clinical meaning
Taste-related AEs (dysgeusia / ageusia)	First-gen (Gefapixant) 50 % + incidence; newer P2X3 **< 10 %**, so probability reduced	Affects adherence **> 20 %**, but not approval	**Medium (3)**	**Medium (3)**	Differentiate new P2X3s (Camlipixant **< 10 %** AEs); embed AE mitigation in patient-support programs
FDA approval uncertainty (post-Gefapixant precedent)	Two CRLs (2022 & 2023) **= > 70 %** chance bar remains high	Complete loss of U.S. market entry until next review cycle	**High (5)**	**High (5)**	Early FDA engagement; pre-NDA alignment on endpoints & MCID; integrate objective cough frequency data
HTA / payer skepticism (cost-effectiveness gap)	NICE terminated, Japan applied **–7.7 %** price cut → **> 60 %** likelihood of strict assessment.	Determines price corridor and launch delay	**High (4–5)**	**High (4–5)**	Strengthen HEOR dossier with LCQ→ EQ-5D mapping and productivity models; pilot BIA with payers.
Crowded pipeline (P2X3 class competition)	**> 6** active P2X3 assets globally; some overlap in 2025–26	Competition may compress price **~15–25 %**	**Medium (3)**	**High (4)**	Emphasize selectivity & safety advantages; pursue drug + DTx differentiation and KOL advocacy
Uncertain combination therapy value	No published trials; early preclinical discussion only	Clinical relevance modest initially	**Medium (3)**	**Medium (3)**	Explore DTx + drug or neuromodulator combos post-approval; track off-label use
Patient heterogeneity / no biomarkers	No validated cough endotypes → common across trials	Reduces response predictability → trial variance up to **40 %**	**High (4)**	**Medium (3)**	Develop phenotyping tools and AI-based predictive algorithms via cough monitoring partnerships
Underdiagnoses / delayed referral	**Avg. 6.5** years to diagnosis (literature)	Impacts launch uptake **10–20 %**	**High (4)**	**Medium (3)**	Increase HCP awareness and EHR alerts; launch digital self-screening initiatives
Speech therapy comparative advantage (BCST)	BCST success **40–70 %**, guideline-endorsed	Raises efficacy threshold for payers	**Medium (3)**	**Medium-High (3–4)**	Position drug/DTx as adjunct to BCST; generate RWE on QoL and adherence benefits
Economic evidence gap (QALY / CEA)	No published cost-utility studies → almost certain barrier	Directly limits HTA reimbursement	**High (5)**	**High (5)**	Develop early BIA & CEA models; use Japan data for benchmark pricing scenarios
Market access delay (U.S. & EU)	Two failed approvals and current FDA stance on substantial evidence make a third quick approval unlikely before 2026+	Delays revenue, compresses pricing potential, and allows alternative entrants or digital therapeutics (Hyfe DTx) to capture early adopters	**High (4)**	**High (4)**	Sequence launch EU/Japan first; maintain DTx bridge for real-world data and payer education

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Exhibit 28 RISK ASSESSMENT FRAMEWORK

Criterion	Operational Scale (1–5)	Cutoff for Label	Definition
Likelihood	1 = Rare (<10%) 2 = Unlikely (10–30%) 3 = Possible (30–60%) 4 = Likely (60–80%) 5 = Almost Certain (>80%)	1–2 = Low 3 = Medium 4–5 = High	Probability that the risk will occur within the next 12–24 months, given historical precedent and current evidence.
Impact	1 = Negligible (<5%) 2 = Minor (5–15%) 3 = Moderate (15–30%) 4 = Major (30–50%) 5 = Critical (>50%)	1–2 = Low 3 = Medium 4–5 = High	Potential magnitude of the risk if realized, measured as effect on regulatory approval, reimbursement probability, or commercial uptake.

Scenario Analysis (Bear/Base/Bull)

- Sensitize to efficacy, AEs, approval timing, access, duration.

Exhibit 29 SCENARIO MATRIX

Lever	Bear Scenario	Base Scenario	Bull Scenario	Evidence Supporting Likelihood & Impact
Clinical Efficacy	≤25% reduction in cough frequency	30–35% improvement	≥40% improvement	Phase 3 CALM-1/2 readouts; gefapixant CRLs show FDA bar for clinical meaningfulness
Adverse Events	>50% dysgeusia; poor adherence	≤30% dysgeusia; improved tolerability	Minimal taste effects	Taste AEs are the primary determinant of drop-off
Regulatory Timing	Approval delayed to 2027+	Approval 2026; global launch within 12 months	Early 2025 approval; rapid adoption	Gefapixant precedent vs Camlipixant's cleaner profile
Market Access	HTA rejections; limited coverage	Moderate discounts (~35%)	Premium pricing retained; HTA favorable	NICE 2024 termination of gefapixant appraisal critical precedent
Digital Integration	Low adoption (<10%)	15–20% DTx use at launch	30%+ uptake with full integration	Based on GSK PDURS framework and real-time feedback loop integration
Adherence / Persistence	60–65%	70–80%	85–90%	GSK/Hyfe DTx pilot data: 8–10% adherence gain
Market Penetration	≤20% eligible patients (~200k)	25–30% (~420k adherent)	40–50% (>600k)	Market map of 28M → 10M ≥1yr → 2M obtainable → 1M qualified
Revenue Trajectory	$7.0B cumulative NPV	$9.4B cumulative (+DTx)	$12.0B+	NPV model shows +$1.6B lift with DTx integration
Timing of Peak Sales	2033–34 plateau	2032 (~$2.1B peak)	2030 (~$2.5B peak)	Aligned with market expansion curve 2026–36
Competitive Dynamics	≥4 P2X3 entrants; price erosion	Two entrants + DTx hybrids	Camlipixant ecosystem dominance	Bellus acquisition ($2B) validates class
Market Access Delay (U.S./EU)	≥2 years delay	<1 year post-approval	Simultaneous roll-out (9 months)	FDA/EMA precedent with gefapixant (2022–2023)

Exhibit 30 MARKET MAP FUNNEL

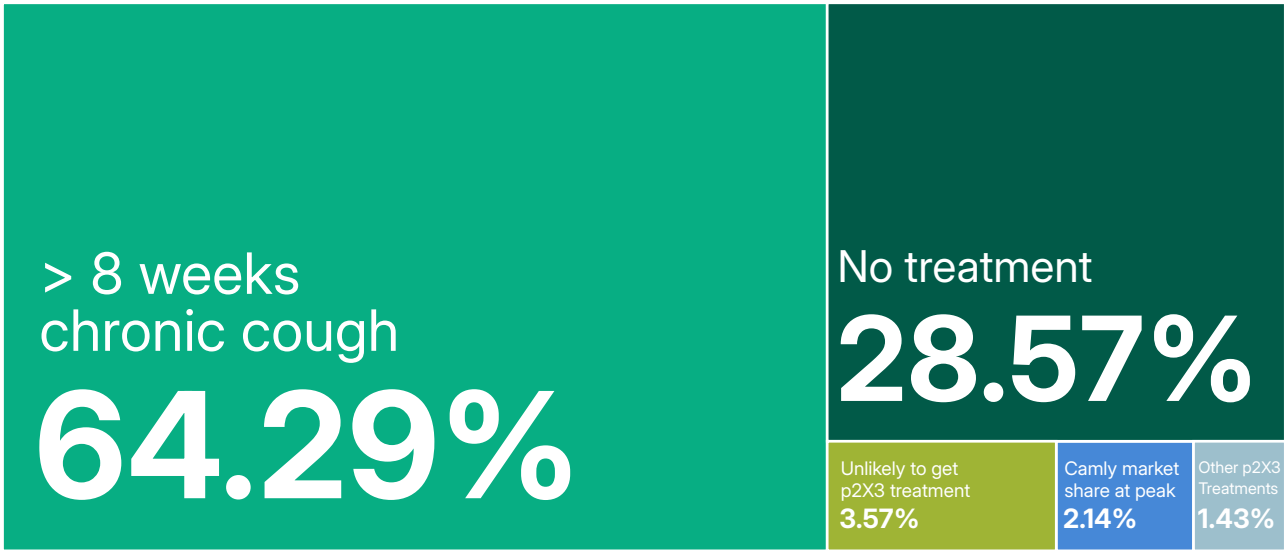

Exhibit 31 SCENARIO 1: DRUG+ COMPANION

Patients & Revenue, Base vs DtX

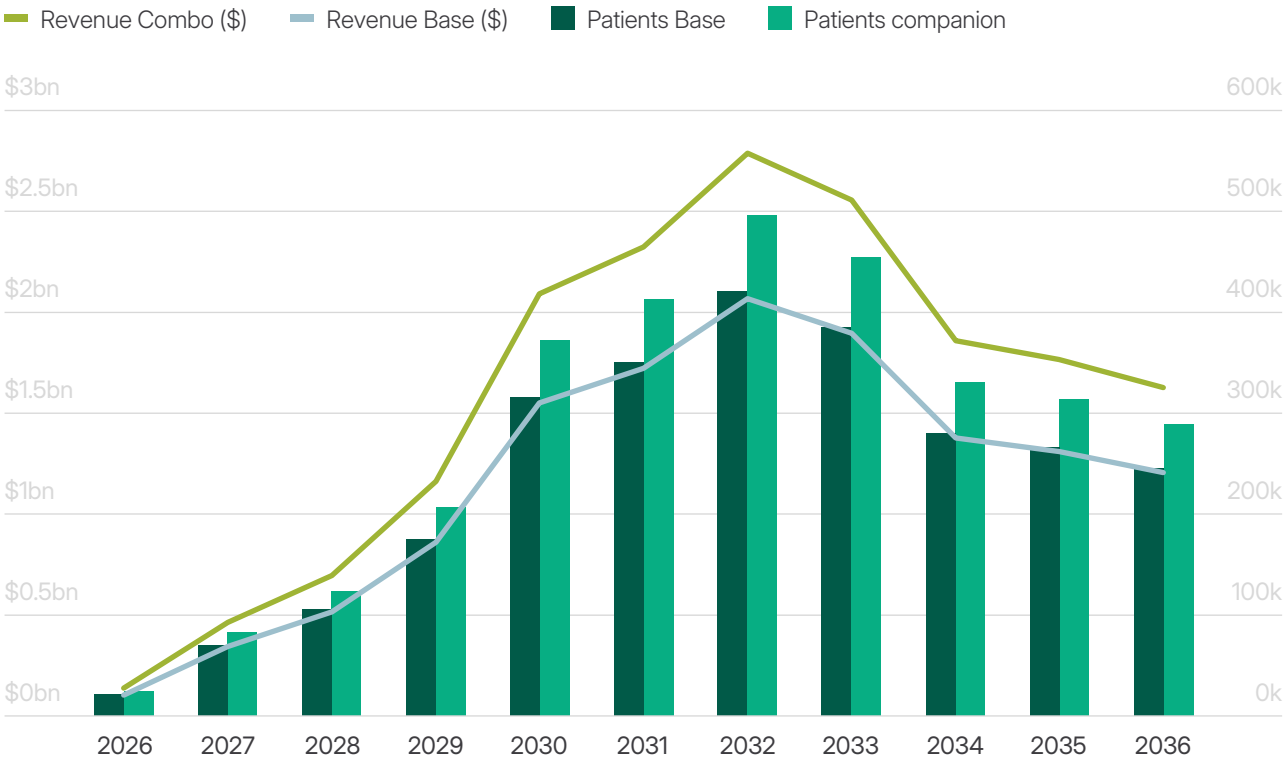

Exhibit 32 ADDITIONAL REVENUE FROM INCREASED ADHERENCE (10-YEAR FORECAST)

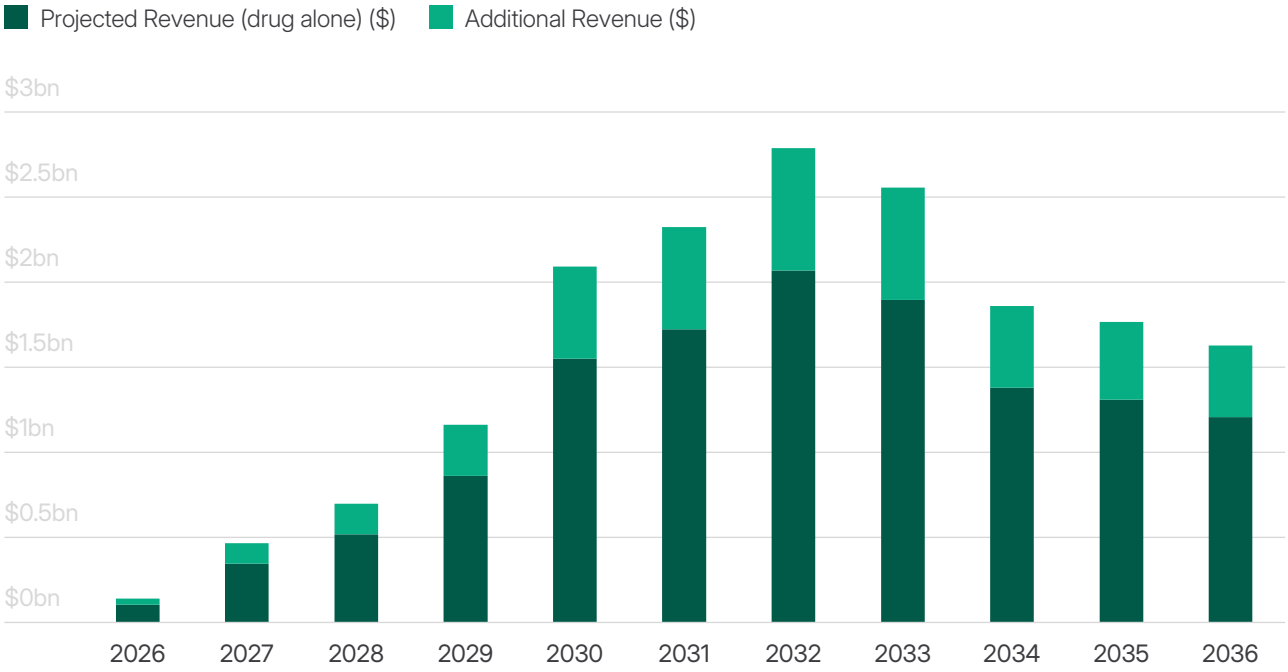

Exhibit 33 SCENARIO 2: ADJUNCTIVE DTX
Market Share vs Revenue

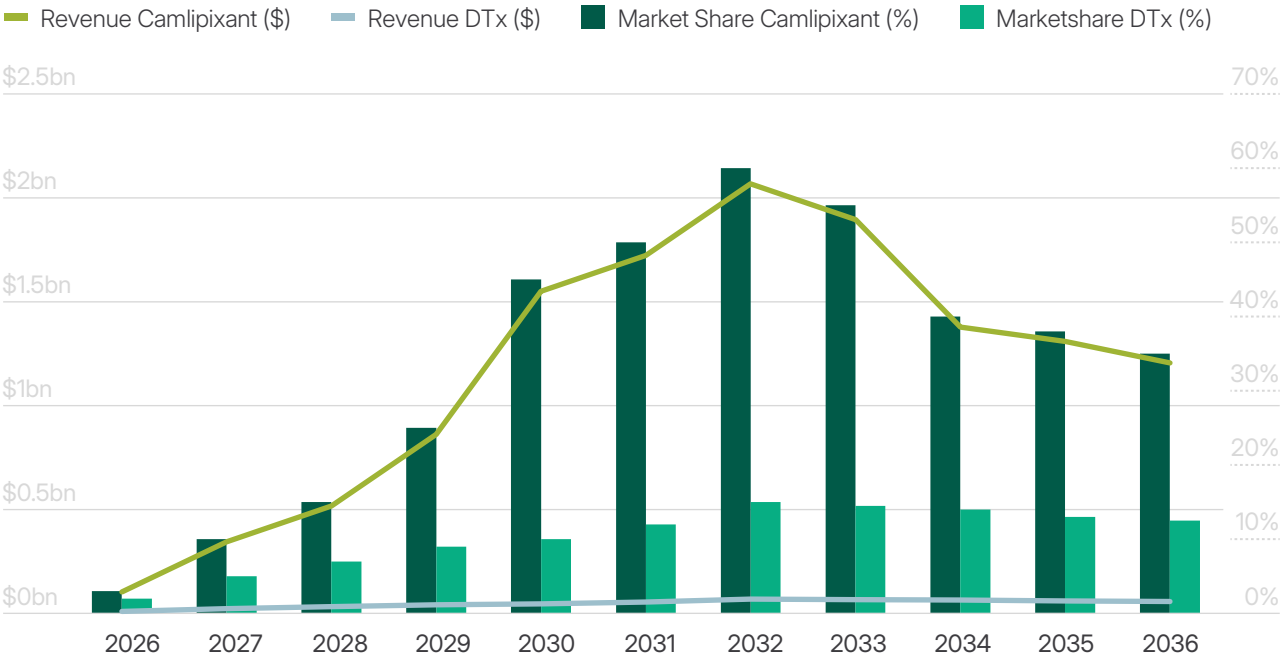

Exhibit 34 SCENARIO 3: STANDALONE DTX

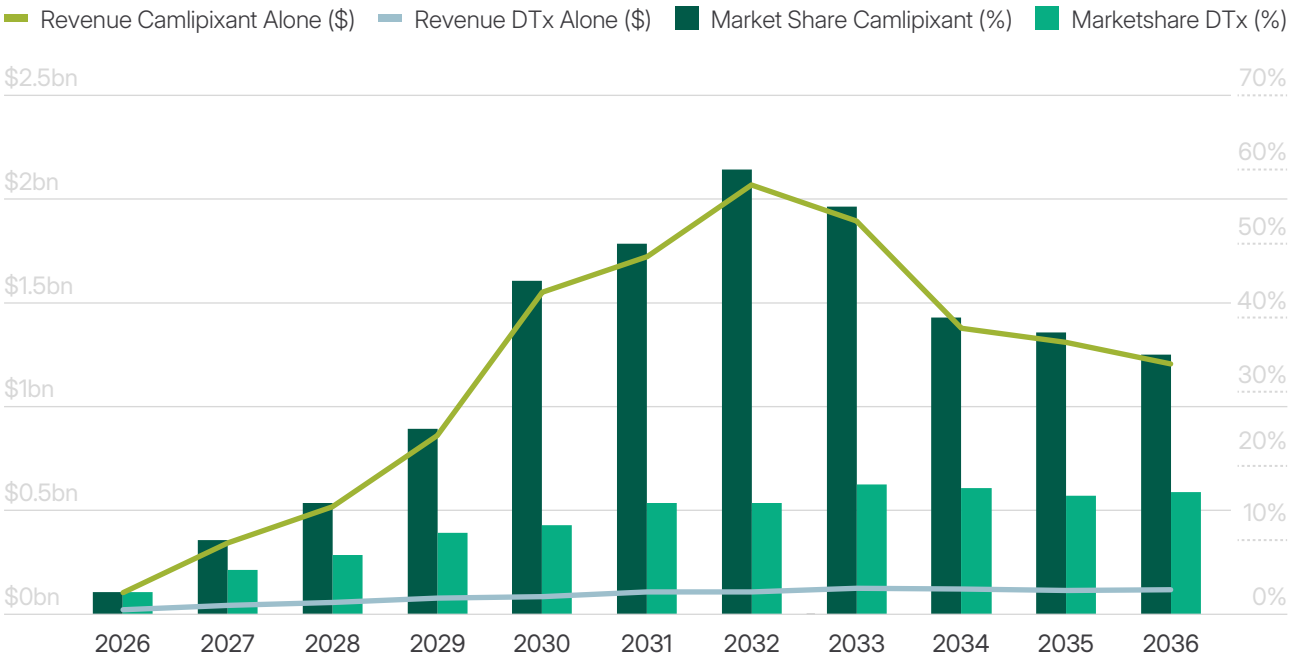

Exhibit 35 NPV MODEL COMPARISON

Scenario	Discounted Revenue ($B)	Δ vs Base
Bull Case (Integrated DTx)	12.0+	+4.10
Base + Digital Add-on	9.44	+1.57
Base Case	7.87	-

Interpretation & Key Insights

- Bear case reflects continued regulatory hurdles, persistent dysgeusia, and payer resistance delaying uptake.
- Base case assumes approval by 2026 with integration of a companion DTx yielding an 8–10% adherence improvement.
- Bull case envisions early approval, fully integrated digital adherence solutions, and high-quality-of-life (QoL) gains driving broad adoption.
- NPV impact analysis: $7.87B (Base) → $9.44B → +$1.57B value lift (+20%).

Bull Case

- $3–5B US market, zero approved drugs: 12M patients, no competition, first-mover captures market
- High unmet need: 31% of patients fail all current treatments; off-label options show 31–40% AE rates
- GSK's $2B bet validates opportunity: £40B+ projected sales contribution through 2031
- Digital therapeutics promise: Early results demonstrate DTx as a viable intervention, introducing software-level scalability and economics to a traditional pharma market