2022년도 제5회 기침 연구회 심포지엄
10월 8일(토) 14:30-14:55

# Novel Pharmacologic Treatment of Cough

가천대 길병원 호흡기 알레르기내과
강성윤

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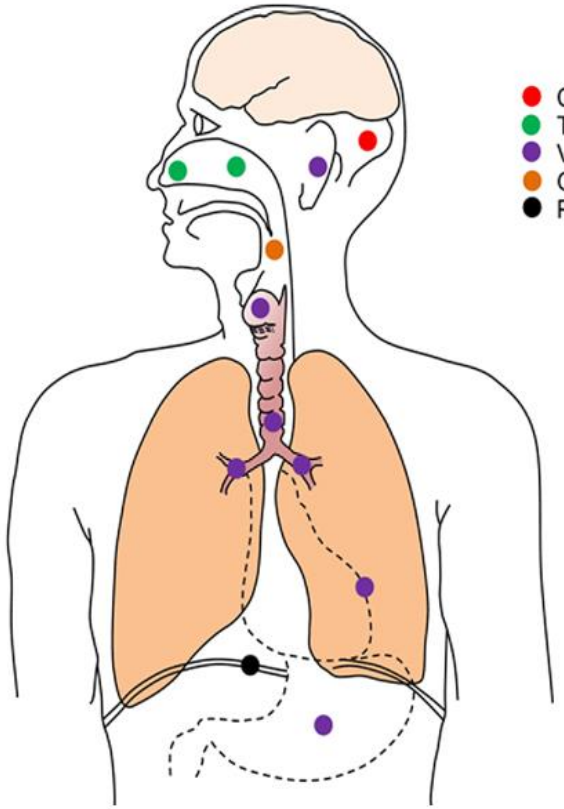
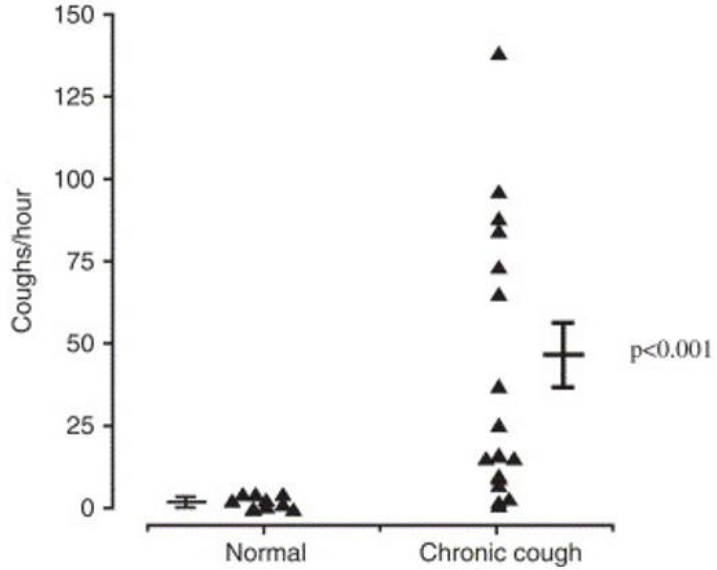
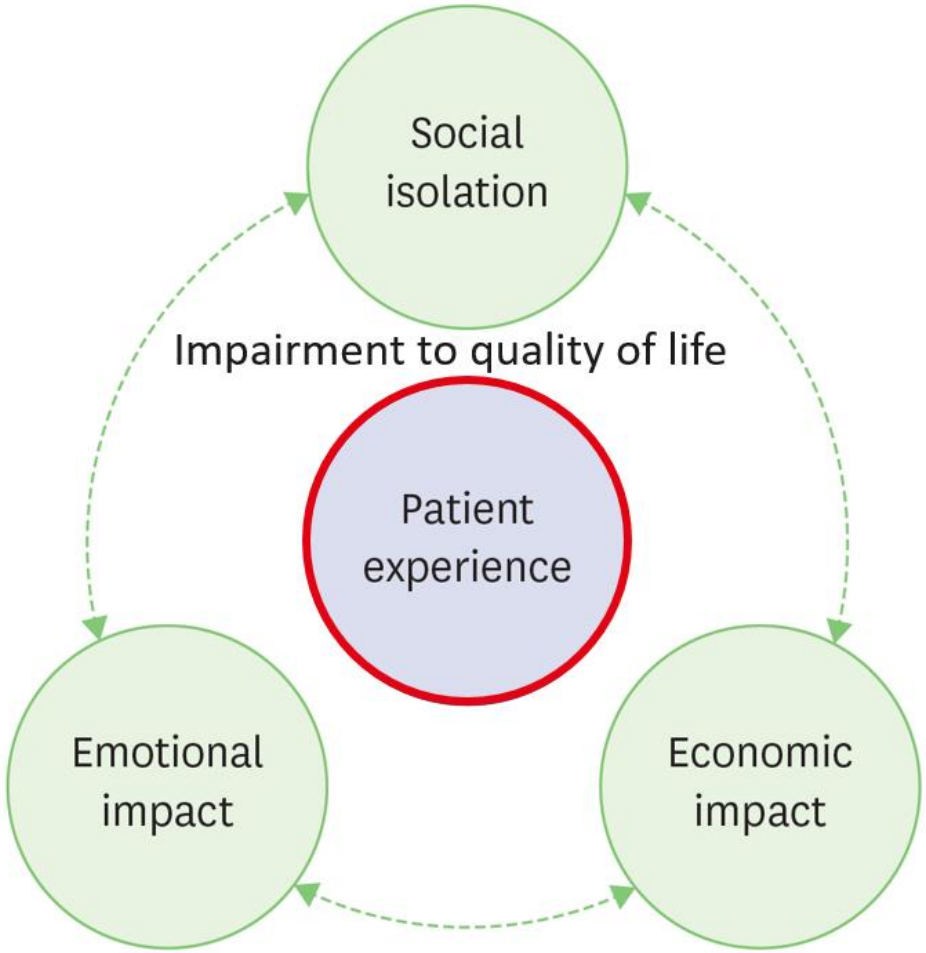
    - $GABA_B$ agonist
  - Central neuronal targets
    - Neurokinin receptor 1 antagonist
    - α7- acetylcholine receptor agonist
- What to consider from several trials in chronic cough
- Summary

# A significant impact of chronic cough




Important role in protection of the airway → In disease excessive coughing

# Empirical antitussives for chronic cough

| Drug (publication or clinical trial ID) | Phase | Patients: Disease | Patients: Number | Significant benefit on cough outcome (intervention vs. control): Frequency | Severity | QoL |
|---|---|---|---|---|---|---|
| **Codeine** (Smith 2006) | PoC | COPD cough | 21 | *p*=0.52* | *p*=0.96 | |
| **Morphine** (Morice 2007) | PoC | CRC | 27 | | Not specified | *p*<0.02* |
| **Morphine** (Al-Sheklly 2017†) | PoC | CRC (responder) | 22 | *p*<0.05* | *p*<0.05 | *p*<0.05 |
| **Gabapentin** (Ryan 2012) | PoC | CRC | 62 | *p*=0.028 | *p*=0.029 | *p*=0.004* |
| **Pregabalin** (Vertigan 2016) | PoC | CRC | 40 | *p*=0.671* | *p*=0.002* | *p*=0.024* |
| **Amitriptyline** (Jeyakumar 2006††) | PoC | PVVN cough | 28 | | | Not specified |

Not measured
$p \geq 0.05$
$0.01 \leq p < 0.05$
$0.001 \leq p < 0.01$
$p < 0.001$

TRPV1 antagonist$_a$ = SB-705498

Summary of guideline recommended options for the pharmacologic treatment of chronic refractory cough [2,3,12].

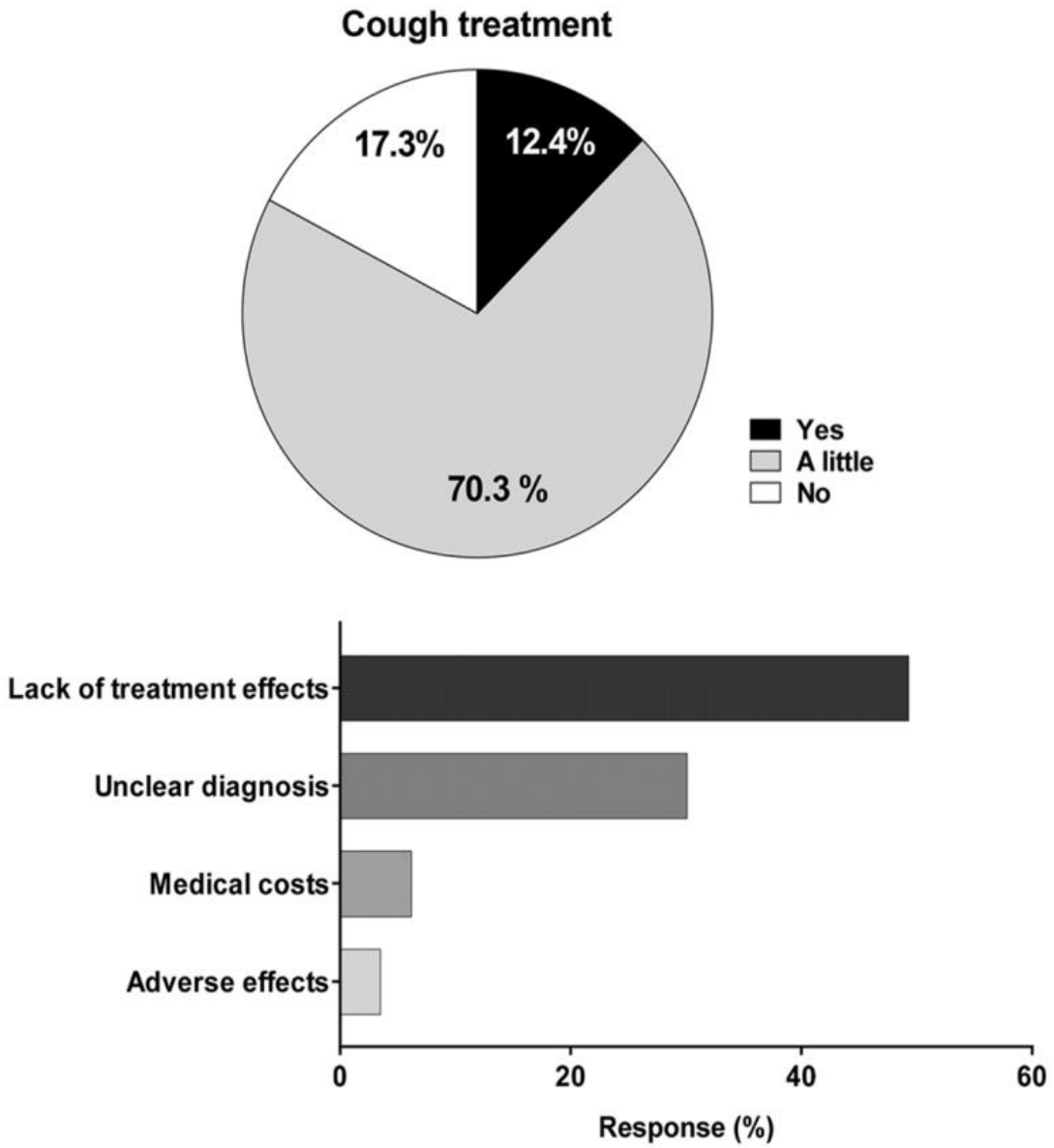
| Drugs | Smith and Woodcock 2016 | CHEST Guidelines 2018 | ERS guidelines 2020 |
|---|---|---|---|
| Morphine | Recommended | Discouraged | Recommended |
| Gabapentin | Recommended | Recommended | Recommended |
| Pregabalin | Recommended | Recommended | Recommended |
| Amitriptyline | To be considered | Neither recommended nor discouraged | Neither recommended nor discouraged |
| Codeine | Neither recommended nor discouraged | Neither recommended nor discouraged | Not recommended |
| Dextromethorphan | Neither recommended nor discouraged | Neither recommended nor discouraged | Neither recommended nor discouraged |

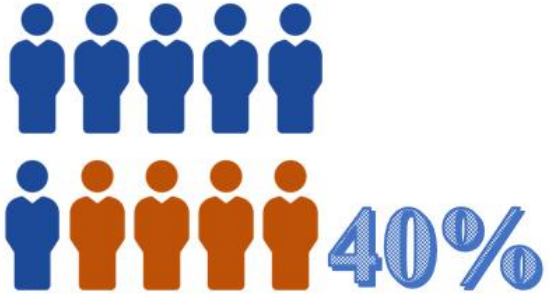
- Central acting

Opioid: codeine/Non-opioid: dextromethorphan
Neuromodulator: gabapentin, pregabalin, amitriptyline

- Peripheral acting

benzonatate, benproperine, theobromine,levodropropizine

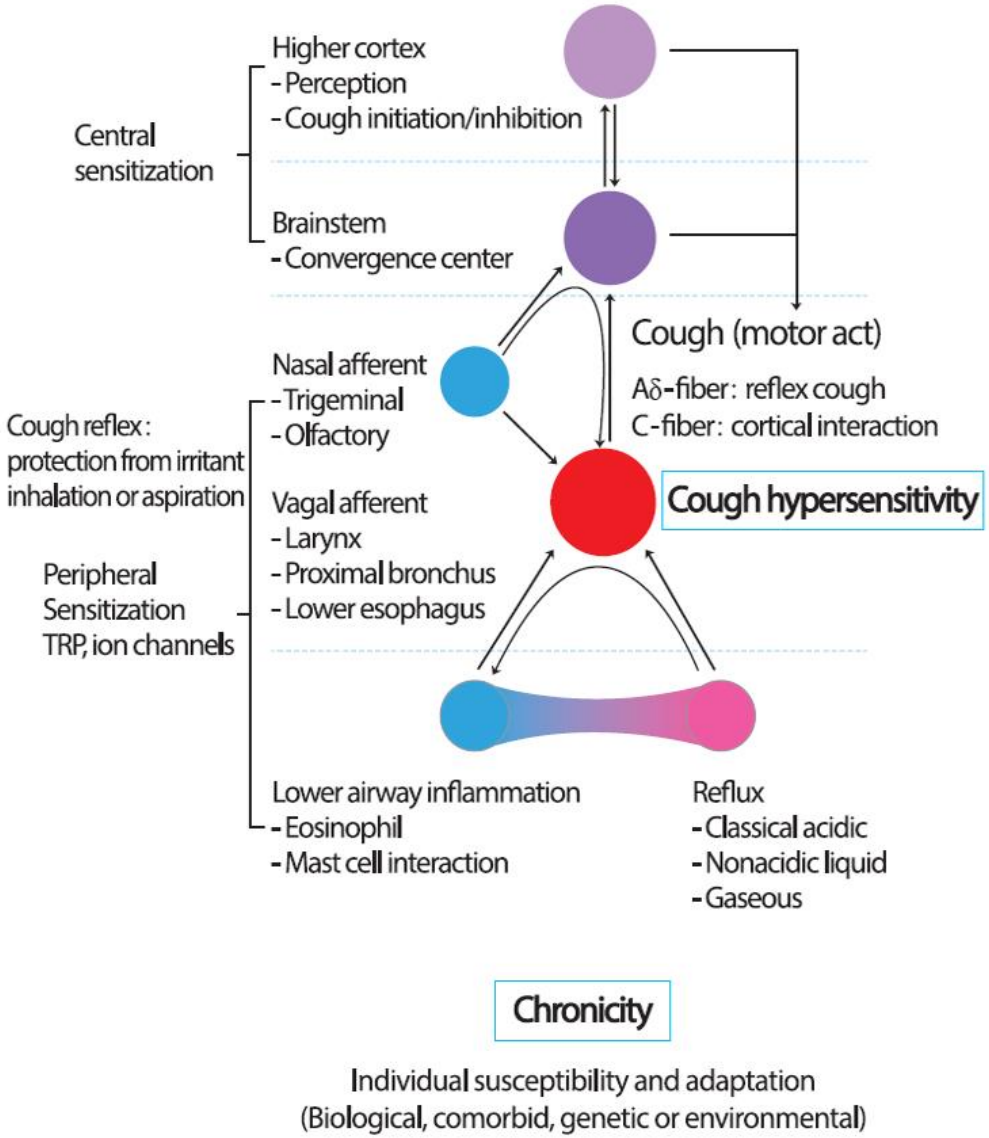


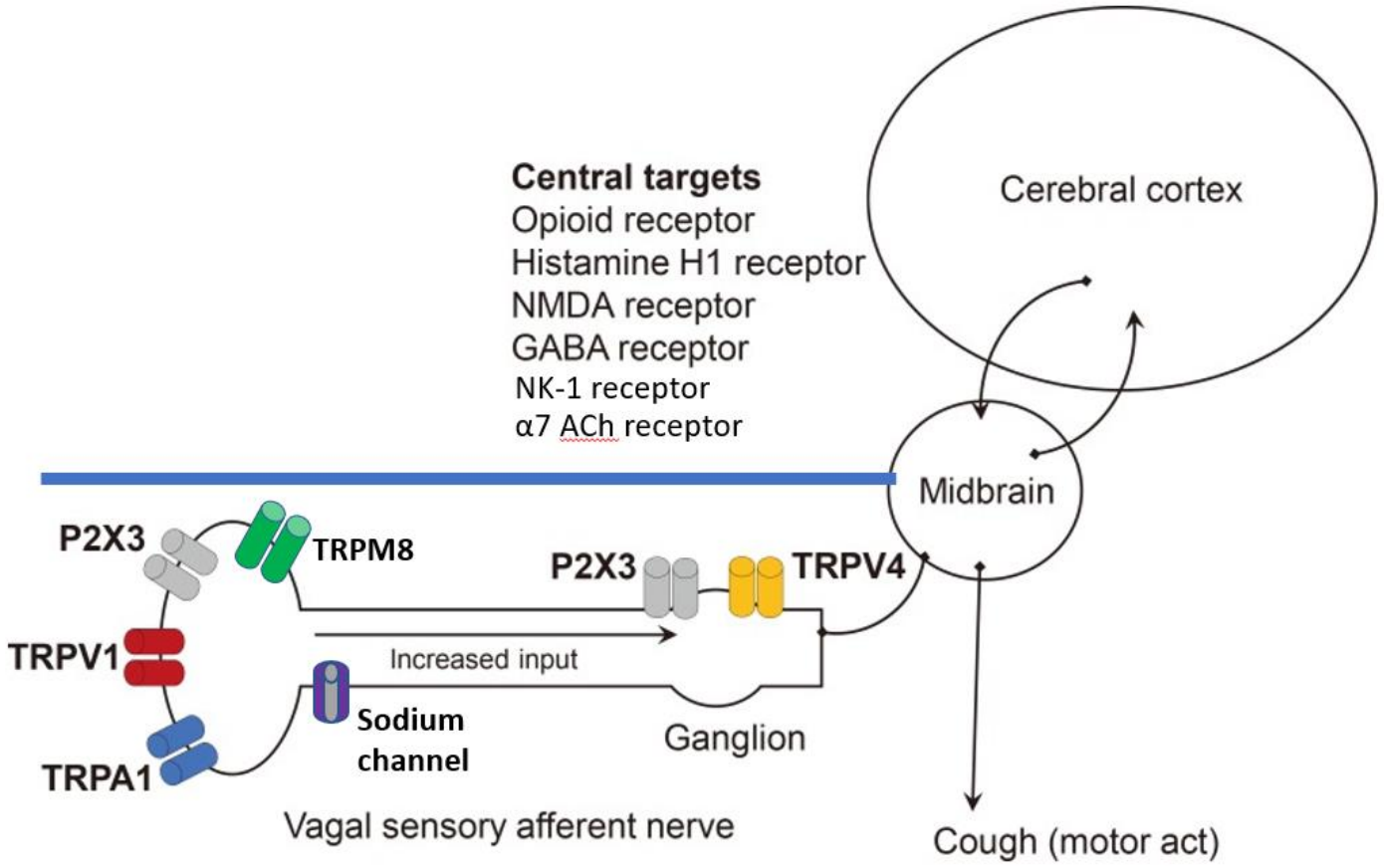




## Unmet Needs in the Unexplained Chronic Cough Group

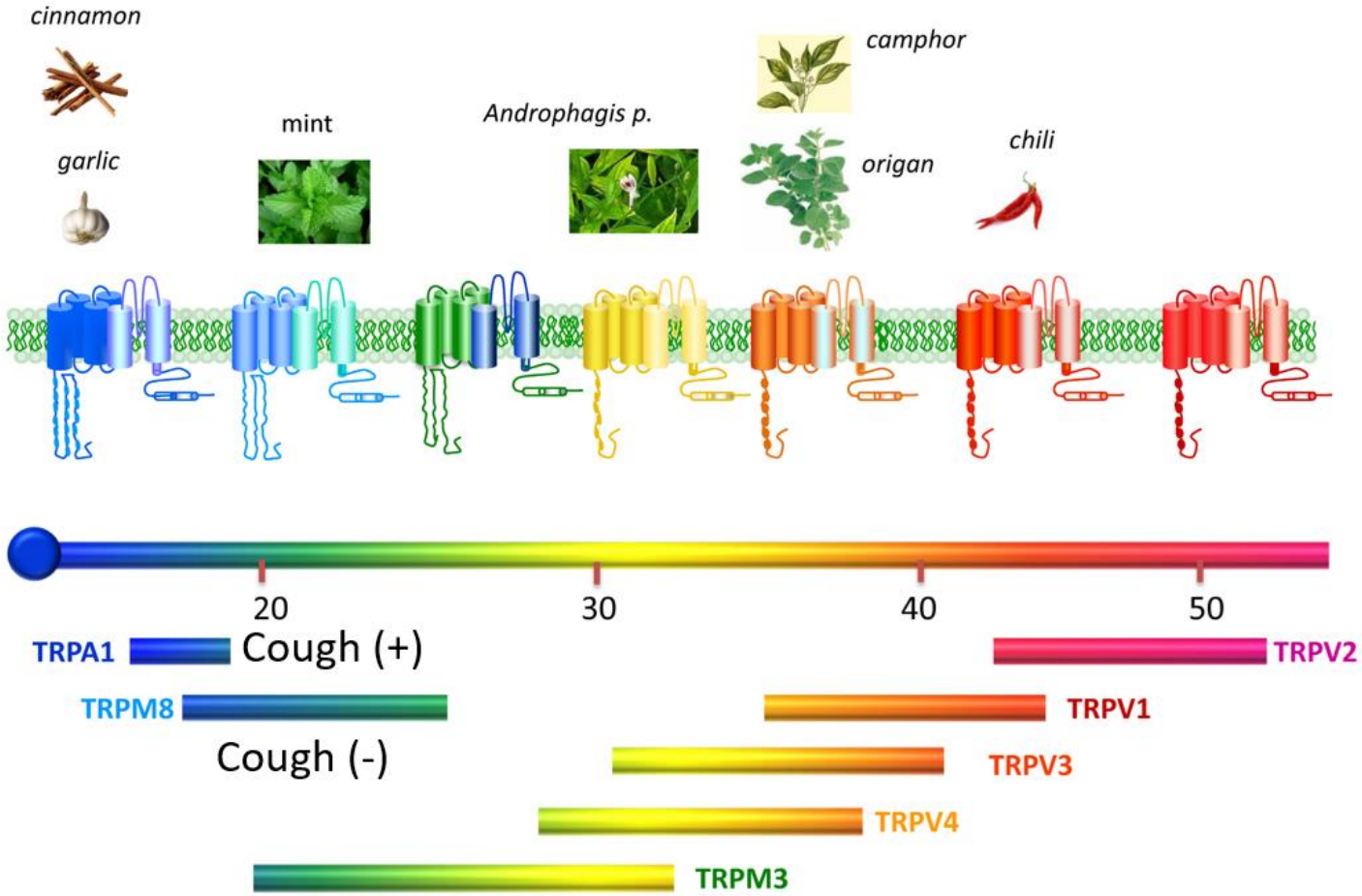
An open-ended questionnaire assessing unmet needs while receiving tertiary care was administered to the 39 patients with unexplained chronic cough. Two common items were generated: poor control of cough despite treatments (64.0%) and incurable coughing (36.0%). The majority (83.8%) reported a lack of information about their disease and wanted further information, including cough treatment ($n=7$), prevention ($n=4$), cure ($n=4$), self-management ($n=2$), general knowledge ($n=2$), diagnosis ($n=2$), causes ($n=2$), and supplementary foods (n = 1).

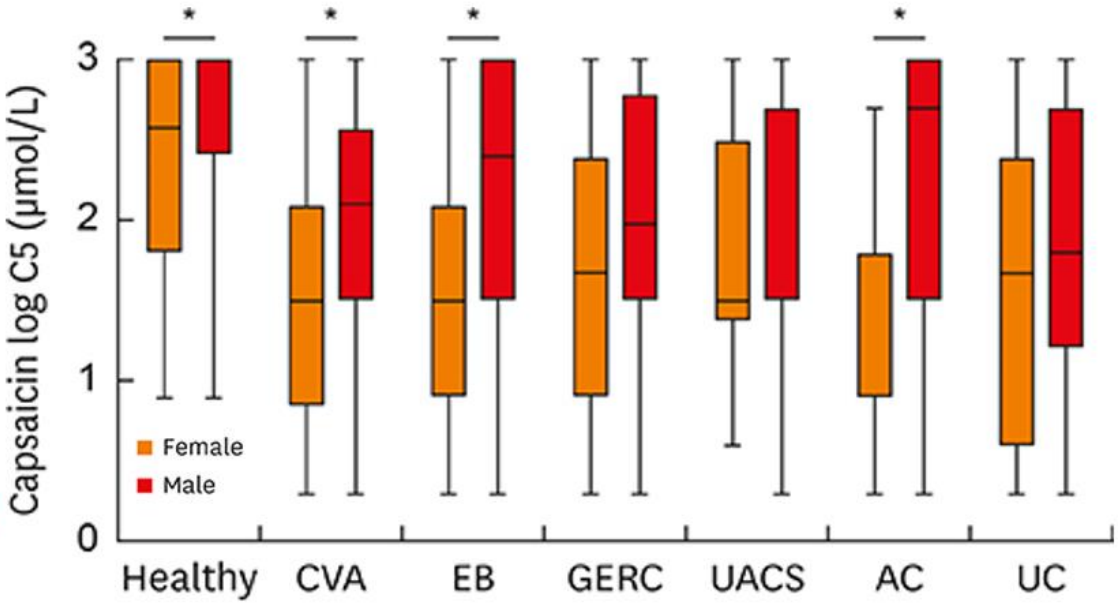
# Recent advances in understanding the neural control of coughing



# Transient receptor potential (TRP) channels



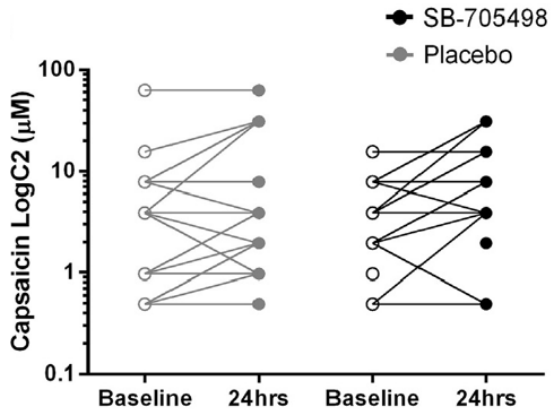



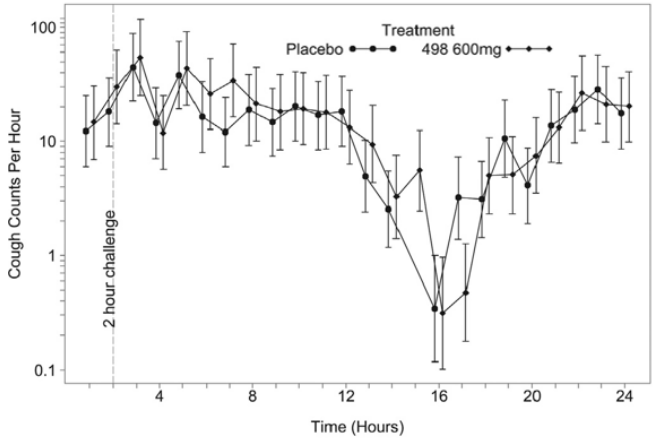

Membranes 2014; Allergy Asthma Immunol Res 2019

# Phase Ⅱ, XEN-D0501(TRPV1, n=20) in refractory cough

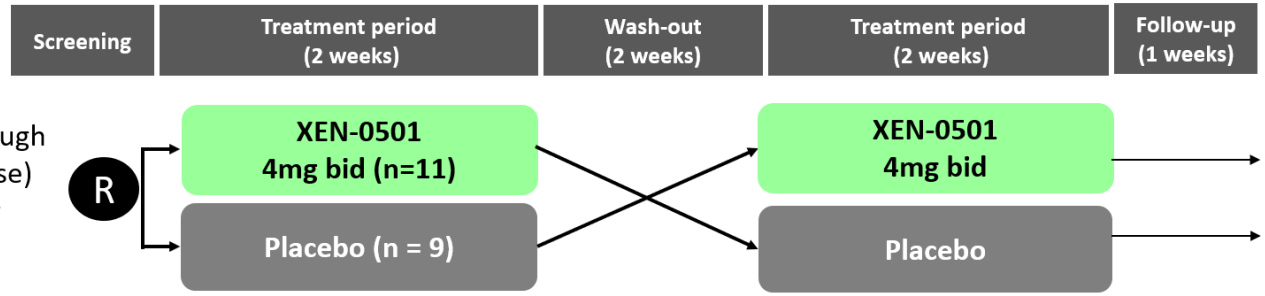
## Phase Ⅱ, SB-705498 (TRPV1) in refractory cough

| | |
|---|---|
| Primary Objective | • **Cough responses to inhaled capsaicin (2 hours after dose)**<br>• **Objective 24-hour cough frequency** |



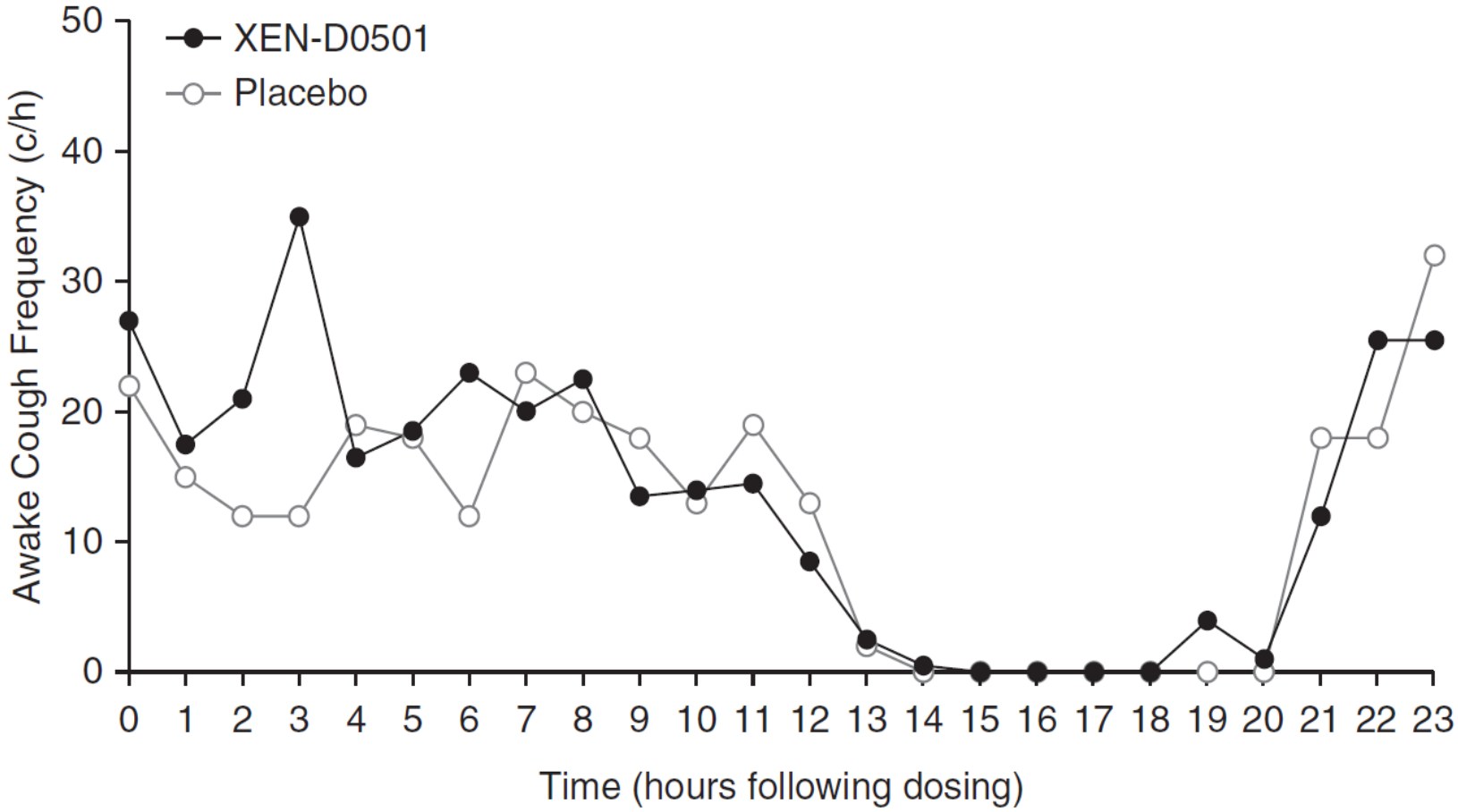



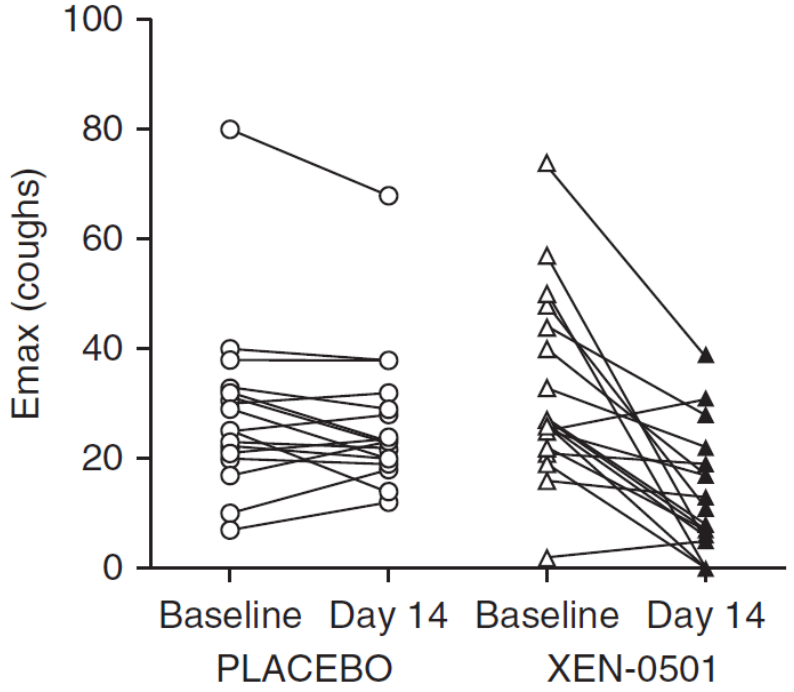

- Refractory chronic cough (capsaicin cough response) (awake cough frequency ≥ 1.5 coughs/h)
- Non/Ex-smokers




| | |
|---|---|
| Primary Objective | • **Awake, sleep and 24-hour objective cough frequency** |
| Secondary Objective | • Change from baseline in cough VAS and Leicester Cough Questionnaire (LCQ)<br>• Cough responses to inhaled capsaicin |

J Allergy Clin Immunol 2014 ;Am J Respir Crit Care Med 2017


XEN-D0501
Placebo
Awake Cough Frequency (c/h)
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
Time (hours following dosing)


Emax (coughs)
100
80
60
40
20
0
Baseline
Day 14
Baseline
Day 14
PLACEBO
XEN-0501

# Phase Ⅱ, Inhaled GRC17536 (TRPA1, n=45) in refractory cough
# Phase Ⅱa, GSK2798745 (TRPV4, n=32) in refractory cough

| | |
|---|---|
| Primary Objective | • **Change in objective 24-hour cough frequency following 4 weeks of dosing (GRC 17536)**<br>• **Total cough counts during day time hours following 7 days of dosing(GSK2798745)** |

| | | |
|---|---|---|
| End point title | Change in log 24 hour cough frequency from baseline to end of treatment between GRC 17536 and placebo | |
| End point description | | |
| End point type | Primary | |
| End point timeframe | 4 weeks | |
| **End point values** | GRC 17536 | Placebo |
| Number of subjects analysed | 23 | 22 |
| Units: Number | | |
| log mean (standard deviation) | -0.2 ± 0.397 | -0.21 ± 0.479 |

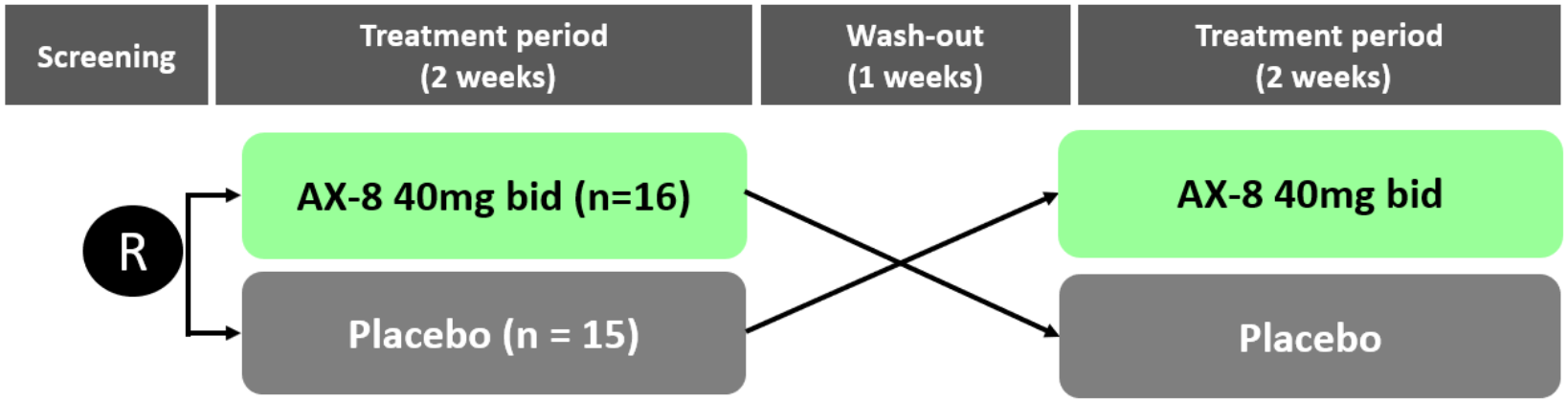
| Endpoint | Treatment | Posterior Median (SD) | Ratio of Posterior Median (90% Credible Intervals) | % Increase from placebo |
|---|---|---|---|---|
| 10 hour (daytime) cough count | GSK2798745 (n=15) | 241.1 (35.4) | 1.336 (0.965, 1.847) | 34% |
| | Placebo (n=17) | 180.6 (24.8) | | |
| 24 hour cough count | GSK2798745 (n=15) | 450.7 (50.8) | 1.090 (0.848, 1.402) | 9% |
| | Placebo (n=17) | 413.4 (43.6) | | |

# Phase Ⅱa, AX8 (TRPM8, n=51) in refractory cough

- Refractory or unexplained chronic cough

(lasting 1yrs or longer)

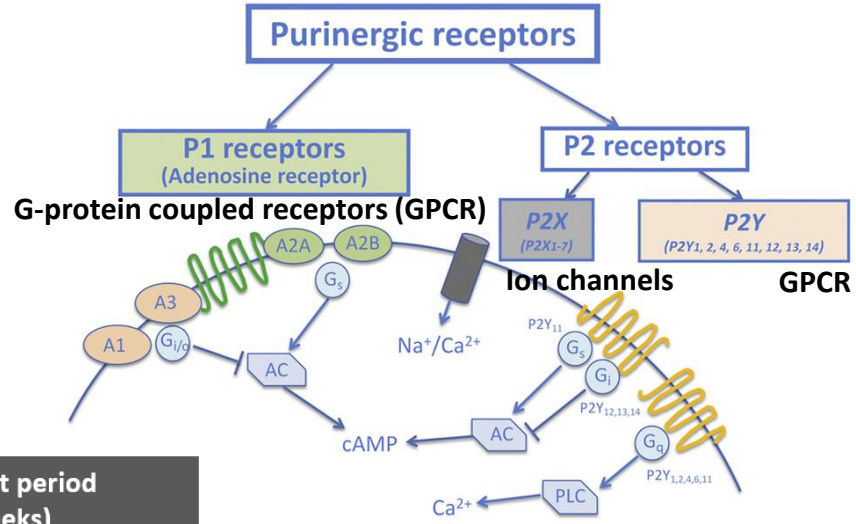
- No substantial abnormalities on CXR/CT
- Non/Ex-smokers




- Treatment with AX-8 40 mg BID compared to placebo showed a reduction in cough frequency within the first 15 minutes after treatment and lasting for more than 4 hours. This included a 44% reduction in cough frequency over two hours compared to 18% with placebo and a 35% reduction over 4 hours compared to 20% with placebo.
- Reduction in cough frequency was seen across patients in the study irrespective of high/low baseline cough frequency, duration of coughing, age or sex.
- In a pre-determined subset of patients with higher baseline throat discomfort, there was a statistically significant reduction of cough, including a 49% reduction over two hours compared to 8% with placebo and a 32% reduction over 24 hours compared to 13% with placebo.
- Overall improvements in patient- and clinician-reported outcomes over 14 days were observed in:
  -Leicester Cough Questionnaire (LCQ)
  -patient's global impression of change (very much improved or much improved)
  -clinician's global impression of change (very much improved or much improved)
- Good safety profile, with no serious adverse events

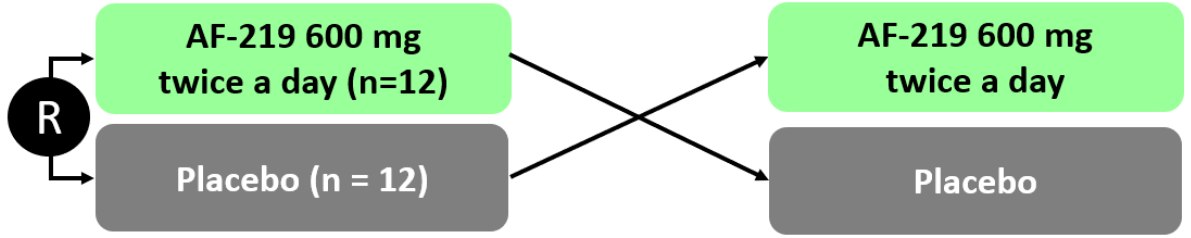
https://clinicaltrials.gov/ct2/show/study/NCT04866563; http://axalbion.com/2022/06/29/axalbion-announces-positive/

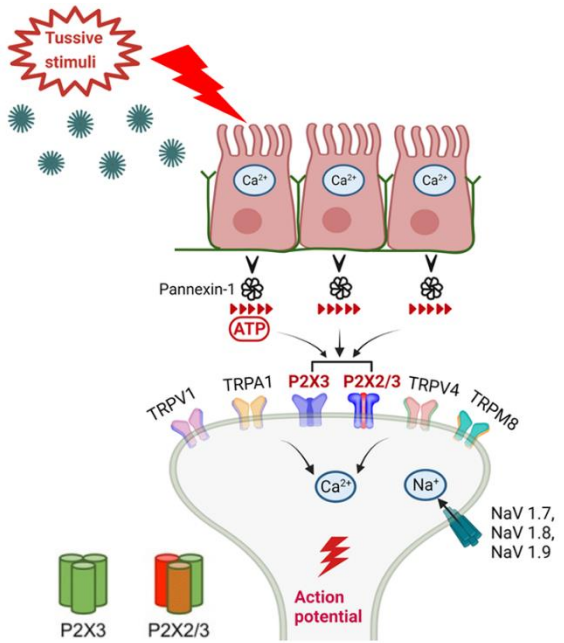
# Phase Ⅱ, AF-219 (P2X3) in refractory cough (n=24)




| Screening | Treatment period (2 weeks) | Wash-out (2 weeks) | Treatment period (2 weeks) |
|---|---|---|---|

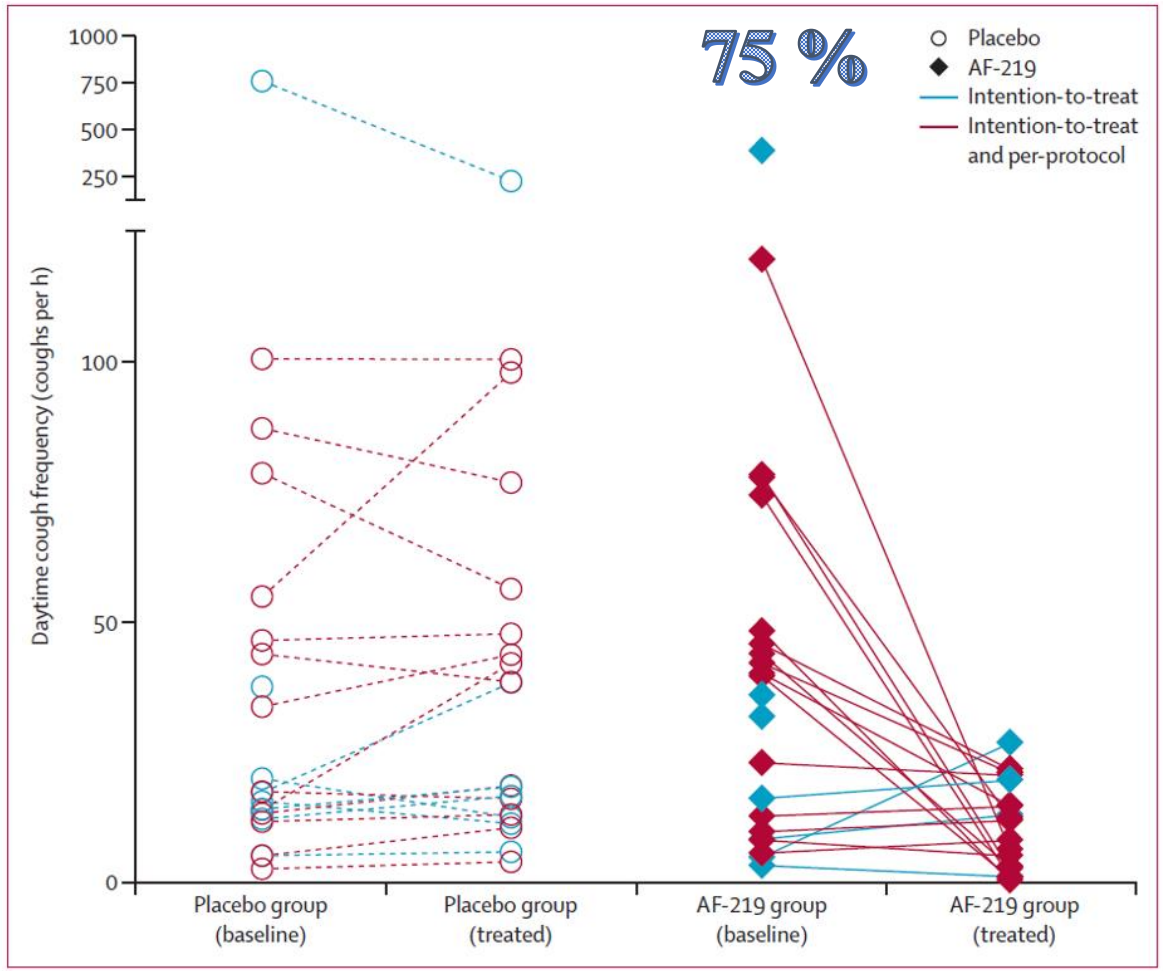
- Refractory chronic cough
- Non-smoker
- FEV1/FVC > 60%
- No treatment that might modulate cough
- No evidence of an underlying cough trigger



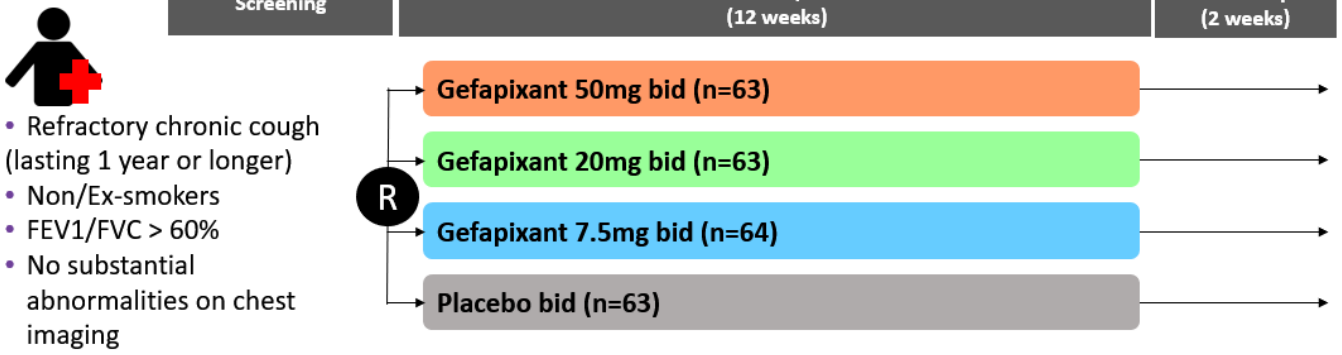

| | |
|---|---|
| Primary Objective | • **Daytime objective cough frequency** |
| Secondary Objective | • Change from baseline in cough VAS<br>• Change from baseline in cough VAS<br>• Change from baseline in Cough Quality of Life Questionnaire (CQLQ) |

Lancet 2015; Purinergic Signal 2022

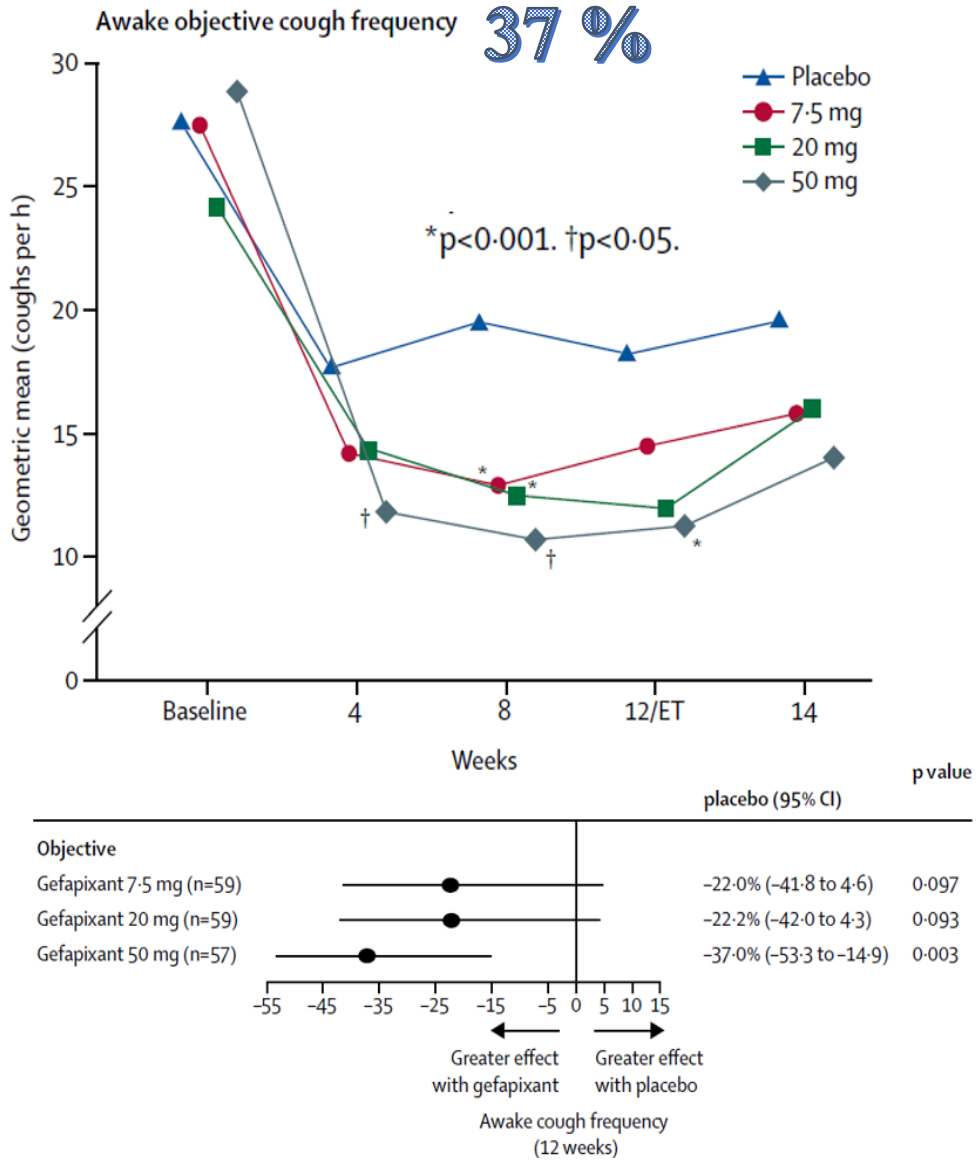



| | Placebo (n=22) | AF-219 (n=24) |
|---|---|---|
| Dysgeusia | 0 | 21 (88%) |
| Hypogeusia* | 0 | 13 (54%) |
| Nausea | 1 (5%) | 9 (38%) |
| Oropharyngeal pain | 1 (5%) | 5 (21%) |
| Headache | 1 (5%) | 3 (13%) |
| Salivary hypersecretion | 1 (5%) | 3 (13%) |
| Cough | 1 (5%) | 3 (13%) |
| Anosmia | 0 | 2 (8%) |
| Constipation | 0 | 2 (8%) |
| Gastro-oesophageal reflux disease | 0 | 2 (8%) |
| Glossodynia | 0 | 2 (8%) |
| Depressed mood | 0 | 2 (8%) |
| Vision blurred | 0 | 2 (8%) |

# Phase Ⅱb, Gefapixant (P2X3) in refractory or unexplained cough (n=253)

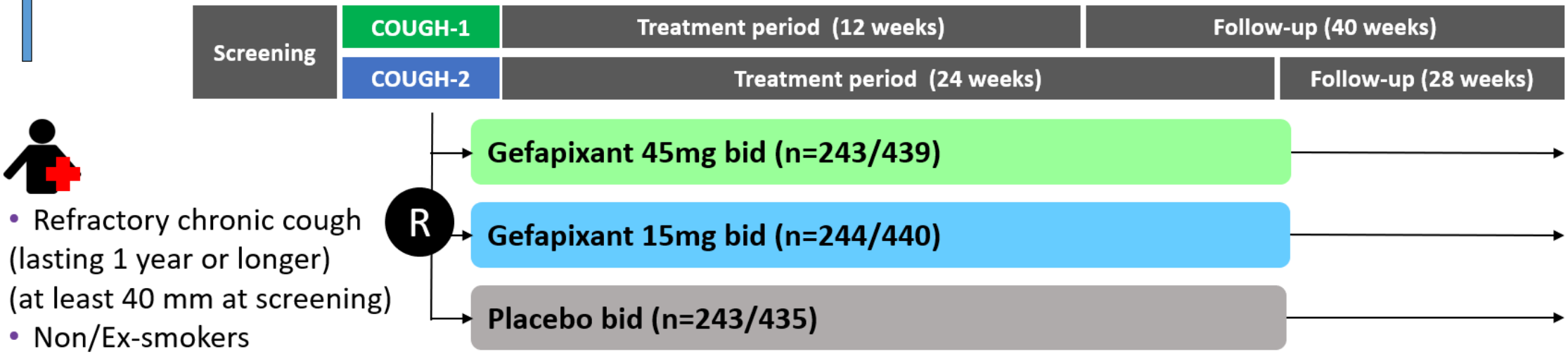



- Refractory chronic cough (lasting 1 year or longer)
- Non/Ex-smokers
- FEV1/FVC > 60%
- No substantial abnormalities on chest imaging




| | Placebo (n=63) | Gefapixant 7·5 mg (n=63) | Gefapixant 20 mg (n=63) | Gefapixant 50 mg (n=63) |
|---|---|---|---|---|
| Serious adverse event | 0 | 0 | 0 | 1 (2%) |
| Adverse event related to treatment* | 22 (35%) | 19 (30%) | 43 (68%) | 55 (87%) |
| Adverse events of special interest† | | | | |
| Renal or urological event | 3 (5%) | 1 (2%) | 2 (3%) | 1 (2%) |
| Taste related event‡ | 4 (6%) | 6 (10%) | 31 (49%) | 51 (81%) |

# Phase Ⅲ, Gefapixant in refractory or unexplained cough (n=2,044)



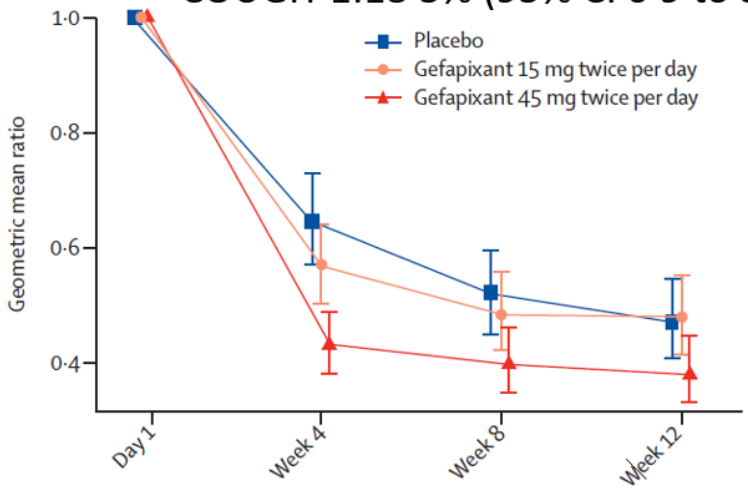

- Refractory chronic cough (lasting 1 year or longer) (at least 40 mm at screening)
- Non/Ex-smokers
- FEV1/FVC > 60%
- No substantial abnormalities on chest imaging

| | |
|---|---|
| Primary Objective | • **24-h cough frequency—reported as coughs per hour—through week 12 and 24 (COUGH-1 (n=730), COUGH-2 (n=1,314)** |
| Secondary Objective | • Change in awake cough frequency (1,2)<br>• Proportion of participants with ≥30% reduction from baseline in 24-hour cough frequency (1,2)<br>• Proportion of participants with ≥1.3 increase from baseline in LCQ (2) |

Relative reduction (45mg) vs placebo

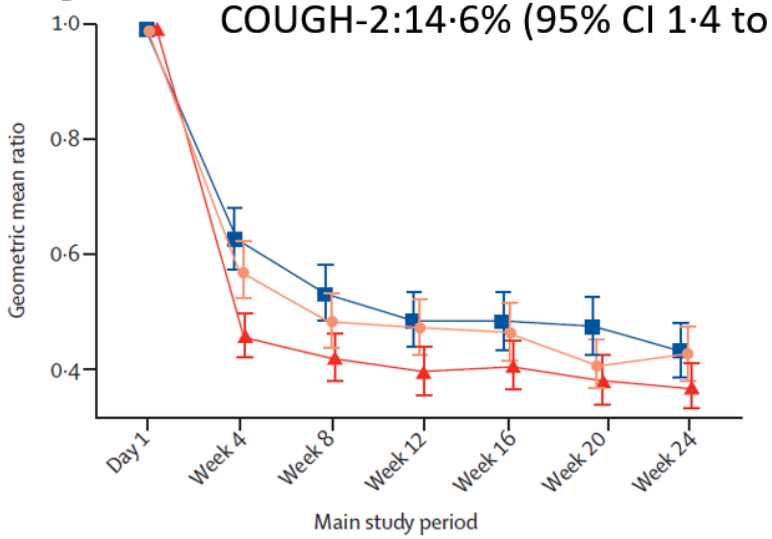
A

COUGH-1:18·5% (95% CI 0·9 to 32·9; p=0·041)

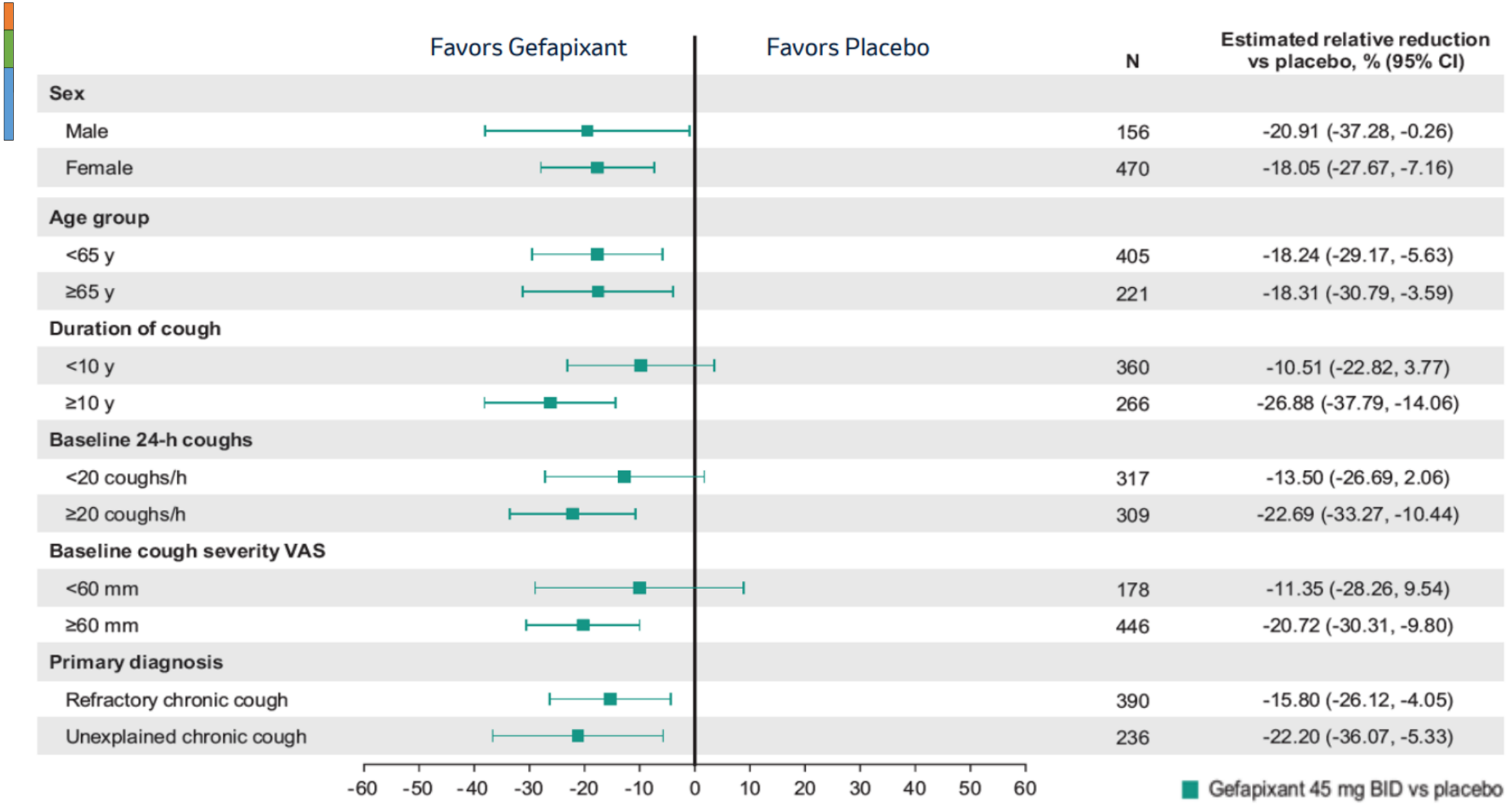



B

COUGH-2:14·6% (95% CI 1·4 to 26·1; p=0·031




| | Placebo | Gefapixant 15 mg twice per day | Gefapixant 45 mg twice per day |
|---|---|---|---|
| **COUGH-1** | | | †p≤0·001. ‡p≤0·05. |
| Number of participants | 243 | 244 | 243 |
| Any adverse event | 184 (75·7%) | 186 (76·2%) | 208 (85·6%) |
| Serious adverse events | 14 (5·8%) | 17 (7·0%) | 13 (5·3%) |
| Adverse events related to treatment* | 47 (19·3%) | 49 (20·1%) | 158 (65·0%) |
| Adverse events of special interest | | | |
| Taste-related adverse events | 11 (4·5%) | 31 (12·7%)† | 144 (59·3%)† |
| **COUGH-2** | | | |
| Number of participants | 432 | 442 | 440 |
| Any adverse event | 349 (80·8%) | 373 (84·4%) | 399 (90·7%) |
| Serious adverse events | 25 (5·8%) | 24 (5·4%) | 25 (5·7%) |
| Adverse events related to treatment* | 91 (21·1%) | 145 (32·8%) | 312 (70·9%) |
| Adverse events of special interest | | | |
| Taste-related adverse events | 36 (8·3%) | 89 (20·1%)† | 303 (68·9%)† |


Favors Gefapixant
Favors Placebo
N
Estimated relative reduction vs placebo, % (95% CI)
Sex
Male 156 -20.91 (-37.28, -0.26)
Female 470 -18.05 (-27.67, -7.16)
Age group
<65 y 405 -18.24 (-29.17, -5.63)
≥65 y 221 -18.31 (-30.79, -3.59)
Duration of cough
<10 y 360 -10.51 (-22.82, 3.77)
≥10 y 266 -26.88 (-37.79, -14.06)
Baseline 24-h coughs
<20 coughs/h 317 -13.50 (-26.69, 2.06)
≥20 coughs/h 309 -22.69 (-33.27, -10.44)
Baseline cough severity VAS
<60 mm 178 -11.35 (-28.26, 9.54)
≥60 mm 446 -20.72 (-30.31, -9.80)
Primary diagnosis
Refractory chronic cough 390 -15.80 (-26.12, -4.05)
Unexplained chronic cough 236 -22.20 (-36.07, -5.33)
-60 -50 -40 -30 -20 -10 0 10 20 30 40 50 60
Gefapixant 45 mg BID vs placebo

# Phase Ⅲ, Safety and efficacy of gefapixant (n=169) in Japanese participants

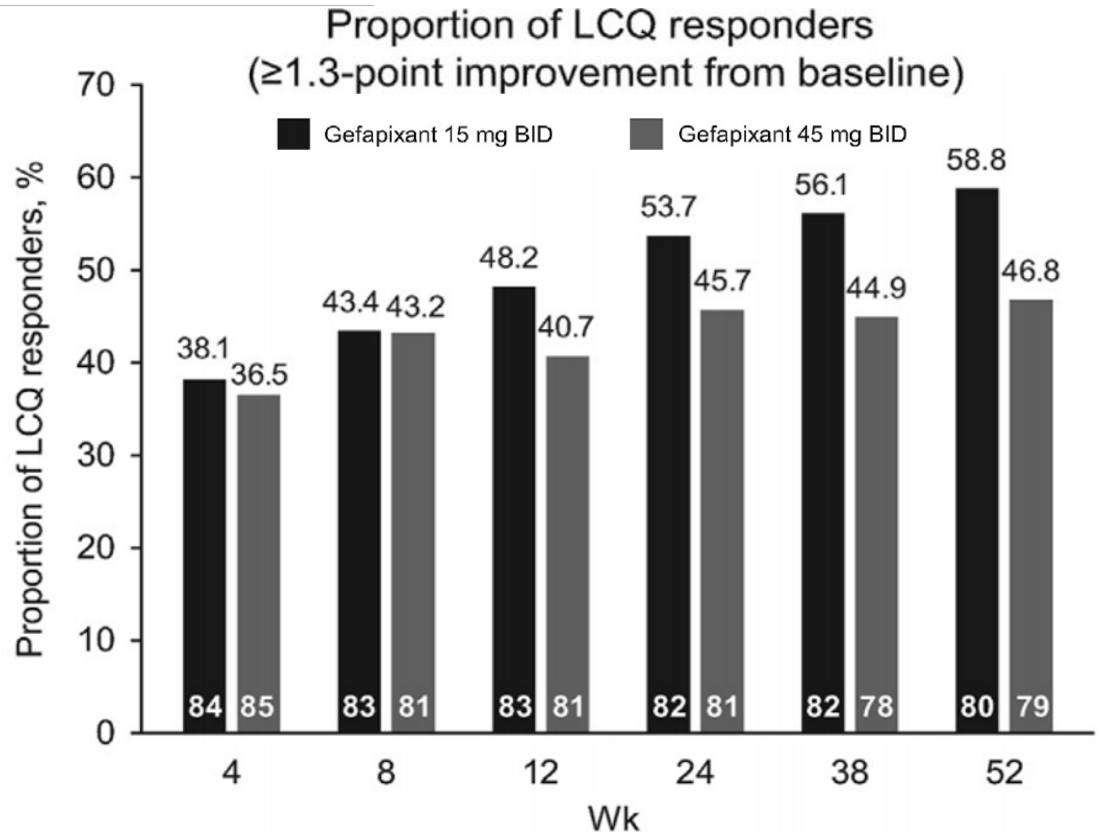
- Refractory/unexplained chronic cough (lasting 4M or longer)
- Non/Ex-smokers
- FEV1/FVC > 60%
- No substantial abnormalities on chest imaging

| Screening | Treatment period (52 weeks) |
|---|---|
| R | Gefapixant 45mg bid (n=85) |
| | Gefapixant 15mg bid (n=84) |

| | |
|---|---|
| Primary Objective | • Safety and tolerability of gefapixant, including adverse events (AEs) and discontinuations |
| Secondary Objective | • Change in LCQ |

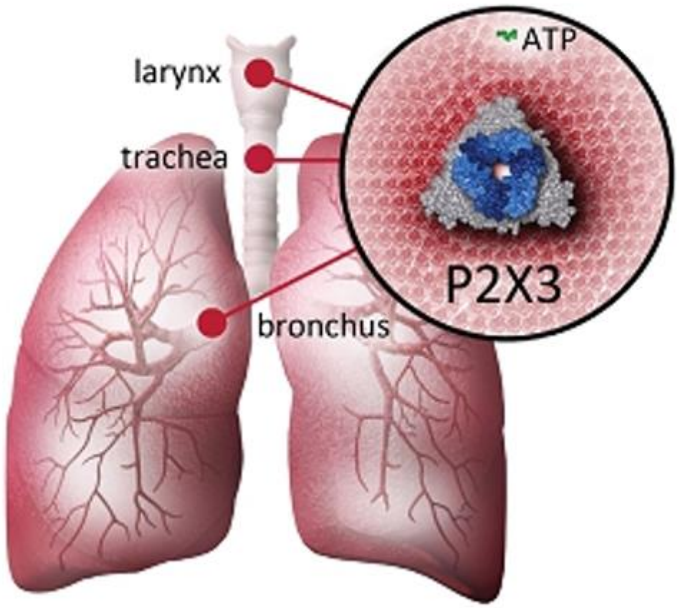

| Parameter, n (%) | Gefapixant 15 mg BID (n = 84) | Gefapixant 45 mg BID (n = 85) | Total (N = 169) |
|---|---|---|---|
| ≥1 AE | 79 (94) | 82 (96) | 161 (95) |
| Treatment-related AE | 33 (39) | 65 (76) | 98 (58) |
| Serious AE | 2 (2) | 10 (12) | 12 (7) |
| Pneumonia‡ | 0 | 3 (4) | 3 (2) |
| Discontinuations | | | |
| Due to AE | 6 (7) | 17 (20) | 23 (14) |
| Due to treatment-related AE | 3 (4) | 15 (18) | 18 (11) |
| Due to serious AE | 0 | 1 (1) | 1 (1) |
| Due to serious treatment-related AE | 0 | 0 | 0 |

| Parameter, n (%) | Gefapixant 15 mg BID (n = 84) | Gefapixant 45 mg BID (n = 85) | Total (N = 169) |
|---|---|---|---|
| ≥1 taste-related AE | 27 (32) | 66 (78) | 93 (55) |
| Ageusia | 0 | 5 (6) | 5 (3) |
| Ageusia | 0 | 4 (5) | 4 (2) |
| Taste loss | 0 | 1 (1) | 1 (1) |
| Dysgeusia | 14 (17) | 40 (47) | 54 (32) |

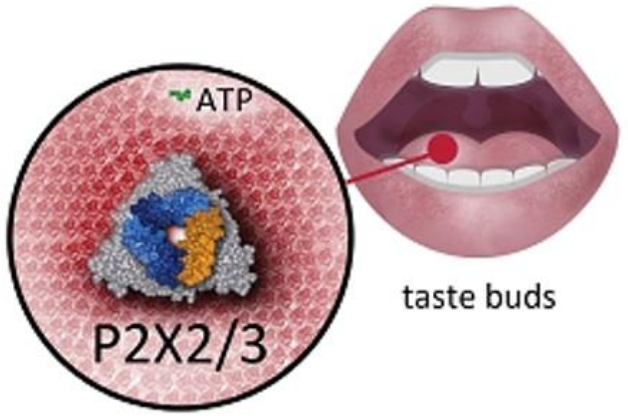


# Several other compounds have been subsequently developed to target the high selectivity for P2X3 receptors

**COUGH REFLEX:**
P2X3 **homotrimers** have primary role in cough




**TASTE:**
P2X2/3 **heterotrimers** have major role in taste




Eliapixant
(~ 13–20 fold)

BLU-5937
(>1500 fold)

Sivopixant
(>250 fold)

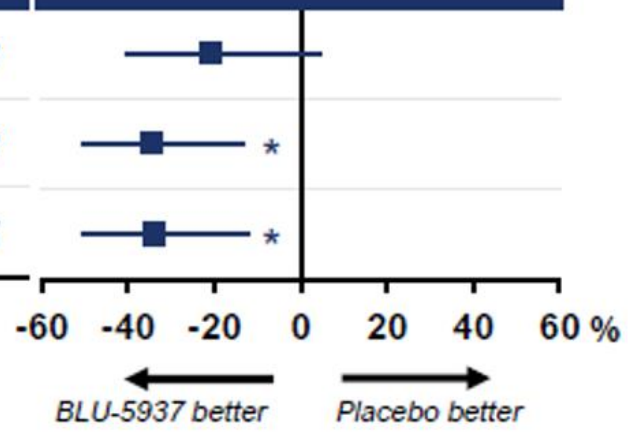
# Phase IIb, SOOTHE study (BLU-5937, n=249) in refractory cough

**Main Population: ≥25 awake coughs/h**

*Placebo-adjusted 24H cough frequency change from baseline at Day 28*

*Main Population (n=249)*

| Dose | Δ | p-value | 95% CI |
|---|---|---|---|
| 12.5 mg | -21.1% | 0.098 | |
| 50 mg | -34.4% | 0.003 | * |
| 200 mg | -34.2% | 0.005 | * |



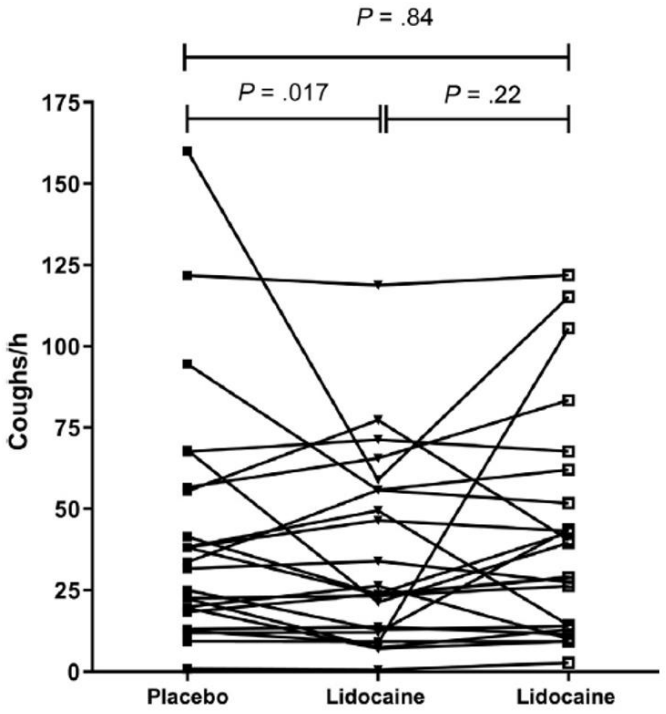

* $p \leq 0.005$; 2-sided

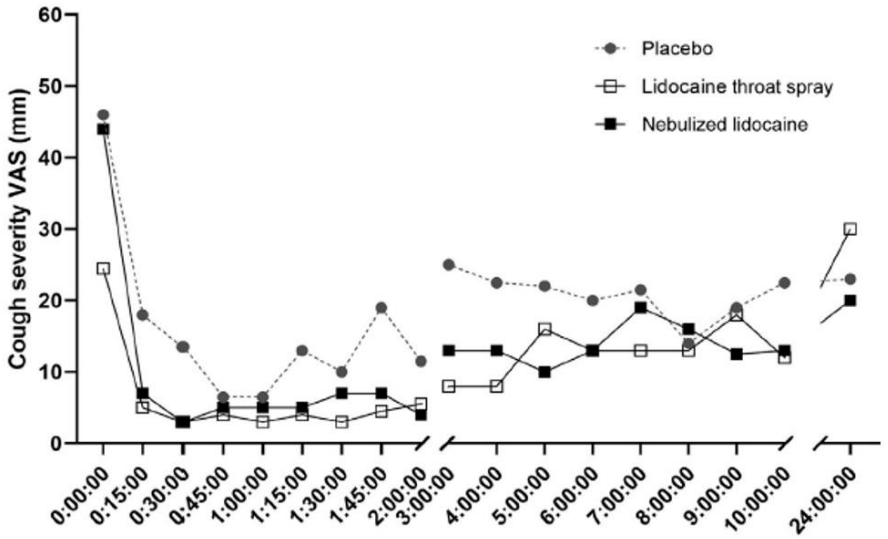
| | Placebo (BID) (n= 63) | BLU-5937 (BID) 12.5 mg (n= 62) | BLU-5937 (BID) 50 mg (n= 62) | BLU-5937 (BID) 200 mg (n= 62) |
|---|---|---|---|---|
| Subjects with ≥1 TEAE | 22 (34.9%) | 23 (37.1%) | 13 (21.0%) | 19 (30.6%) |
| Subjects with ≥1 TESAE | 0 | 0 | 0 | 0 |
| Subjects with TEAE leading to discontinuation, n (%) | 1 (1.6%) | 0 | 0 | 2 (3.2%) |
| *Most Common TEAEs (≥5% at any dose)†* | | | | |
| Nausea | 0 | 0 | 5 (8.1%) | 2 (3.2%) |
| Dysgeusia (taste alteration) | 0 | 3 (4.8%) | 4 (6.5%) | 3 (4.8%) |
| UTI | 0 | 3 (4.8%) | 0 | 0 |
| *Taste Disturbance Adverse Events (any incidence) ††* | | | | |
| Dysgeusia (taste alteration) | 0 | 3 (4.8%) | 4 (6.5%) | 3 (4.8%) |
| Hypogeusia (partial taste loss) | 0 | 0 | 0 | 0 |
| Ageusia (complete taste loss) | 0 | 0 | 0 | 0 |

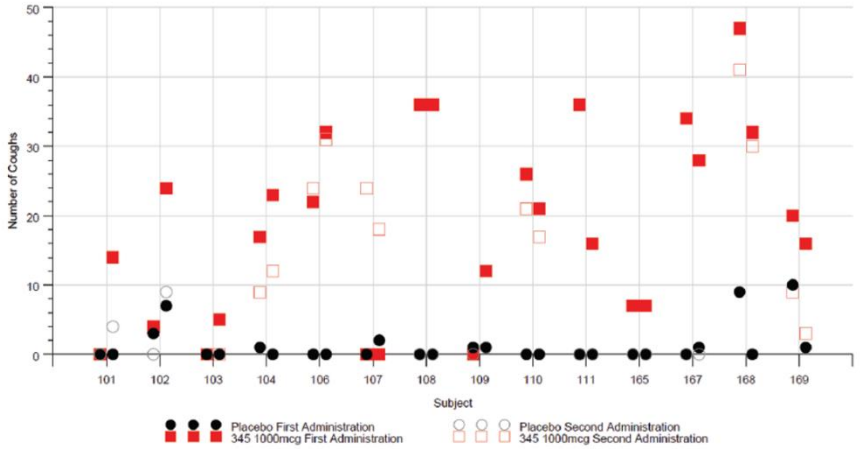
# Phase Ⅳ, Lidocaine in refractory cough (n=26)

**Nonselective inhibitor of voltage-gated sodium channels**

# Phase Ⅱ, GSK2339345 (NaV1.7, n=14) in refractory cough



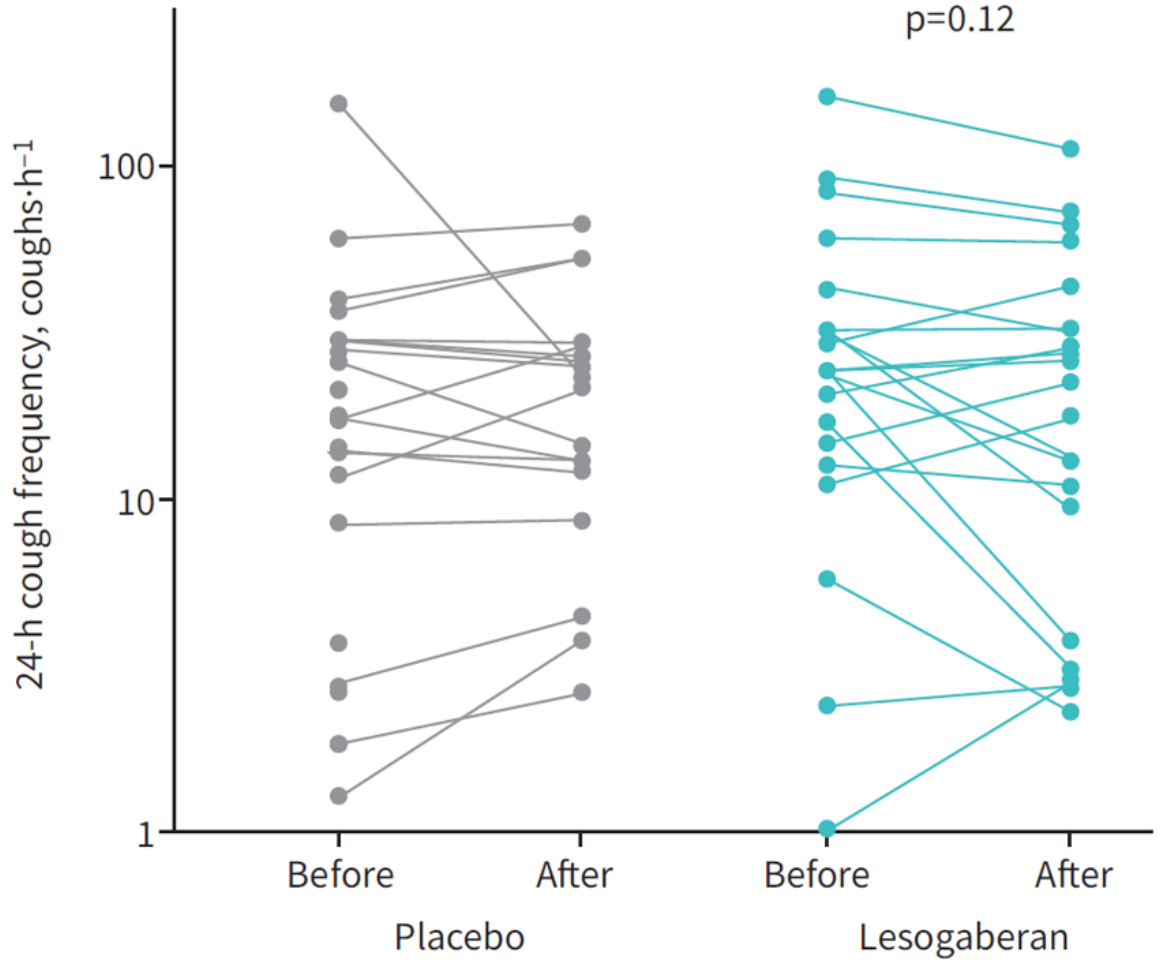



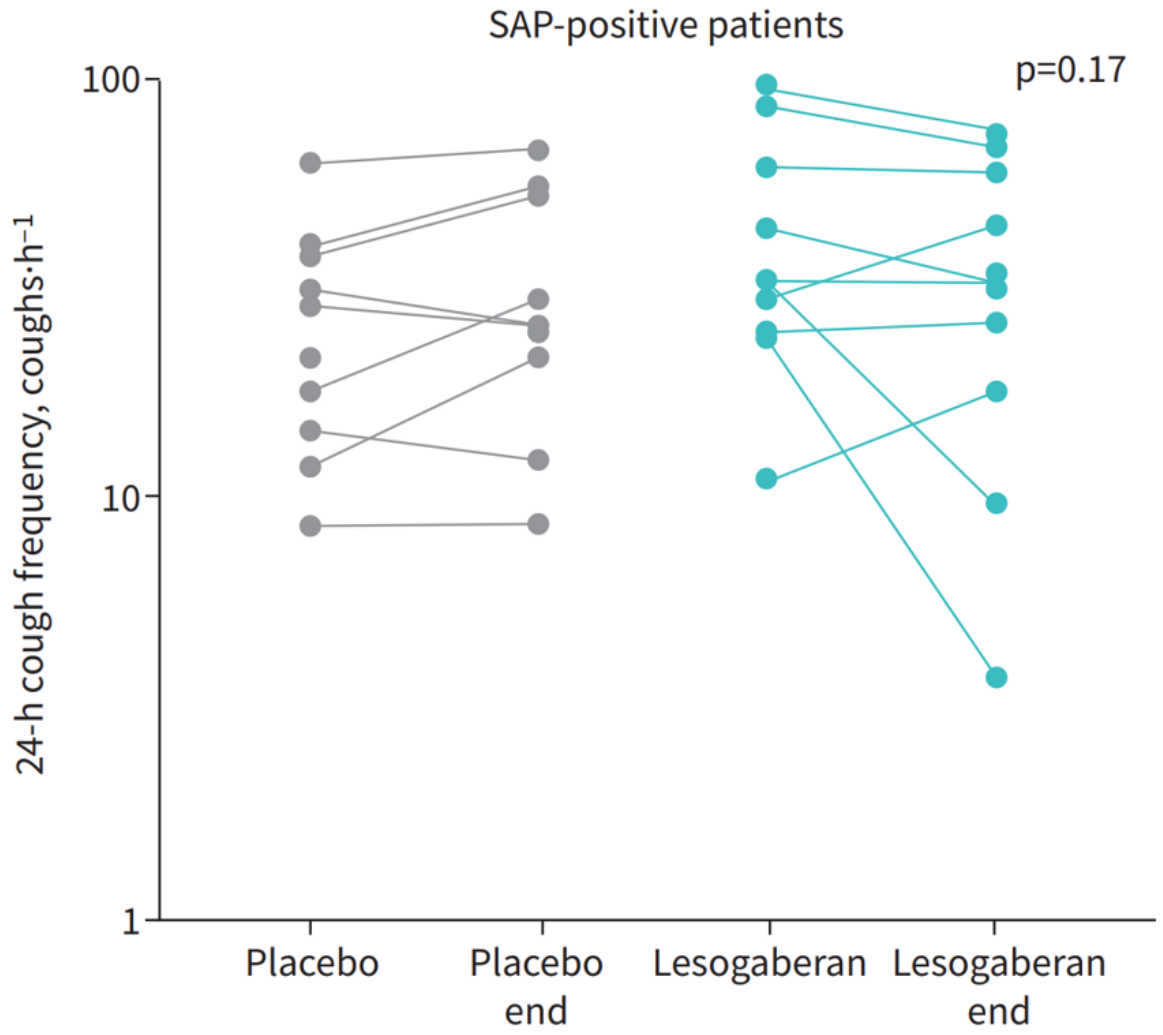




| Arm/Group Title | Placebo | GSK2339345 1000 Microgram (mcg) |
|---|---|---|
| ▼ Arm/Group Description: | | |
| Overall Number of Participants Analyzed | 14 | 14 |
| Geometric Mean (Standard Error)<br>Unit of Measure: cough count | | |
| | 152.7 (0.226) | 192.5 (0.226) |

# Phase Ⅱ, Lesogaberan in refractory cough (n=22)

**$GABA_B$ receptor agonist**

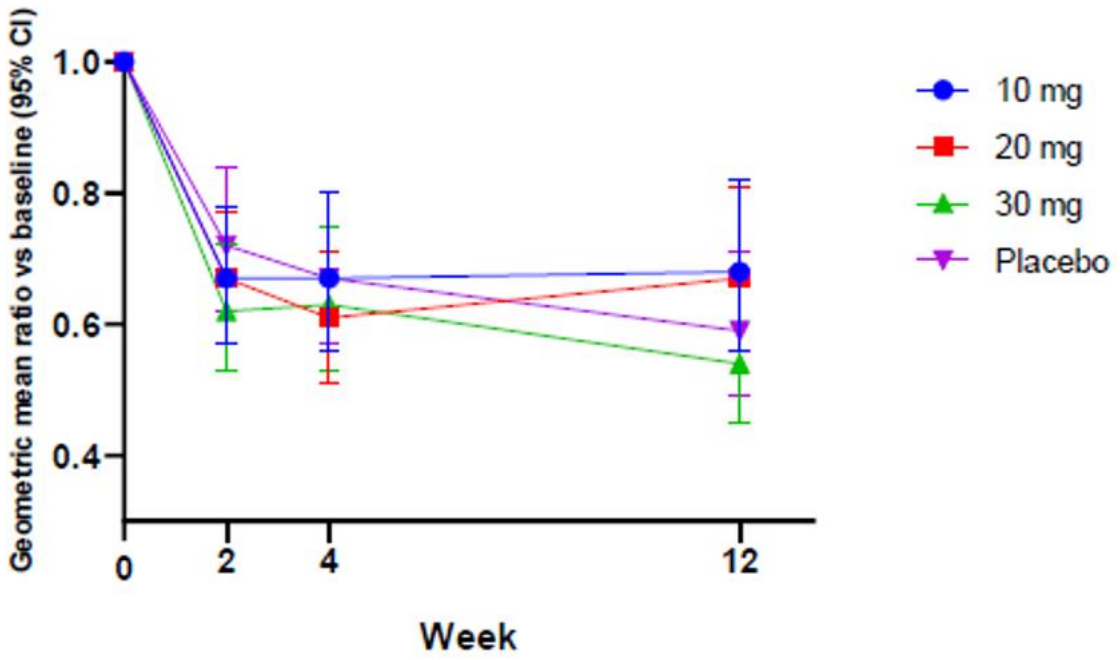


# Phase Ⅱb, VOLCANO-2 study (orvepitant, n=315) in refractory cough

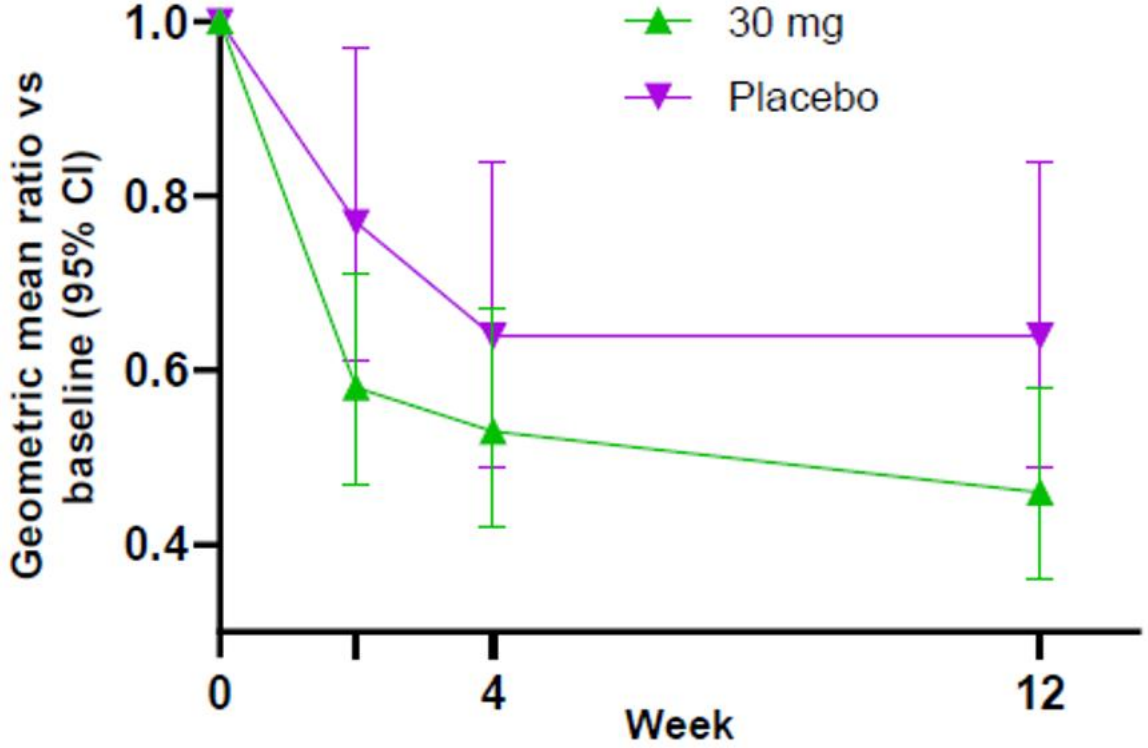
**Neurokinin receptor 1 antagonist**

## Awake Cough Frequency in the Full Analysis Set




## Awake Cough Frequency in the Higher Frequency Cough Group

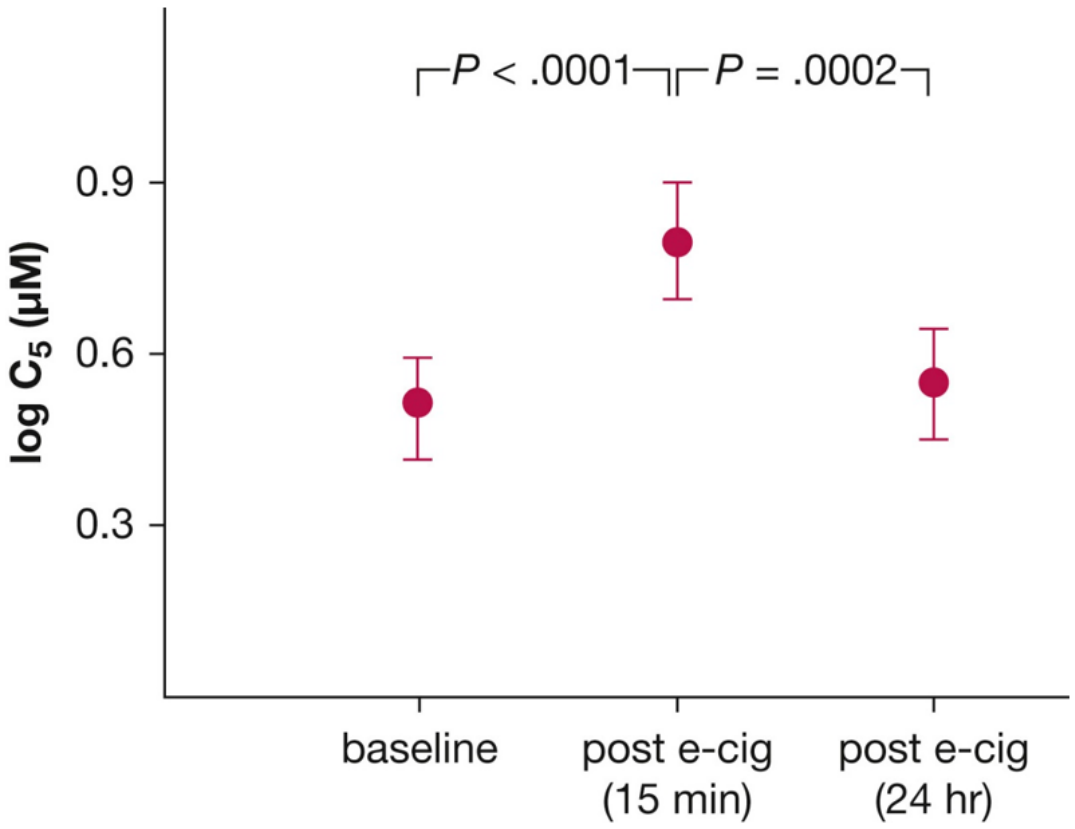
In the higher CF subjects (≥study median awake CF at baseline)




| Analysis Group | Full Analysis Set |
|---|---|
| N | 315 |
| Cough duration (mean, years) | 12.8 |
| Awake cough frequency (mean, coughs/hour) | 43.0 |

# Phase Ⅱ, Bradanicline in refractory cough (n=46)

**α7- nicotinic acetylcholine receptor (nAChR) agonist**



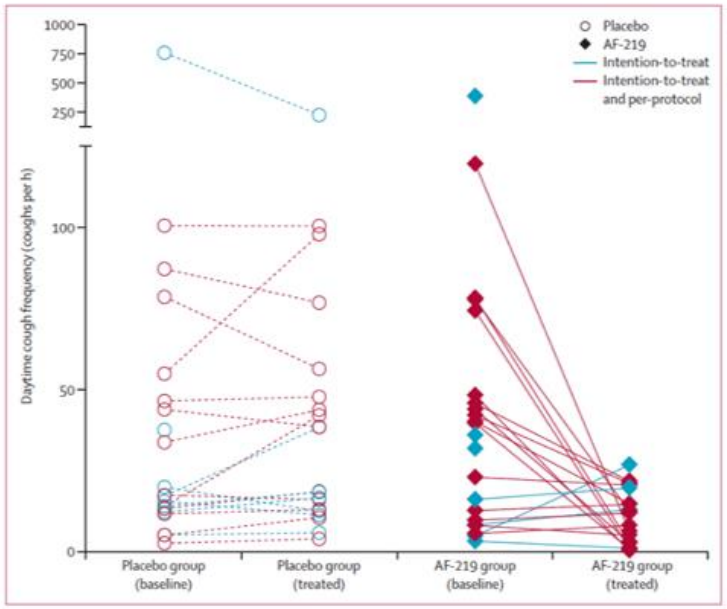

**Methods:** This randomized, double-blinded, placebo-controlled, crossover study recruited 46 RCC patients (39 females, mean age 63 years, median cough duration 18 years) from November 2018 to February 2019. Patients were allocated to bradanicline-placebo or placebo-bradanicline, 1:1 ratio, after screening for a minimum ≥10 coughs/hr. Following an initial loading dose (50mg bradanicline or matched placebo), study treatment was escalated weekly from 25mg to 75mg, and then 150mg or a matched placebo regimen for a total of 3 weeks of treatment. After a 14-day washout, patients were crossed over. Cough frequency was monitored for 24 hours (VitaloJAK). The primary endpoint was the relationship between bradanicline dose and awake cough frequency (ACF).

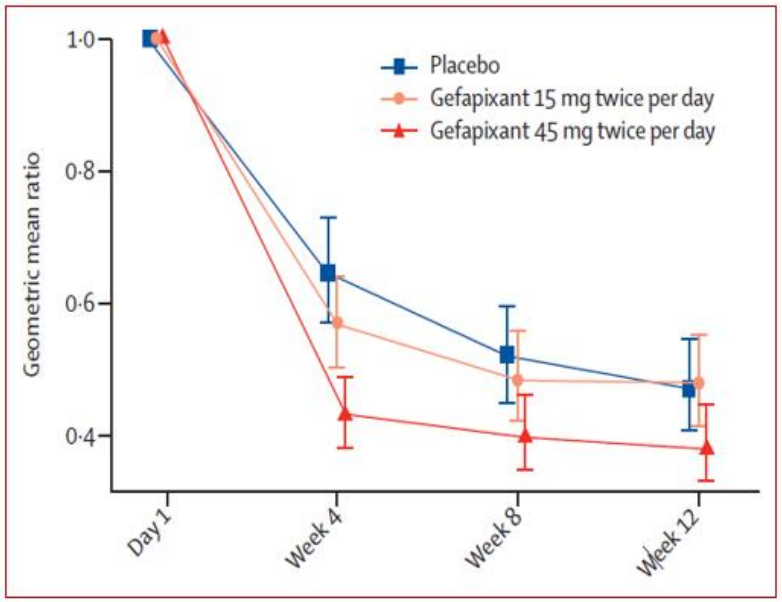
**Results:** All but one patient completed the study and 409/414 cough recordings were available for analysis. Mean ACF at baseline was 36.4 (SD 29.3) coughs/hour. Neither bradanicline nor placebo reduced ACF, with no meaningful difference between the two treatments. Patient reported outcomes also showed no treatment effects. The frequency of adverse effects was similar for bradanicline (n = 16) and placebo (n = 17).

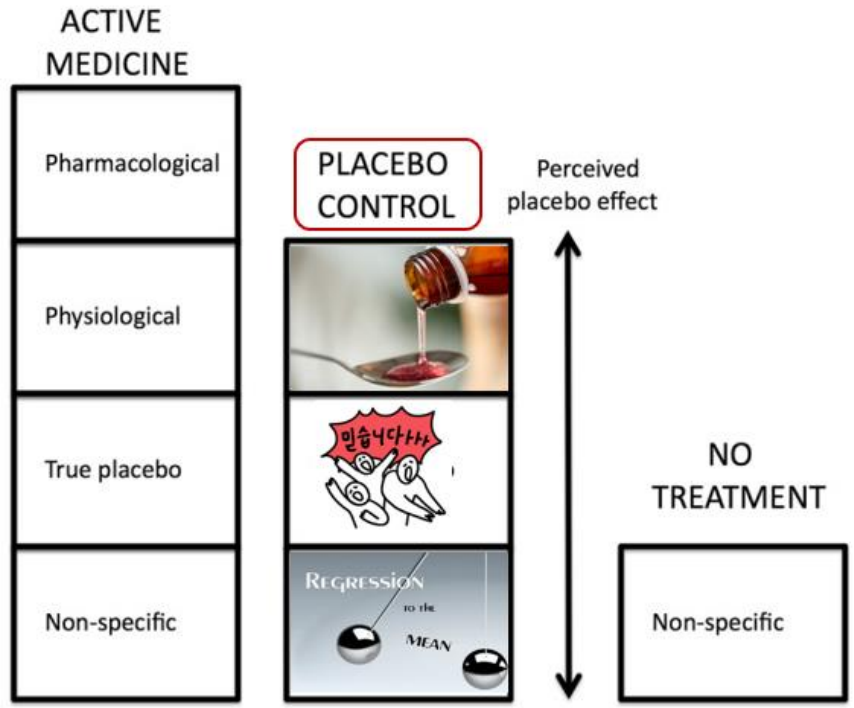
**Conclusions:** Despite good tolerability, escalating doses of bradanicline did not reduce awake cough frequency in RCC patients compared with placebo.

# Following points may be worth further consideration

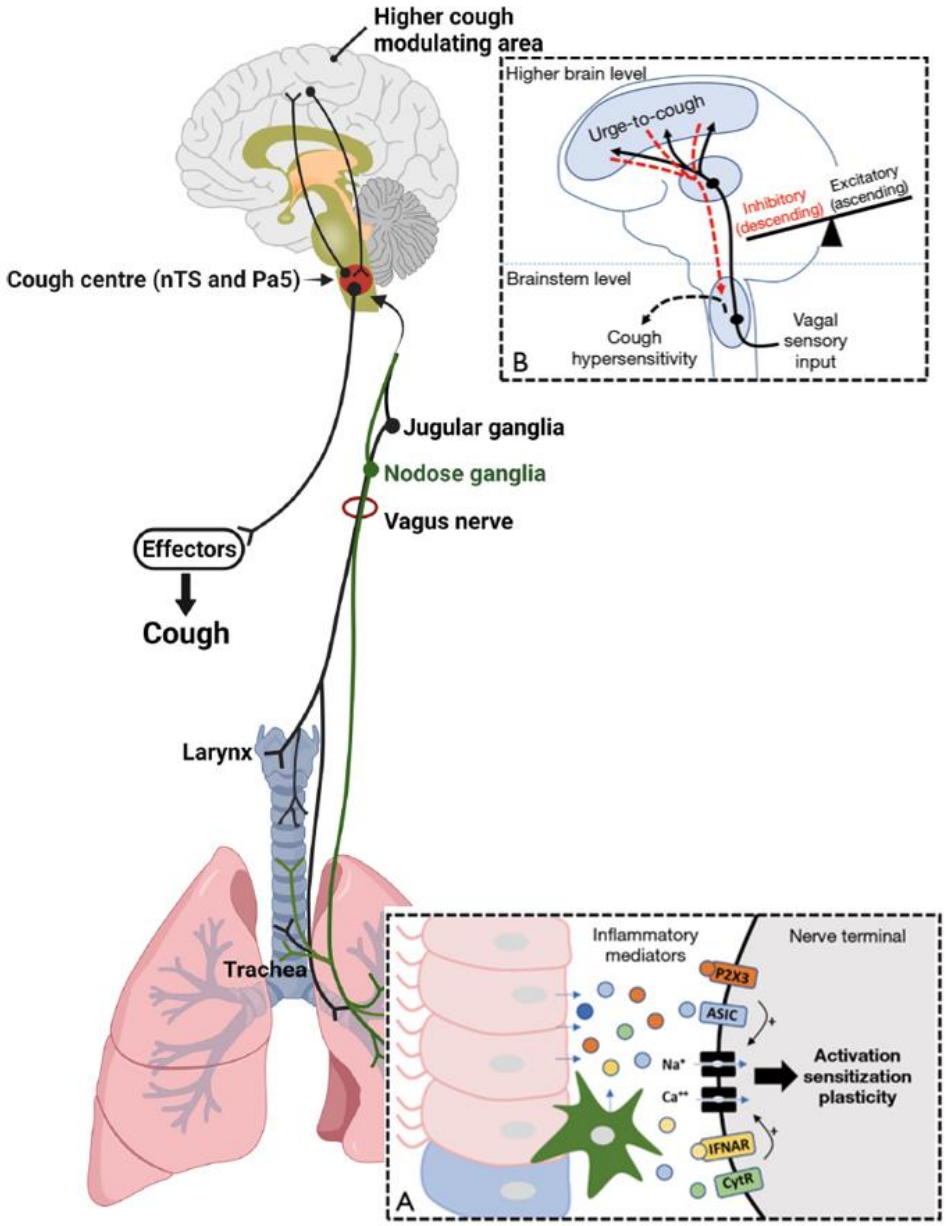
## Placebo effects in chronic cough



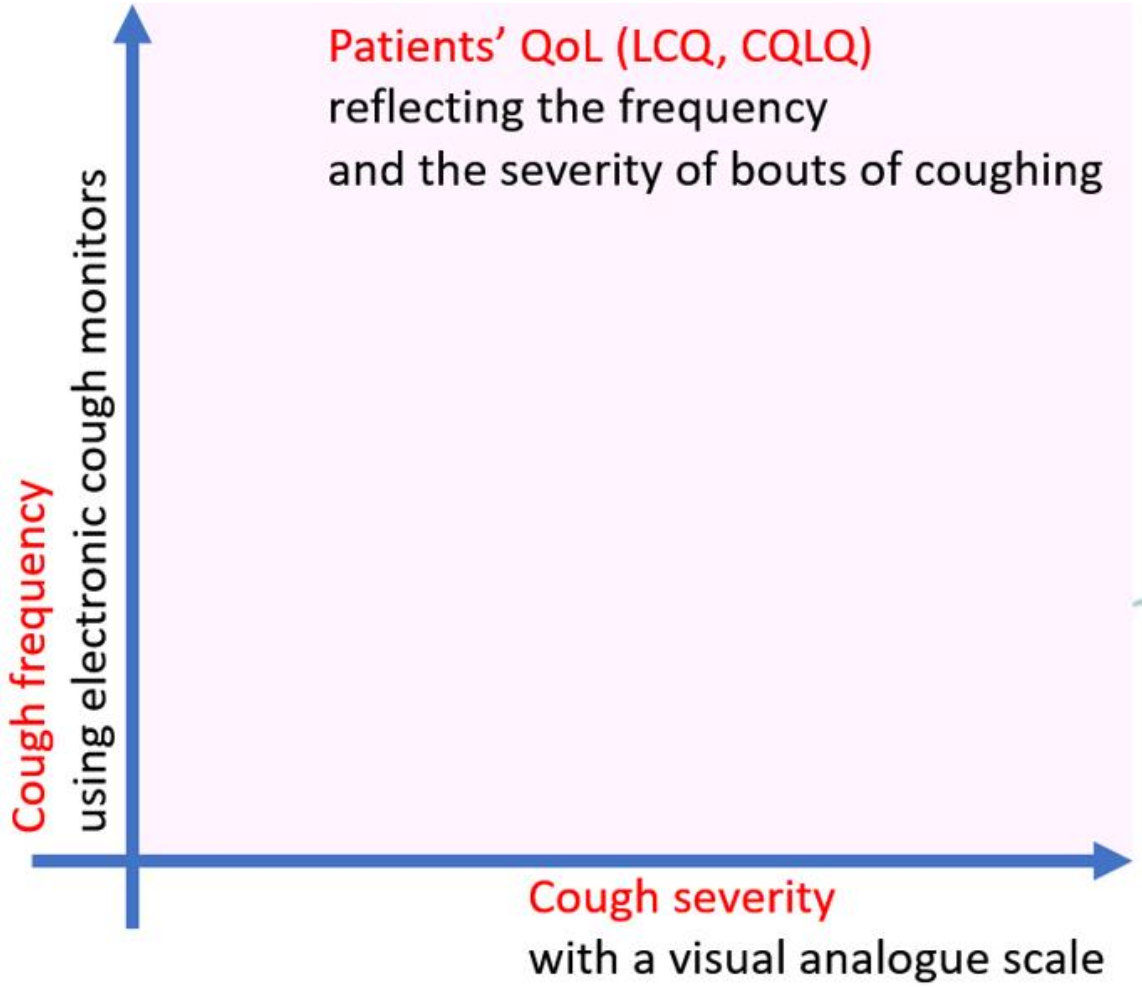



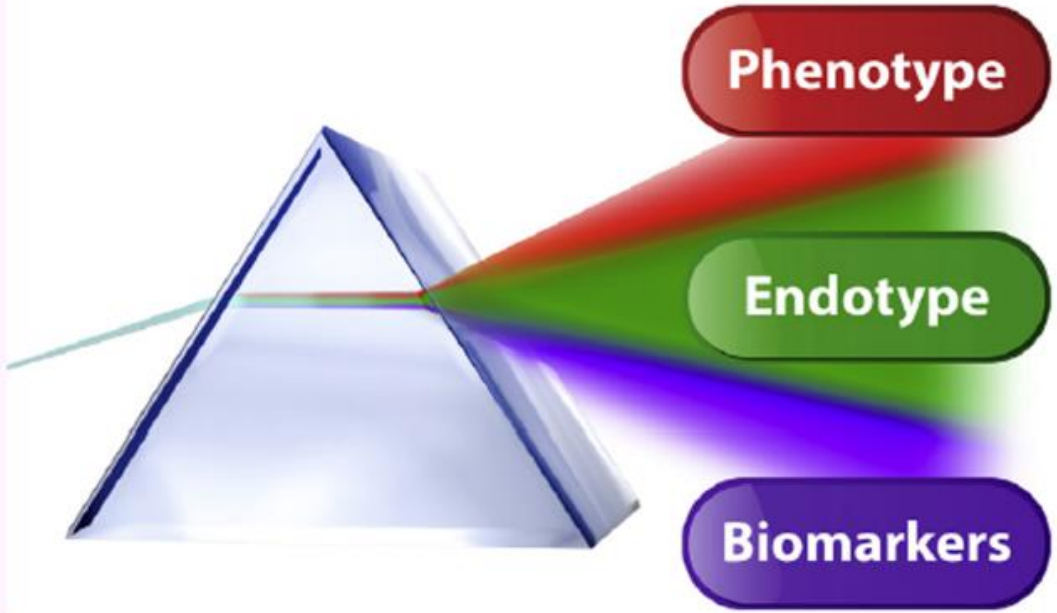



- Complex dysfunction of the neurological circuit to the production of cough
- Discrepancies in therapeutic effects between different clinical conditions



- Presence of non-responders
- The need of biomarker identified for predicting responses



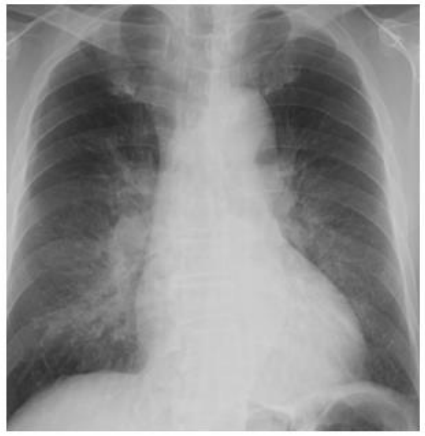



## Optimal control of cough

Cough reflex inhibition

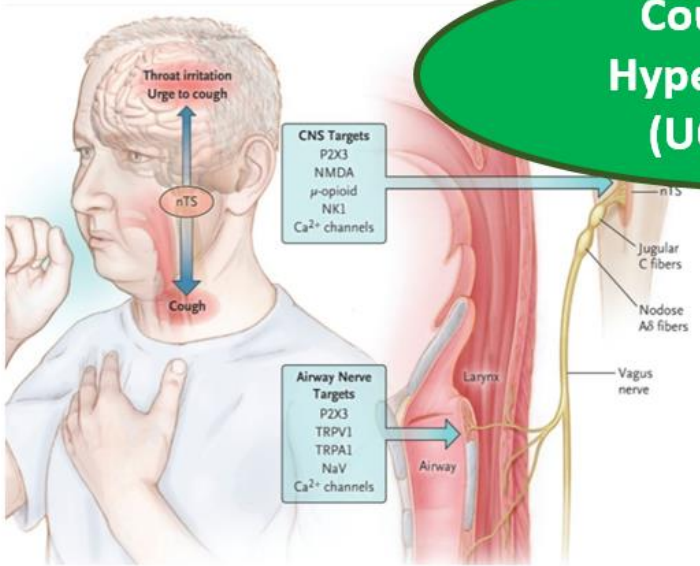
The protective cough reflex

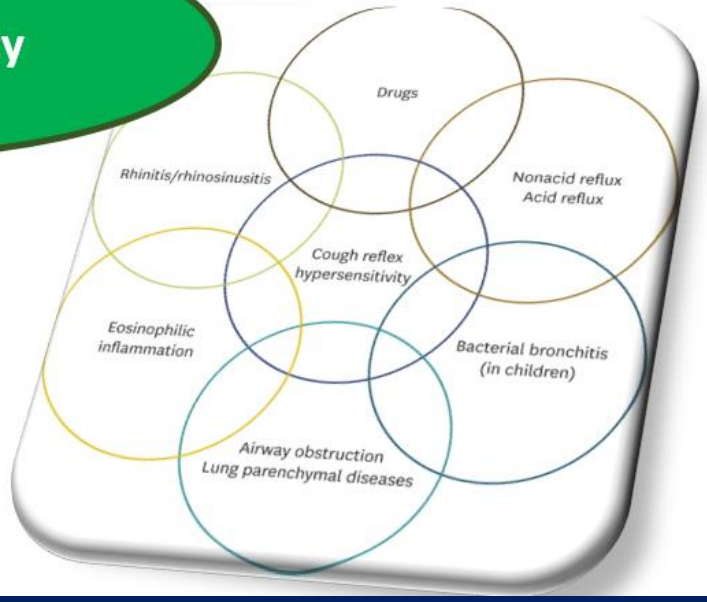
Cough reflex  cough excitability



**Cough Reflex Hypersensitivity (UCC, RUCC)**

| Drugs |
| --- |
| Morphine |
| Gabapentin |
| Pregabalin |
| Amitriptyline |
| Codeine |
| Dextromethorphan |



# Summary

- Chronic cough and RCC has been recognized as a distinct condition and a considerable disease burden, including physical and psychological effects that significantly impair QoL.

- These features, together with a limited success rate of available therapies, imply an urgent need to search for new, more effective and safe antitussives.

- There has been a very significant growth in the development of therapeutic agents to treat cough. Number of new molecules entered preclinical and clinical trials, including P2X3 receptor antagonists which seem to be the most promising drugs for refractory cough.

- It is unlikely that a single treatment will be effective in all patients and combination therapy, such as combine drugs of different mechanism of antitussive action and non-pharmacological management, may be required in selected patients.

- Further work is still needed for better characterization of different cough phenotypes and endotypes, more comprehensive measures of cough, and the pursuits to match the appropriate therapy to the underlying cough mechanism.

# 경청해 주셔서 감사합니다.