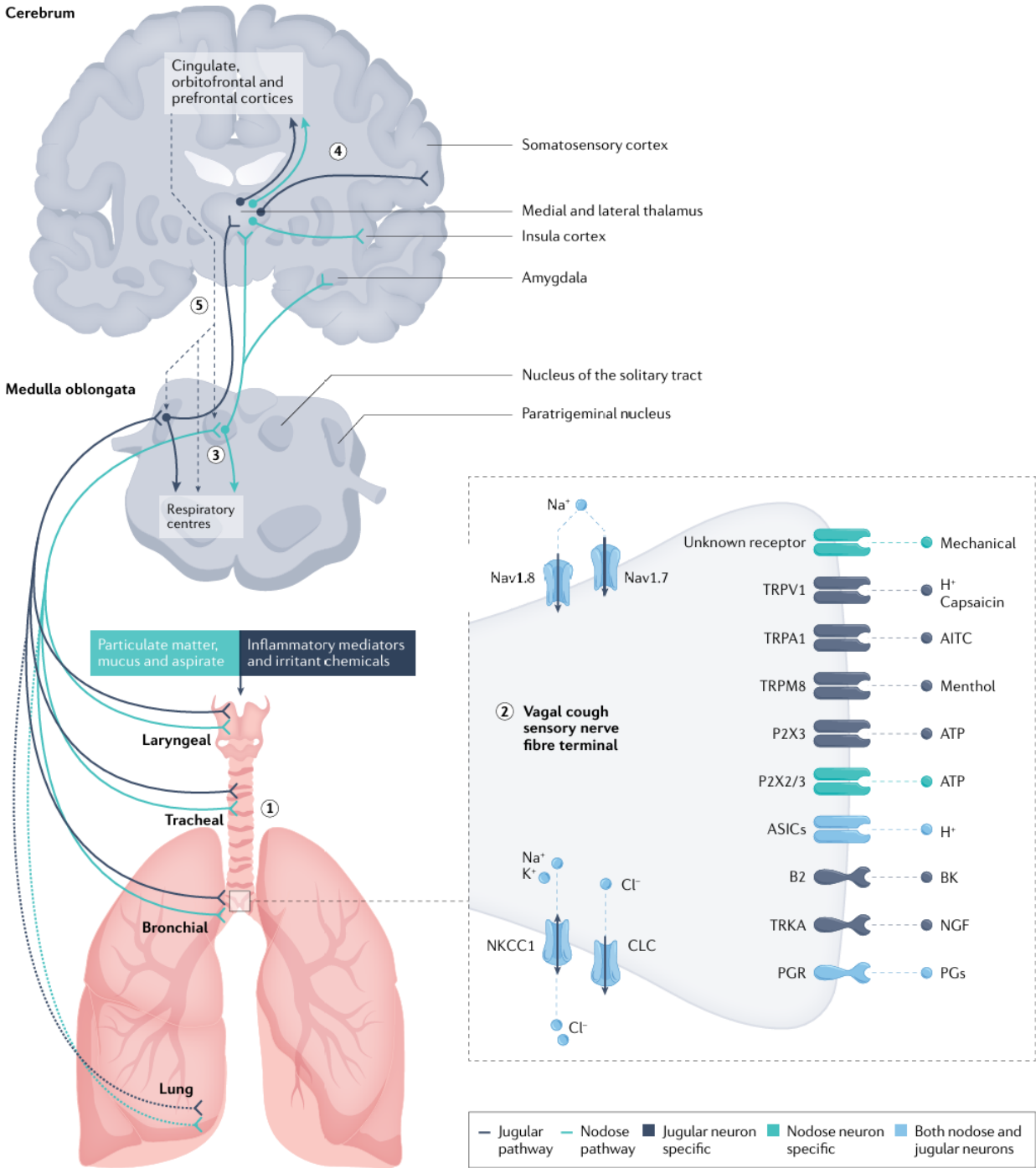


P2X3 Antagonists and Beyond

문성우 (건국의대 호흡기내과)

Part I

Introduction



Cough mechanism

C-fiber (화학자극) 와 Aδ-fiber (기계자극, 산성자극) 의 감각 입력이 미주신경을 통해 중추로 전달

말초 및 중추 Sensitization이 기침 과민성에 관여

P2X3·TRP는 감각 변환, NaV는 활동전위 전도에 관여

P2X3와 P2X2/3의 선택성이 효능·미각 이상에 영향

Part II

P2X3 Antagonist

ATP-P2X3

- AF-219 600mg(gefapixant): double-blind, placebo-controlled, two-period, crossover study, 24 pts, Phase 2

Participants (n=24)	
Sex	
Women	18 (75%)
Men	6 (25%)
Age (years)	54.5 (24-70)
Body-mass index (kg/m²)	25.9 (20-35)
White, non-Hispanic individuals	24 (100%)
Duration of cough (years)	9 (3-25)
Type of cough	
Dry	18 (75%)
Productive	6 (25%)
Lung function	
FEV ₁ (L)	2.7 (1.8-3.8)
FVC (L)	3.3 (2.2-4.8)
Ratio (%)*	79.5% (67.6-88.0)
Data are n (%), median (IQR), or mean (SD), unless otherwise indicated. FEV ₁ =forced expiratory volume in 1 s. FVC=forced vital capacity. *FEV ₁ to FVC.	
Table 1: Baseline demographic and clinical characteristics	

	AF-219		Placebo		Difference at 2 weeks	
	Baseline	Week 2	Baseline	Week 2	Placebo-adjusted effect of AF-219 (95% CI)*	p value
24 h cough frequency						
ITT population						
Patients in analysis	18	18	20	20	..	..
Coughs	26.63 (22-63)	7.74 (6-02)	44.70 (105-16)	28.85 (31-17)	-74% (-87 to -46)	0.001
PP population						
Patients in analysis	12	12	12	12	..	..
Coughs	33.24 (24-13)	6.96 (5-63)	28.42 (22-46)	30.44 (22-29)	-89% (-97 to -67)	0.001
Urge to cough VAS						
ITT population						
Patients in analysis	24	24	20	20	..	..
Score‡	63.1 (23-10)	35.9 (35-49)	62.5 (19-99)	56.0 (24-86)	-21.3 (-41.0 to -1.5)	0.035
PP population						
Patients in analysis	14	14	14	14	..	..
Score‡	64.4 (23-50)	19.9 (28-91)	62.3 (21-67)	55.0 (28-43)	-34.6 (-57.9 to -11.4)	0.005
CQLQ total score						
ITT population						
Patients in analysis	19	19	17	17	..	..
Score§	56.3 (10-40)	45.4 (12-82)	56.2 (10-28)	54.9 (8-79)	-9.2 (-16.8 to -1.7)	0.018
PP population						
Patients in analysis	12	12	12	12	..	..
Score§	57.7 (9-99)	44.8 (14-15)	58.3 (9-76)	55.8 (8-44)	-10.70 (-20.83 to -0.57)	0.040

- AF-219(gefapixant): double-blind, placebo-controlled, two-period, crossover study, 24 pts

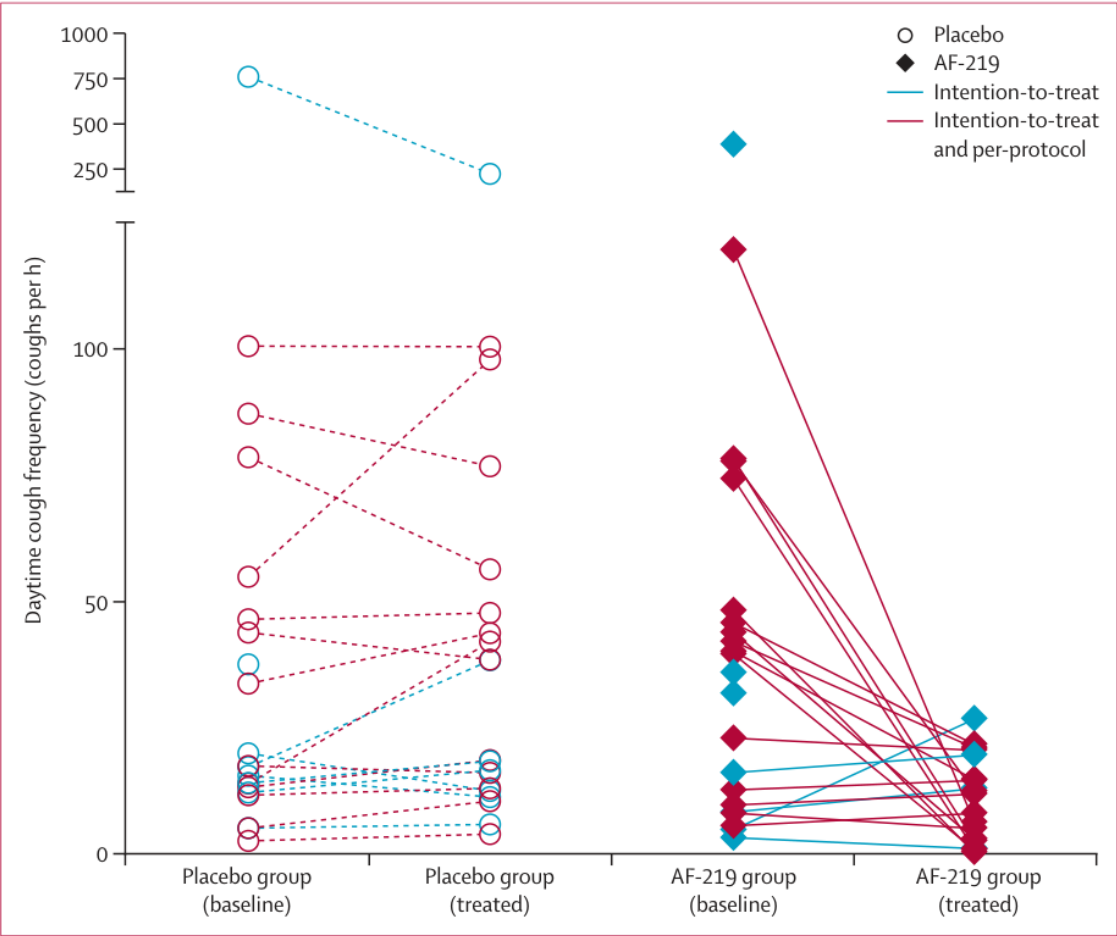


Figure 2: Changes in objective daytime cough frequency from baseline to end of the treatment period
Intention-to-treat analysis included the blue and red data points, whereas the per-protocol included data in red only.

	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%)

Adverse events were classified according to MedDRA Version 14.0 and displayed by preferred term. *Reports of hypogeusia or ageusia were categorised as hypogeusia. Every patient reported at least one type of taste adverse event during AF-219 treatment.

Table 4: Treatment-emergent adverse events reported by more than one AF-219-treated patient

COUGH-1/2 ; two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials

McGarvey LP, Lancet 2022;399:909-923

	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day	Total
COUGH-1				
Number of participants	243	244	243	730
Sex				
Female	181 (74.5%)	181 (74.2%)	180 (74.1%)	542 (74.2%)
Male	62 (25.5%)	63 (25.8%)	63 (25.9%)	188 (25.8%)
Age (years)				
Mean	57.9 (13.1)	59.6 (11.7)	59.4 (13.1)	59.0 (12.6)
Range	21-81	22-89	19-85	19-89
Race				
American Indian or Alaska native	7 (2.9%)	6 (2.5%)	8 (3.3%)	21 (2.9%)
Asian	35 (14.4%)	35 (14.3%)	34 (14.0%)	104 (14.2%)
Black or African American	4 (1.6%)	3 (1.2%)	4 (1.6%)	11 (1.5%)
Multiple	8 (3.3%)	5 (2.0%)	11 (4.5%)	24 (3.3%)
White	189 (77.8%)	195 (79.9%)	186 (76.5%)	570 (78.1%)
Duration of chronic cough (years)				
Mean	11.7 (9.9)	11.8 (9.1)	11.2 (9.4)	11.6 (9.5)
Range	2-59	2-45	2-56	2-59
Region				
Asia-Pacific	35 (14.4%)	34 (13.9%)	34 (14.0%)	103 (14.1%)
Europe	121 (49.8%)	123 (50.4%)	121 (49.8%)	365 (50.0%)
North America	56 (23.0%)	55 (22.5%)	56 (23.0%)	167 (22.9%)
Others	31 (12.8%)	32 (13.1%)	32 (13.2%)	95 (13.0%)
Primary diagnosis				
Refractory chronic cough	148 (60.9%)	141 (57.8%)	139 (57.2%)	428 (58.6%)
Unexplained chronic cough	95 (39.1%)	103 (42.2%)	104 (42.8%)	302 (41.4%)
Mean HARQ at baseline	40.2 (13.6)	39.4 (13.3)	39.3 (13.0)	39.6 (13.3)
Baseline values for efficacy endpoints				
24-h cough frequency				
Geometric mean coughs per h	22.0	19.7	17.7	19.7
Leicester Cough Questionnaire total score				
Mean baseline total score	10.0 (3.1)	10.5 (2.9)	10.5 (2.7)	10.3 (2.9)
Cough severity visual analogue scale (mm)				
Weekly mean	69.1 (13.9)	68.2 (15.0)	67.9 (12.8)	68.4 (13.9)
Cough Severity Diary score				
Weekly mean	6.2 (1.5)	6.1 (1.7)	6.1 (1.5)	6.1 (1.6)

COUGH-2				
Number of participants	435	440	439	1314
Sex				
Female	326 (74.9%)	329 (74.8%)	329 (74.9%)	984 (74.9%)
Male	109 (25.1%)	111 (25.2%)	110 (25.1%)	330 (25.1%)
Age (years)				
Mean	58.0 (12.6)	58.6 (11.4)	57.8 (12.4)	58.1 (12.1)
Range	19-84	22-88	19-87	19-88
Race				
American Indian or Alaska native	20 (4.6%)	28 (6.4%)	24 (5.5%)	73 (5.6%)
Asian	15 (3.4%)	14 (3.2%)	15 (3.4%)	44 (3.3%)
Black or African American	5 (1.1%)	9 (2.0%)	14 (3.2%)	28 (2.1%)
Native Hawaiian or other Pacific Islander	4 (0.9%)	2 (0.5%)	3 (0.7%)	9 (0.7%)
Multiple	36 (8.3%)	31 (7.0%)	37 (8.4%)	104 (7.9%)
White	355 (81.6%)	356 (80.9%)	346 (78.8%)	1057 (80.4%)
Duration of chronic cough (years)				
Mean	10.7 (8.8)	11.9 (10.7)	10.9 (9.9)	11.2 (9.8)
Range	2-51	1-75	2-65	1-75
Region				
Asia-Pacific	26 (6.0%)	27 (6.1%)	28 (6.4%)	81 (6.2%)
Europe	238 (54.7%)	238 (54.1%)	239 (54.4%)	715 (54.4%)
North America	97 (22.3%)	99 (22.5%)	98 (22.3%)	294 (22.4%)
Others	74 (17.0%)	76 (17.3%)	74 (16.9%)	224 (17.0%)
Primary diagnosis				
Refractory chronic cough	277 (63.7%)	273 (62.0%)	279 (63.6%)	829 (63.1%)
Unexplained chronic cough	158 (36.3%)	167 (38.0%)	160 (36.4%)	485 (36.9%)
Mean HARQ at baseline	40.1 (13.2)	39.3 (13.7)	39.6 (13.5)	39.7 (13.5)
Baseline values for efficacy endpoints				
24-h cough frequency				
Geometric mean coughs per h	19.4	18.9	18.5	18.9
Leicester Cough Questionnaire total score				
Mean baseline total score	10.3 (3.0)	10.4 (3.0)	10.4 (3.0)	10.4 (3.0)
Cough severity visual analogue scale (mm)				
Weekly mean	68.5 (14.3)	67.4 (14.8)	67.7 (13.9)	67.8 (14.3)
Cough Severity Diary score				
Weekly mean	6.0 (1.6)	5.9 (1.8)	6.0 (1.6)	5.9 (1.7)
Data are n, n (%), mean (SD), or range. HARQ=Hull Airway Reflex Questionnaire.				
Table 1: Baseline patient characteristics				

COUGH-1/2 ; two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials

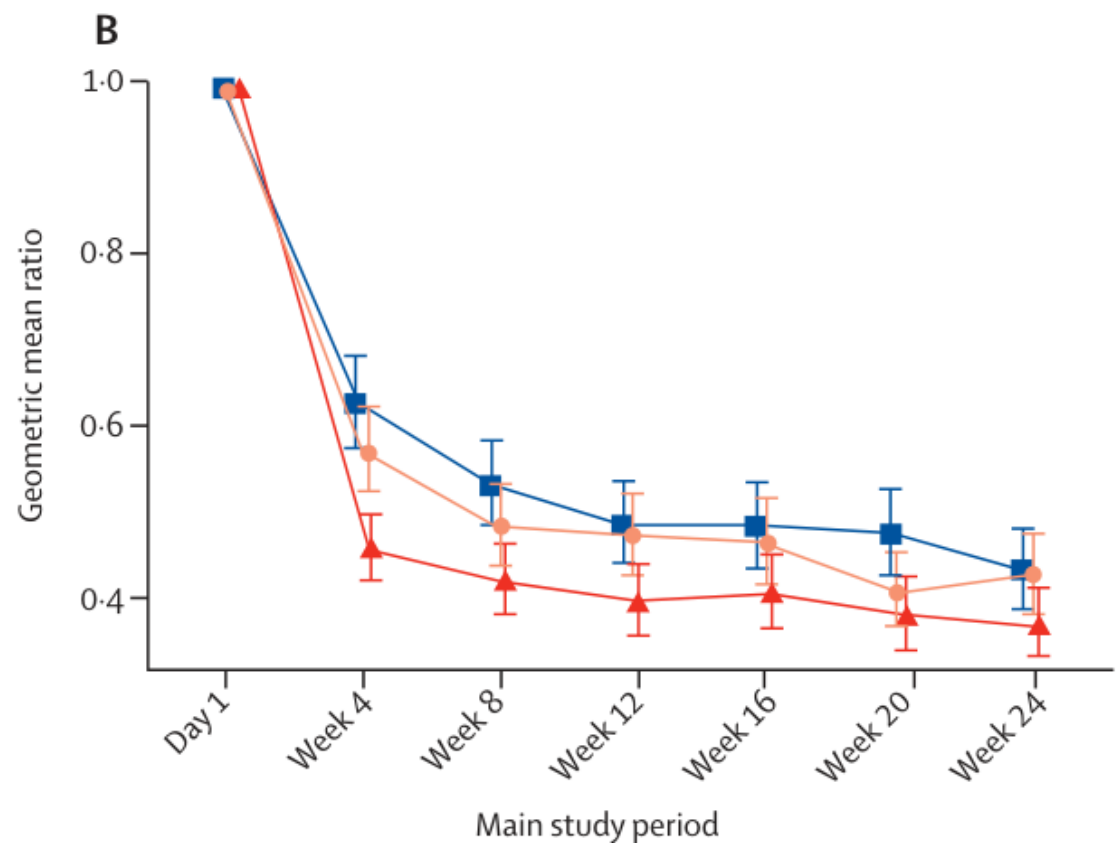
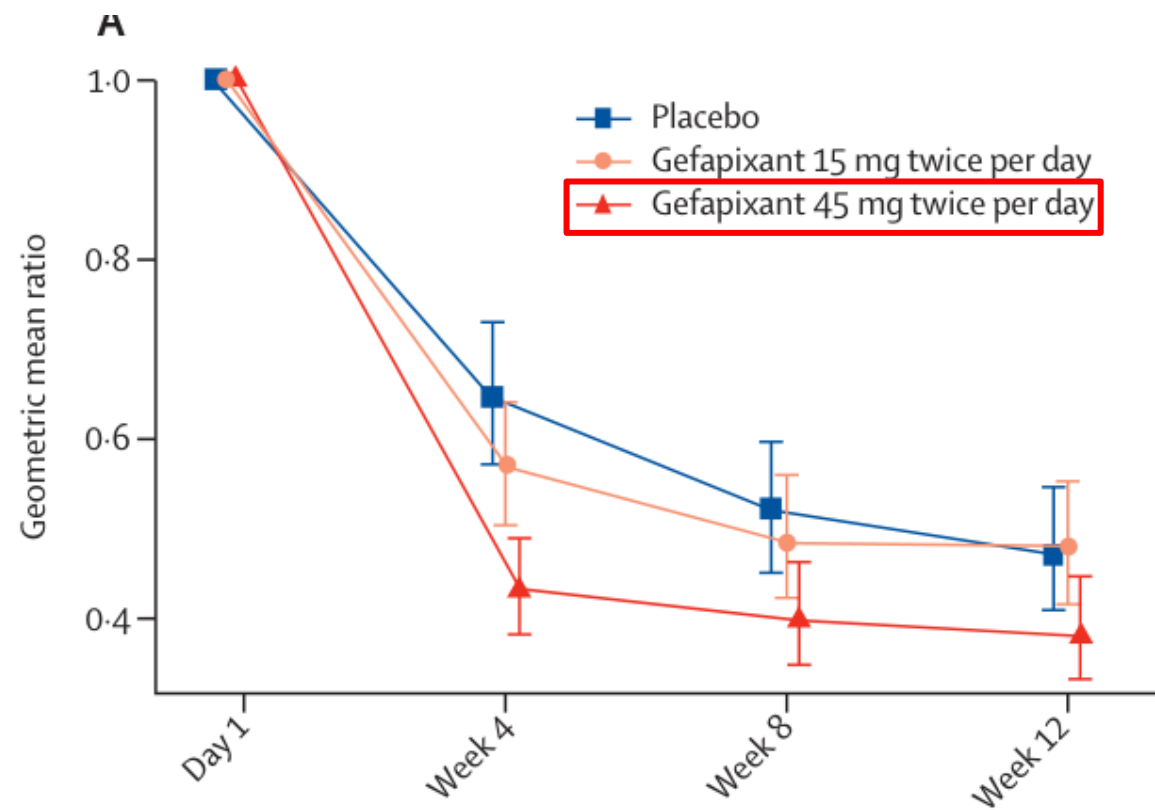
McGarvey LP, Lancet 2022;399:909-923

Primary endpoint

24-h cough frequency				
Number of patients with data	222	227	217	..
Baseline (geometric mean coughs per h)	22.8	19.9	18.2	..
Week 12 (geometric mean coughs per h)	10.3	9.7	7.1	..
Percentage of estimated relative reduction (95% CI) vs placebo	..	-1.56 (-22.99 to 16.13)	18.45 (0.86 to 32.92)	p=0.041

Primary endpoint

24-h cough frequency				
Number of patients with data	419	415	409	..
Baseline (geometric mean cough per h)	19.5	19.4	18.6	..
Week 24 cough frequency (geometric mean coughs per h)	8.3	8.1	6.8	..
Percentage of estimated relative reduction (95% CI) vs placebo	..	1.14 (-14.02 to 14.27)	14.64 (1.43 to 26.07)	p=0.031



COUGH-1/2 ; two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials

McGarvey LP, Lancet 2022;399:909-923

- P2X3 homotrimer(기침·미주신경) vs P2X2/3 heterotrimer(미각신경) 발현 중첩
- 미각 이상 발생률 45mg군에서 최대 59-68% (위약 4-8%)

	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day
COUGH-1			
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%)†
Most common adverse events (>8% in a single treatment group)			
Ageusia	0	3 (1.2%)	33 (13.6%)†
Back pain	19 (7.8%)	14 (5.7%)	20 (8.2%)
Dysgeusia	8 (3.3%)	22 (9.0%)‡	88 (36.2%)†
Headache	31 (12.8%)	34 (13.9%)	29 (11.9%)
Hypogeusia	1 (0.4%)	5 (2.0%)	13 (5.3%)†
Nasopharyngitis	51 (21.0%)	47 (19.3%)	50 (20.6%)
Taste disorder	2 (0.8%)	2 (0.8%)	24 (9.9%)†

COUGH-2

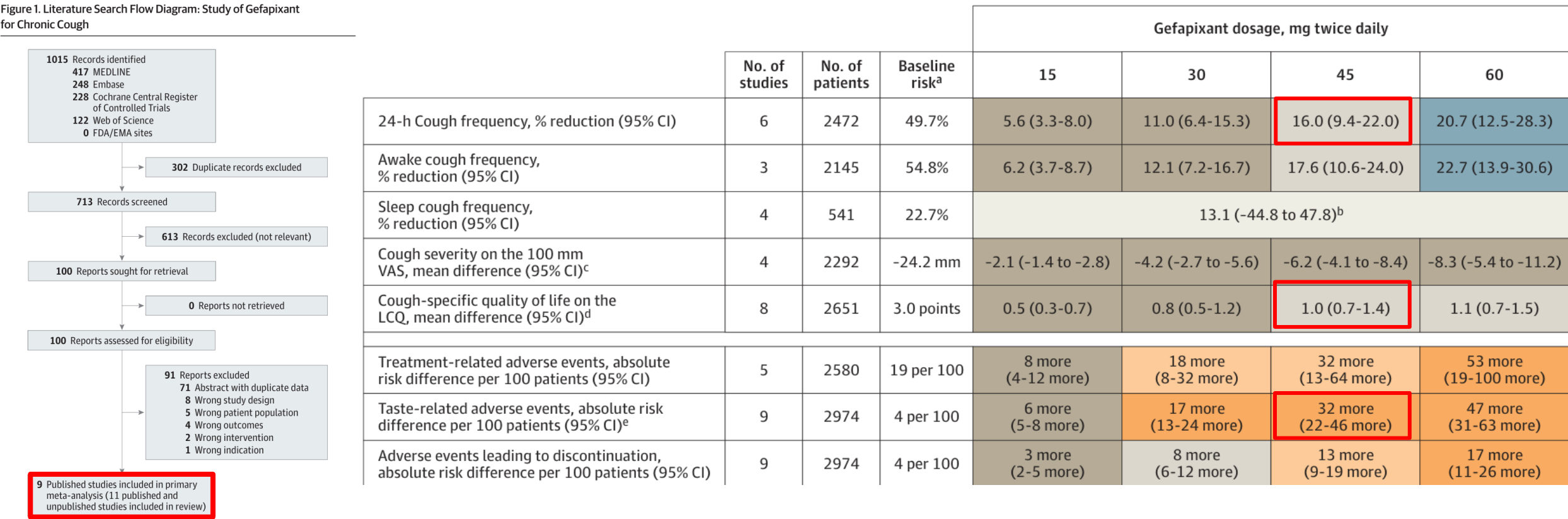
Number of participants	432	442	440
Any adverse event	349 (80.8%)	373 (84.4%)	399 (90.7%)
Serious adverse events	25 (5.8%)	24 (5.4%)	25 (5.7%)
Adverse events related to treatment*	91 (21.1%)	145 (32.8%)	312 (70.9%)
Adverse events of special interest			
Taste-related adverse events	36 (8.3%)	89 (20.1%)†	303 (68.9%)†
Most common adverse events (>8% in a single treatment group)			
Ageusia	6 (1.4%)	13 (2.9%)	67 (15.2%)†
Dysgeusia	28 (6.5%)	56 (12.7%)‡	193 (43.9%)†
Headache	67 (15.5%)	74 (16.7%)	70 (15.9%)
Hypogeusia	3 (0.7%)	17 (3.8%)‡	60 (13.6%)†
Influenza	35 (8.1%)	30 (6.8%)	24 (5.5%)
Nasopharyngitis	70 (16.2%)	93 (21.0%)	70 (15.9%)
Nausea	32 (7.4%)	26 (5.9%)	47 (10.7%)
Taste disorder	1 (0.2%)	8 (1.8%)‡	37 (8.4%)†
Upper respiratory tract infection	27 (6.3%)	38 (8.6%)	30 (6.8%)

Data are n or n (%). Difference in percentage versus placebo for taste-related adverse events were tested for

Gefapixant Dose response meta-analysis

Kum E, JAMA 2023;330(14):1359-1369

Figure 1. Literature Search Flow Diagram: Study of Gefapixant for Chronic Cough

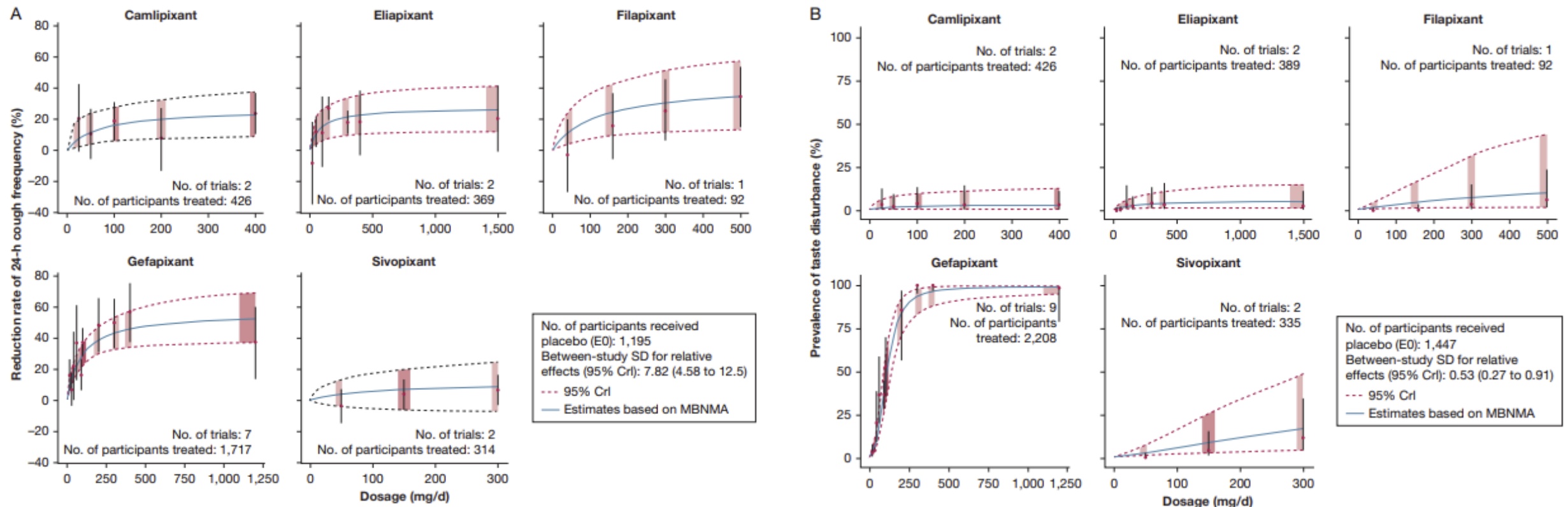


EMA indicates European Medicines Agency; FDA, US Food and Drug Administration.

일본·EU·스위스 승인 / 미국 FDA: 유효성 입증 부족으로 미승인

Other strategies

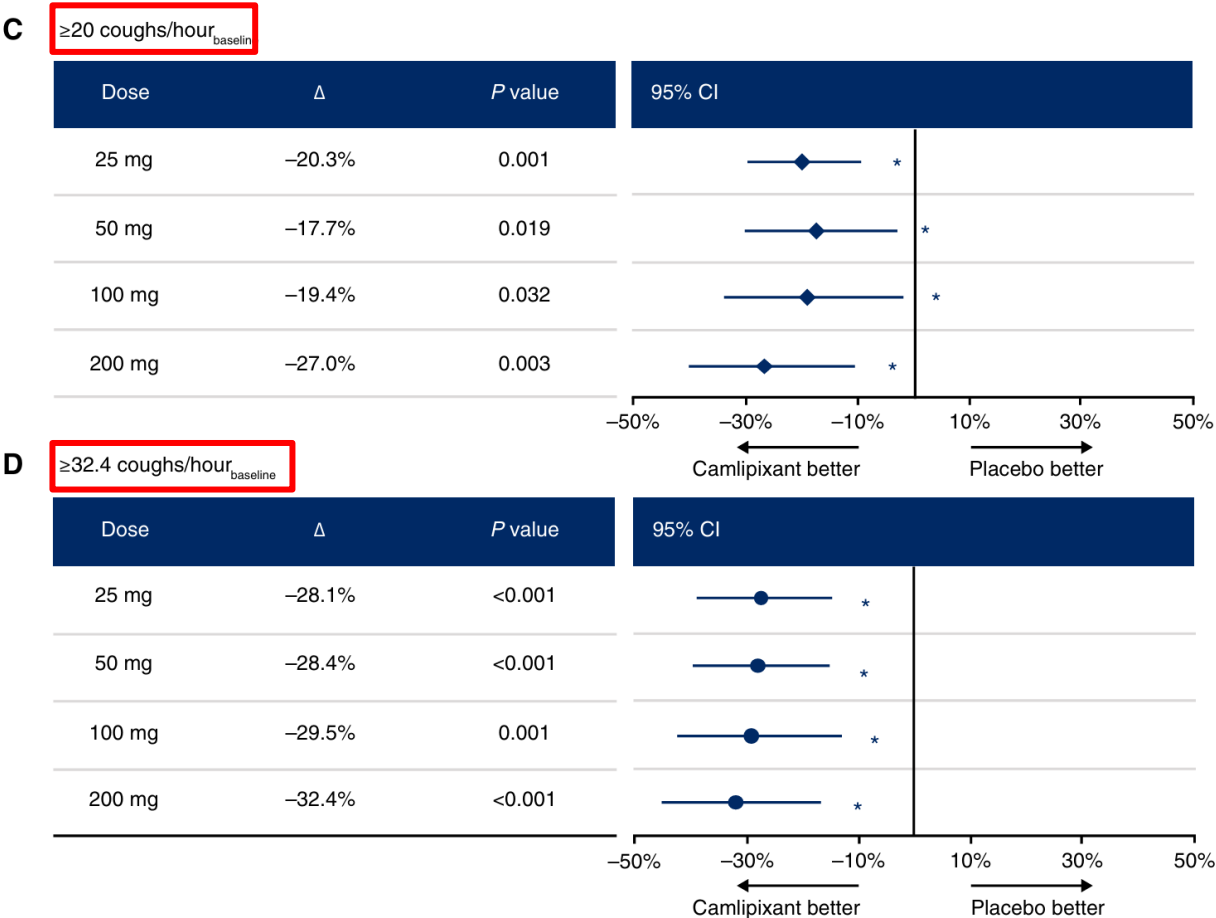
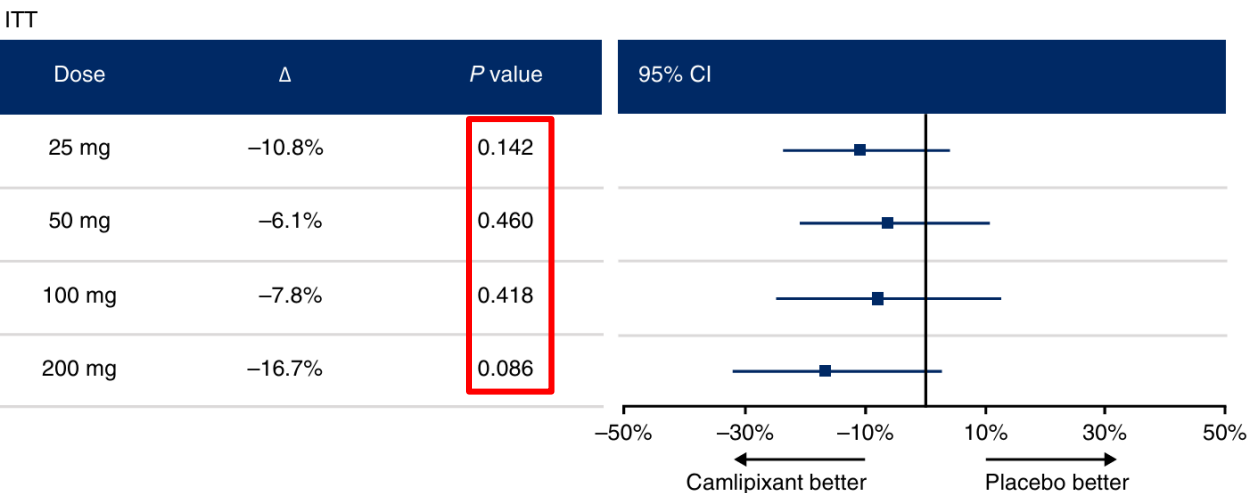
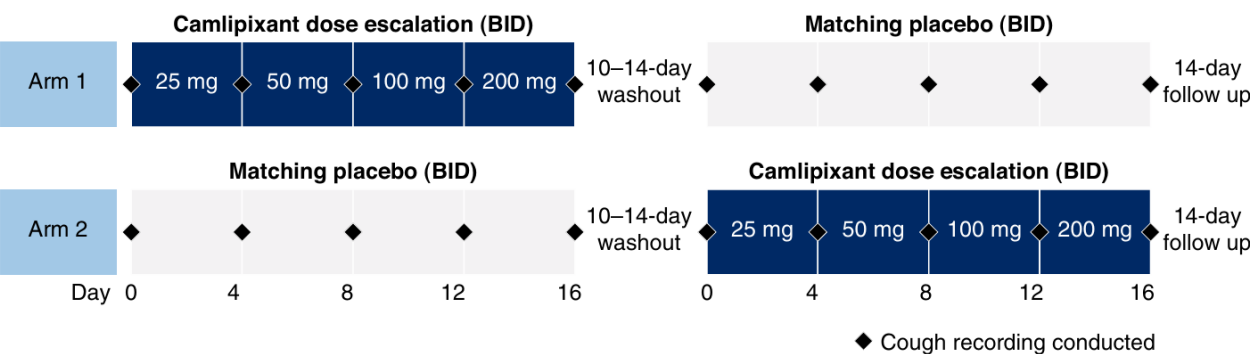
- P2X2/3 → P2X3 homotrimer selective inh. ; Camlipixant/eliapixant/sivopixant/filapixant



Camlipixant (RELIEF)

Smith JA, AJRCCM 2025;211(6):1072-1075

- RELIEF: phase 2a 교차시험, ITT 67명, 안전성 68명



dysgeusia, hypogeusia, or ageusia were reported in 6 patients receiving camlipixant (9.8%) and 3 patients receiving placebo (4.9%)

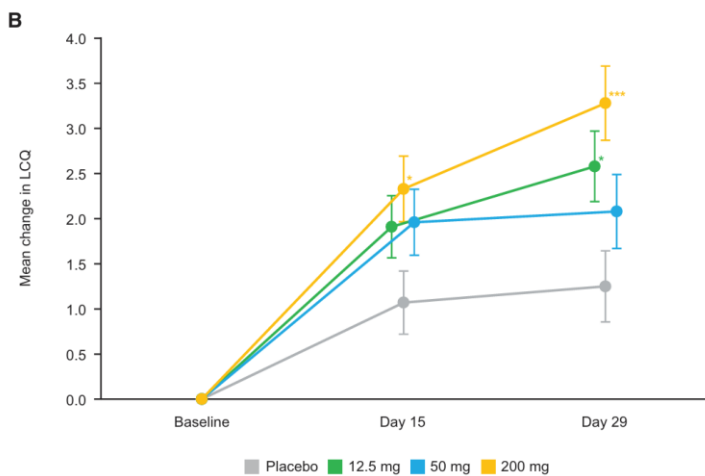
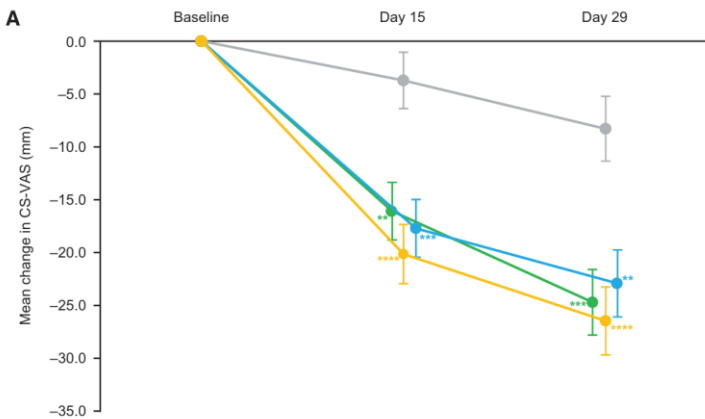
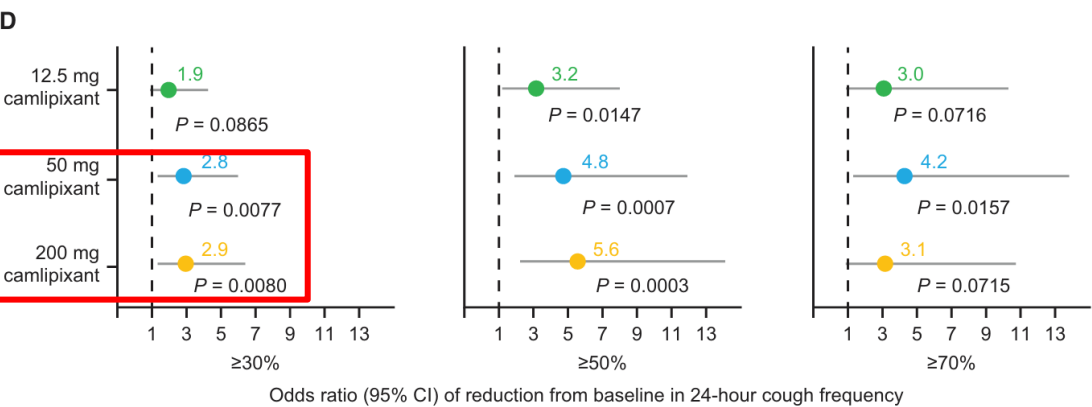
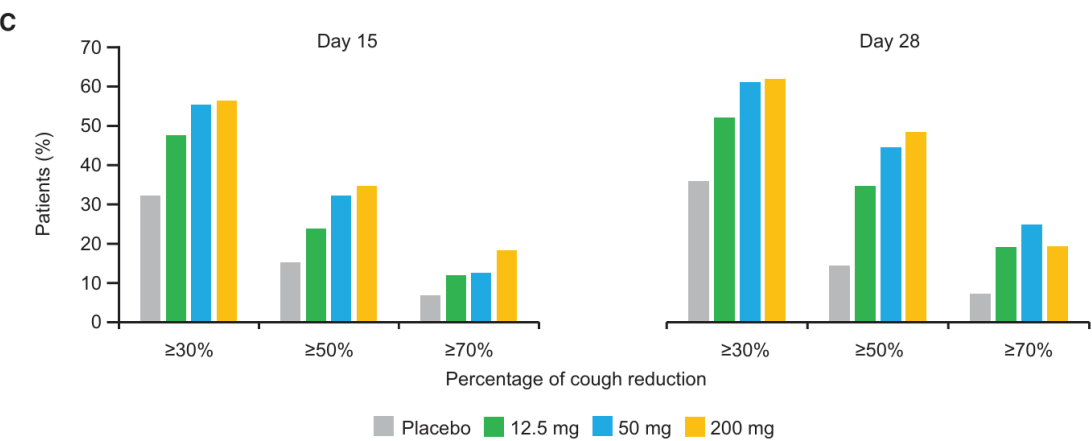
- SOOTHE: phase 2b | 전체 310명, 주분석 고빈도 집단 249명

Table 1. Patient Characteristics and Disposition at Baseline (Main Population: Awake Cough Frequency ≥25 Coughs/h)

	Placebo	Camlipixant (Twice Daily)		
		12.5 mg	50 mg	200 mg
Number of patients, <i>n</i>	63	62	62	62
Sex, <i>n</i> (%)				
Male	14 (22.2)	14 (22.6)	10 (16.1)	7 (11.3)
Female	49 (77.8)	48 (77.4)	52 (83.9)	55 (88.7)
Age, yr, mean (SD)	61.4 (11.3)	60.7 (10.1)	61.6 (9.6)	59.7 (11.4)
BMI, kg/m ² , mean (SD)	27.9 (5.6)	28.1 (5.3)	28.6 (7.3)	27.9 (5.7)
Ethnic origin, <i>n</i> (%)				
Hispanic or Latinx	3 (4.8)	3 (4.8)	5 (8.1)	3 (4.8)
Not Hispanic or Latinx	60 (95.2)	59 (95.2)	57 (91.9)	59 (95.2)
Race, <i>n</i> (%)				
White	62 (98.4)	58 (93.5)	60 (96.8)	60 (96.8)
Asian	1 (1.6)	3 (4.8)	0 (0.0)	0 (0.0)
Black	0 (0.0)	0 (0.0)	1 (1.6)	2 (3.2)
American Indian/Alaska Native	0 (0.0)	1 (1.6)	1 (1.6)	0 (0.0)
Region, <i>n</i> (%)				
United States	25 (39.7)	29 (46.8)	34 (54.8)	34 (54.8)
Canada	7 (11.1)	4 (6.5)	7 (11.3)	2 (3.2)
Europe	31 (49.2)	29 (46.7)	21 (33.8)	26 (41.9)
Cigarette pack-years, mean (SD)	2.2 (4.6)	1.6 (3.9)	1.8 (4.3)	1.6 (4.6)
FEV ₁ /FVC ratio, mean (SD)*	0.77 (0.073)	0.77 (0.071)	0.76 (0.068)	0.77 (0.082)
Cough duration, yr, mean (SD)	11.1 (9.70)	11.9 (9.12)	13.5 (11.53)	10.3 (9.11)
Baseline 24-h cough frequency, coughs/h				
Geometric mean (log scale SD)	39.6 (0.60)	41.3 (0.57)	39.9 (0.47)	35.2 (0.48)
Baseline awake cough frequency (coughs/h)				
Geometric mean (log scale SD)	56.9 (0.60)	58.3 (0.57)	55.8 (0.48)	49.7 (0.46)
CS-VAS, mm				
Mean (SD)	73.9 (14.9)	71.7 (14.5)	74.0 (14.4)	72.0 (15.6)
LCQ total score				
Mean (SD)	10.4 (3.1)	10.7 (3.0)	10.0 (3.1)	11.4 (3.0)

Definitions of abbreviations: BMI = body mass index; CS-VAS = cough severity visual analog scale; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; LCQ = Leicester Cough Questionnaire; SD = standard deviation.
*Measured at screening or within the 2 years before screening and after the onset of cough.

- 4주 24h 기침빈도 위약보정 감소: 50 mg BID 34.4%, 200 mg BID 34.2%



Incidence of taste disturbance TEAE,[‡] n (%)

Dysgeusia (taste alteration)	0 (0.0)	3 (4.8)	4 (6.5)	3 (4.8)
Hypogeusia (partial taste loss)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ageusia (complete taste loss)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SESSION TITLE: Allergic Diseases: Triggers and Treatment

SESSION TYPE: Rapid Fire Original Inv

PRESENTED ON: 10/08/2024 10:20 am - 11:05 am

DESIGN OF THE LANDMARK CALM-1 AND CALM-2 PHASE 3 CLINICAL TRIALS OF CAMLPIXANT IN REFRACTORY CHRONIC COUGH

JACKY SMITH STEVEN G SMITH VIVEK IYER IMRAN SATIA NATHALIE CHAURET LAURENT HARVEY
RONGHUA YANG MARGARET GARIN AND CATHERINE BONUCCELLI

PURPOSE: Refractory Chronic Cough (RCC) is a disease manifesting as a cough that persists for ≥ 8 weeks despite adequate treatment of other cough-associated diseases or for which no cause can be identified (i.e. unexplained [UCC]). In RCC, neuronal hypersensitivity may contribute to an exaggerated cough response that is disproportionate to stimulus intensity. There are currently no commercially available treatments indicated for RCC in the USA and new solutions are needed to alleviate the significant burden of the disease. Camlipixant, a selective P2X3 antagonist, reduced cough frequency in patients with RCC in Phase 2 trials with limited taste disturbance adverse events (TDAEs). Here, we present the design of two Phase 3 trials to evaluate efficacy, safety, and tolerability of camlipixant in RCC (including UCC).

METHODS: CALM-1 (NCT05599191) and CALM-2 (NCT05600777) are randomized, double-blind, placebo-controlled, parallel-arm Phase 3 trials. During screening, both trials will enroll patients with RCC and a persistent cough for ≥ 1 year. After a run-in period, patients will be randomized 1:1:1 to 25 mg camlipixant, 50 mg camlipixant, or placebo BID for 52 weeks in CALM-1 and 24 weeks in CALM-2. Patients will be enrolled in the overall efficacy population in a 3:1 ratio based on a 24-hour cough frequency of ≥ 16 coughs/h at screening and ≥ 20 coughs/h at baseline, or between ≥ 8 and < 40 coughs/h at screening, and between ≥ 8 and < 20 coughs/h at baseline. After the randomized, double-blind treatment period, there will be a 24 and 28 week open-label extension (50 mg camlipixant BID) for CALM-1 and CALM-2, respectively.

RESULTS: Each trial will recruit approximately 825 patients. The primary efficacy endpoint is 24-hour cough frequency in the overall efficacy population at 12 and 24 weeks for CALM-1 and CALM-2, respectively. Secondary efficacy analyses will evaluate other measures of cough frequency and patient-reported outcomes in the overall efficacy population. The effect of camlipixant on TDAEs and other safety measures will be monitored.

CONCLUSIONS: The CALM-1 and CALM-2 trials will evaluate efficacy, safety, and tolerability of camlipixant in a broad population of patients with RCC (including UCC) utilizing a run-in period and novel stratification by cough frequency.

CALM-1/2 — (2026.7.17)

- 25/50mg BID
- CALM-1(52wks, NCT05599191, 825 pts) / CALM-2(24wks, NCT05600777, 975 pts)

GSK plc (LSE/NYSE: GSK) today provides an update on the CALM-1 and CALM-2 phase III clinical trials, which assessed the efficacy and safety of two doses of camlipixant (a P2X3 receptor antagonist) in adults with refractory chronic cough (RCC).^{1,2} RCC is a complex and under-recognised disease with limited treatment options.³⁻⁵

CALM-1 met its primary endpoint with camlipixant 50mg twice daily showing statistically significant reductions in 24-hour cough frequency versus placebo at week 12. CALM-2 did not reach statistical significance in the same primary endpoint with 50mg twice daily at week 24. Camlipixant 25mg twice daily did not reach statistical significance in either study. Key secondary endpoints, including a Chronic Cough Diary (CCD) measure, did not meet target thresholds in either study. Across both trials, the overall incidence and severity of treatment-related adverse events were similar in patients receiving either camlipixant or placebo.

Based on the aggregate data, the limited efficacy demonstrated is unlikely to transform patient care. GSK has decided not to progress further development of camlipixant in RCC. Results from the CALM phase III programme will be submitted for future presentation/publication to contribute to the scientific understanding of RCC.

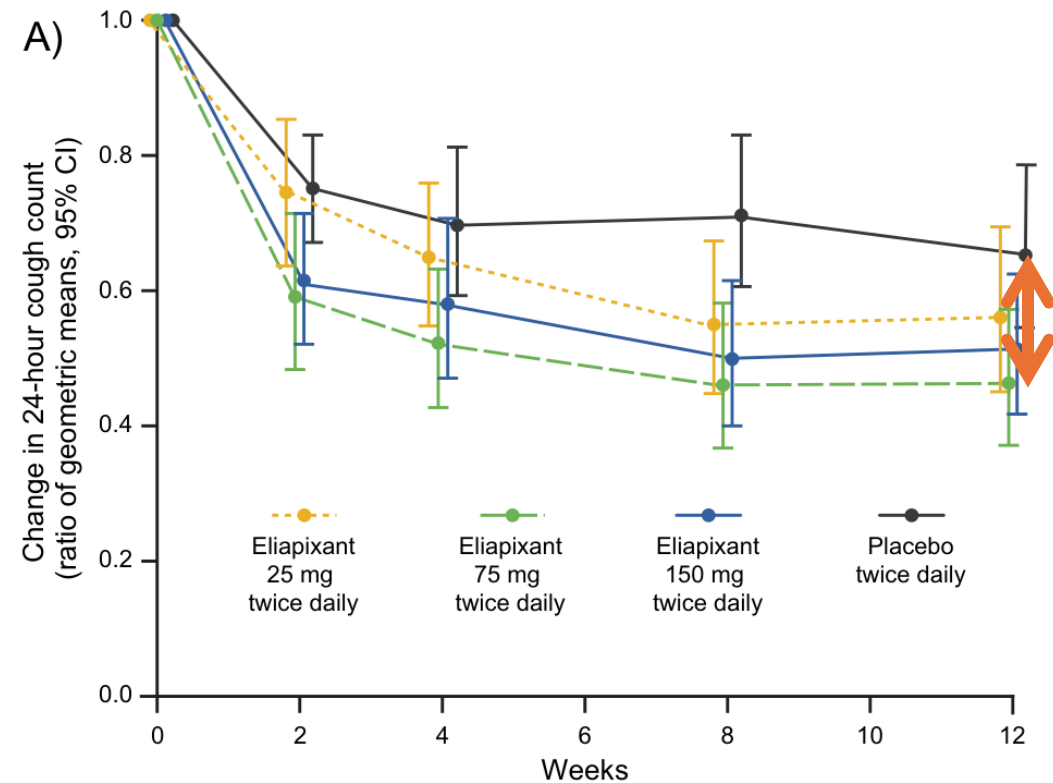
Characteristics	Eliapixant 25 mg twice daily (n = 67)	Eliapixant 75 mg twice daily (n = 69)	Eliapixant 150 mg twice daily (n = 73)	Placebo twice daily (n = 74)
Age, years	61.2 (9.9)	59.1 (12.1)	59.3 (11.9)	56.6 (12.4)
≥ 65 years, n (%)	24 (36)	25 (36)	29 (40)	26 (35)
Female, n (%)	49 (73)	56 (81)	56 (77)	59 (80)
Race, n (%)				
White	56 (84)	60 (87)	66 (90)	64 (86)
Asian	10 (15)	9 (13)	5 (7)	10 (14)
Other/not reported	1 (1)	0	2 (3)	0
Geographic region, n (%)				
Europe	35 (52)	37 (54)	42 (58)	40 (54)
Japan	6 (9)	6 (9)	5 (7)	6 (8)
Rest of the world	26 (39)	26 (38)	26 (36)	28 (38)
Body mass index, kg/m ²	27.1 (4.7)	27.1 (5.5)	27.9 (5.7)	27.2 (5.1)
Duration of cough, years, n (%)				
< 10	38 (57)	39 (57)	46 (63)	39 (53)
≥ 10	29 (43)	30 (43)	27 (37)	35 (47)
Tobacco smoking history, n (%)				
Never	47 (70)	51 (74)	48 (66)	56 (76)
Ex-smoker	20 (30)	18 (26)	25 (34)	18 (24)
Baseline 24-h coughs, per hour ^a				
< 10, n (%)	21 (31)	18 (26)	20 (27)	17 (23)
≥ 10, n (%)	46 (69)	51 (74)	53 (73)	57 (77)
≥ 20, n (%)	30 (45)	37 (54)	31 (42)	37 (50)
≥ 30, n (%)	21 (31)	23 (33)	15 (21)	24 (32)
Baseline awake coughs, per hour				
Geometric mean	23.6 (3.0)	26.4 (3.0)	21.2 (2.4)	24.0 (3.2)
< 20, n (%)	28 (42)	26 (38)	30 (41)	32 (43)
≥ 20, n (%)	39 (58)	43 (62)	43 (59)	42 (57)
Baseline cough severity, VAS 0–100				
Arithmetic mean ^b	65.5 (14.6)	67.1 (14.9)	66.8 (15.9)	61.5 (18.5)
LCQ total score (range 3–21)				
Arithmetic mean	12.0 (2.5)	11.8 (2.8)	11.2 (2.6)	11.5 (3.3)

Data are expressed as mean (SD) unless otherwise stated

LCQ Leicester Cough Questionnaire, SD standard deviation, VAS visual analog scale

^aSee Table 2 for baseline geometric mean (SD) 24-h coughs, per hour

^bEliapixant 25 mg twice daily n=62, eliapixant 75 mg twice daily n=68, eliapixant 150 mg twice daily n=67, placebo twice daily n=69



- 무작위·이중눈가림·위약대조 phase 2b, 310명
- 미각 이상 1–16%, 용량 의존적 증가
- 150 mg, 1pt, 4wk DILI, eliapixant 개발 중단

Eliapixant PAGANINI

Table 4 Summary of treatment-emergent AEs (safety analysis set)

Patients, n (%)	Eliapixant 25 mg twice daily (n = 75)	Eliapixant 75 mg twice daily (n = 78)	Eliapixant 150 mg twice daily (n = 80)	Placebo twice daily (n = 77)
Any AE	43 (57)	51 (65)	51 (64)	39 (51)
Maximum intensity for any AE				
Mild	21 (28)	31 (40)	23 (29)	18 (23)
Moderate	22 (29)	16 (21)	25 (31)	20 (26)
Severe	0	3 (4)	3 (4)	1 (1)
Any study drug-related AE	9 (12)	15 (19)	30 (38)	9 (12)
Maximum intensity for study drug-related AE				
Mild	5 (7)	10 (13)	16 (20)	7 (9)
Moderate	4 (5)	5 (6)	12 (15)	2 (3)
Severe	0	0	2 (3)	0
AEs leading to study drug discontinuation	7 ^a (9)	3 ^b (4)	8 ^c (10)	1 ^d (1)
Any SAE	0	1 (1)	2 (3)	1 (1)
Any study drug-related SAE	0	0	1 (1)	0
SAEs leading to study drug discontinuation	0	0	1 (1)	1 (1)
AEs with outcome death	0	0	0	0

- Sivopixant 150 mg QD, phase 2a, placebo-controlled crossover, 31명

TABLE 2 Changes in cough frequency (full analysis set)

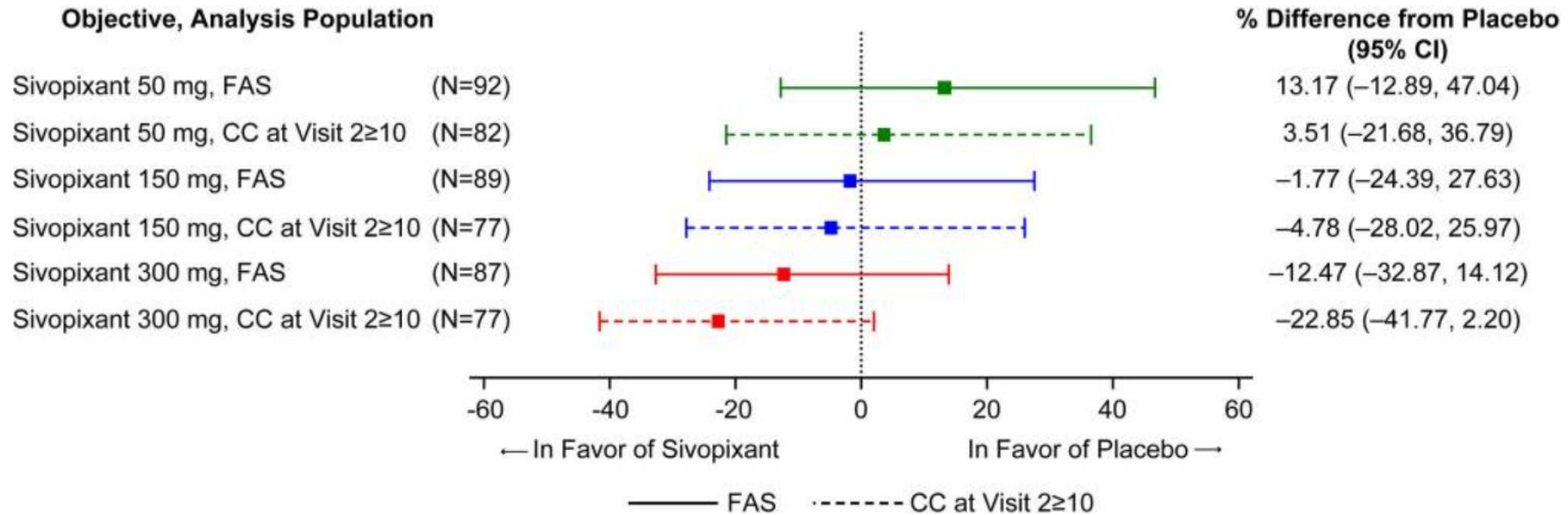
	Baseline cough frequency, h ⁻¹ (geometric mean (95% CI))		Ratio at 2 weeks versus baseline, % (mean (95% CI))		Placebo-adjusted difference at 2 weeks	
	Sivopixant	Placebo	Sivopixant	Placebo	Difference, % (95% CI)	p-value
Daytime	25.9 (16.9–39.8)	26.1 (16.6–41.2)	–54.1 (–66.7––36.8)	–33.0 (–51.6––7.2)	–31.6 (–53.6–0.8)	0.0546
24 h	20.0 (13.7–29.3)	18.9 (11.9–30.2)	–52.6 (–64.7––36.3)	–31.4 (–49.1––7.4)	–30.9 (–51.3––2.1)	0.0386
Night-time	8.8 (5.3–14.7)	9.5 (5.7–15.8)	–45.2 (–60.7––23.5)	–22.7 (–44.8–8.4)	–29.1 (–53.6–8.3)	0.1074
Awake	27.3 (18.5–40.3)	26.2 (16.5–41.5)	–50.5 (–63.1––33.5)	–33.3 (–50.5––10.0)	–25.8 (–48.3–6.5)	0.1022
Asleep	2.5 (1.4–4.7)	1.6 (0.8–3.3)	–14.8 (–48.3–40.6)	7.9 (–35.1–79.6)	–21.0 (–57.1–45.2)	0.4346

TABLE 3 Changes in subjective measures after 2 weeks from baseline

	Baseline (mean±SD)		Change from baseline (mean (95% CI))		Placebo-adjusted difference at 2 weeks	
	Sivopixant	Placebo	Sivopixant	Placebo	Difference (95% CI)	p-value
LCQ [#] total score	12.1±3.8	12.6±4.2	2.46 (1.51–3.41)	1.06 (0.11–2.01)	1.40 (0.06–2.75)	0.0415
EQ-5D-5L [#] score	0.7830±0.1956	0.8166±0.2285	0.10 (0.06–0.15)	0.01 (–0.04–0.06)	0.09 (0.03–0.16)	0.0082
EQ-VAS	58.6±24.7	64.5±24.0	11.4 (5.5–17.4)	2.8 (–3.1–8.7)	8.6 (1.0–16.2)	0.0274
Cough severity (VAS), mm	63.2±20.1	61.1±23.0	–18.8 (–25.5––12.0)	–12.4 (–19.2––5.5)	–6.4 (–14.8–2.0)	0.1334

LCQ: Leicester Cough Questionnaire; EQ-5D-5L: EuroQol Questionnaire-5 Dimensions-5 Levels; EQ-VAS: EuroQol visual analogue scale; VAS: visual analogue scale. [#]: Japanese version.

- Sivopixant phase 2b: 무작위·이중눈가림·위약대조, 406pt.



Percent change relative to placebo in hourly cough count in 24 h at Week 4

- Filapixant: crossover design, 23 patients

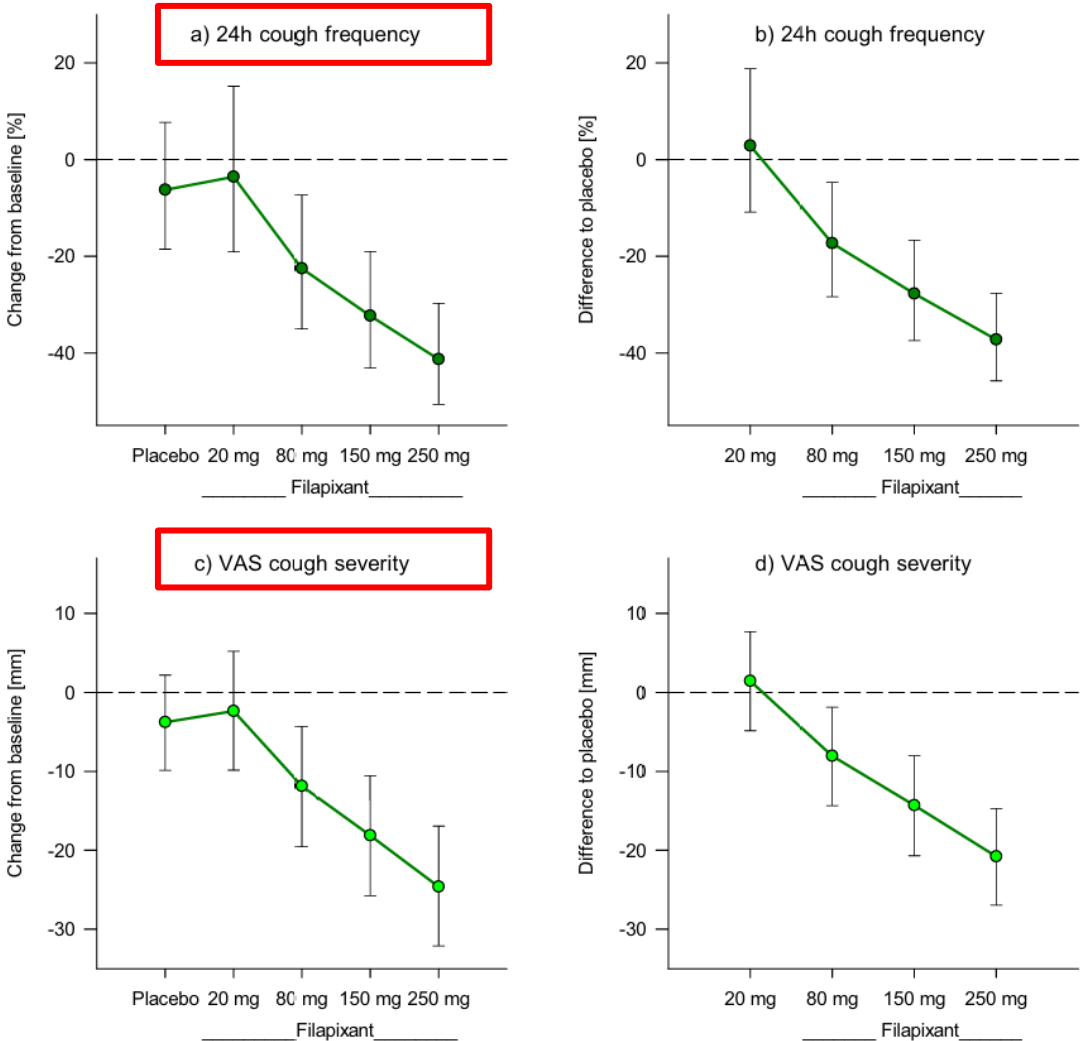
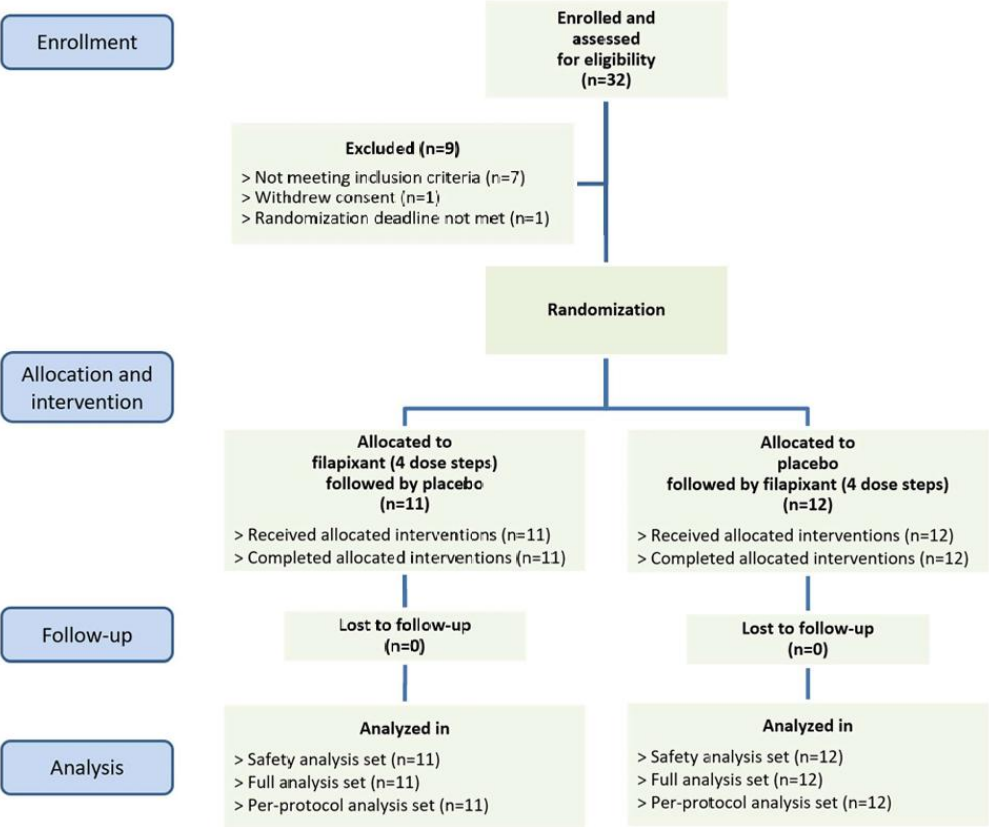


Fig. 3 Cough frequency and severity (Day 4): Changes from baseline and differences to placebo (Bayesian analyses). Error bars represent 90% credible limits. Placebo data were pooled across the four placebo ‘dose’ steps. Lower VAS scores indicate less severe cough. Total number of patients = 23

Table 5 Taste-related adverse events (additional “cumulative” analysis)

Filapixant (N = 23)				Placebo (N = 23)			
20 mg	80 mg	150 mg	250 mg	(20 mg)	(80 mg)	(150 mg)	(250 mg)
N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
1 (4.3%)	3 (13.0%)	10 (43.5%)	13 (56.5%)	2 (8.7%)	2 (8.7%)	4 (17.4%)	3 (13.0%)

P2X3 정리

- Gefapixant: 일부 지역 승인, 미국은 유효성 근거 부족
- Camlipixant: CALM-1 50 mg 성공, CALM-2 미달, 개발 중단
- Eliapixant: DILI 관찰 후 개발 중단
- Sivopixant·filapixant: 효능·미각 내약성의 한계

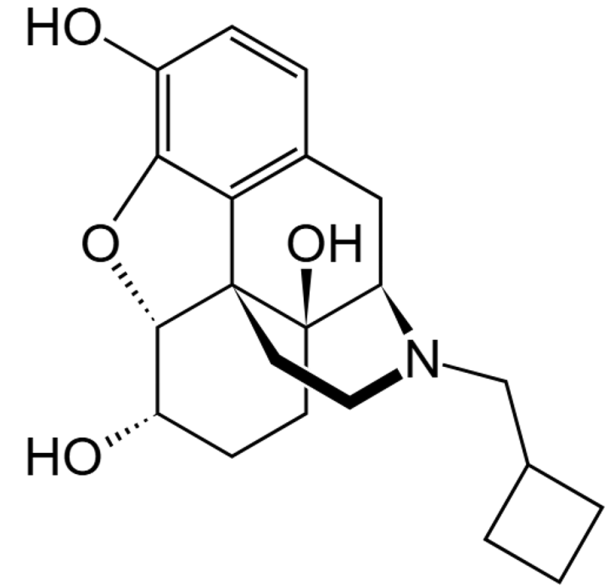
Part III



Beyond P2X3 antagonist

Nalbuphine ER: KAMA 기전과 개발 현황

- κ -opioid agonist + μ -opioid antagonist
- 경구 서방정, 단계적 증량으로 투여
- RCC: RIVER phase 2a
IPF 기침: CORAL phase 2b
- 주요 S/E: 오심·변비·졸림·어지럼
- IPF OCEAN-1 phase 3 및 RCC LAKE phase 2b 모집 중



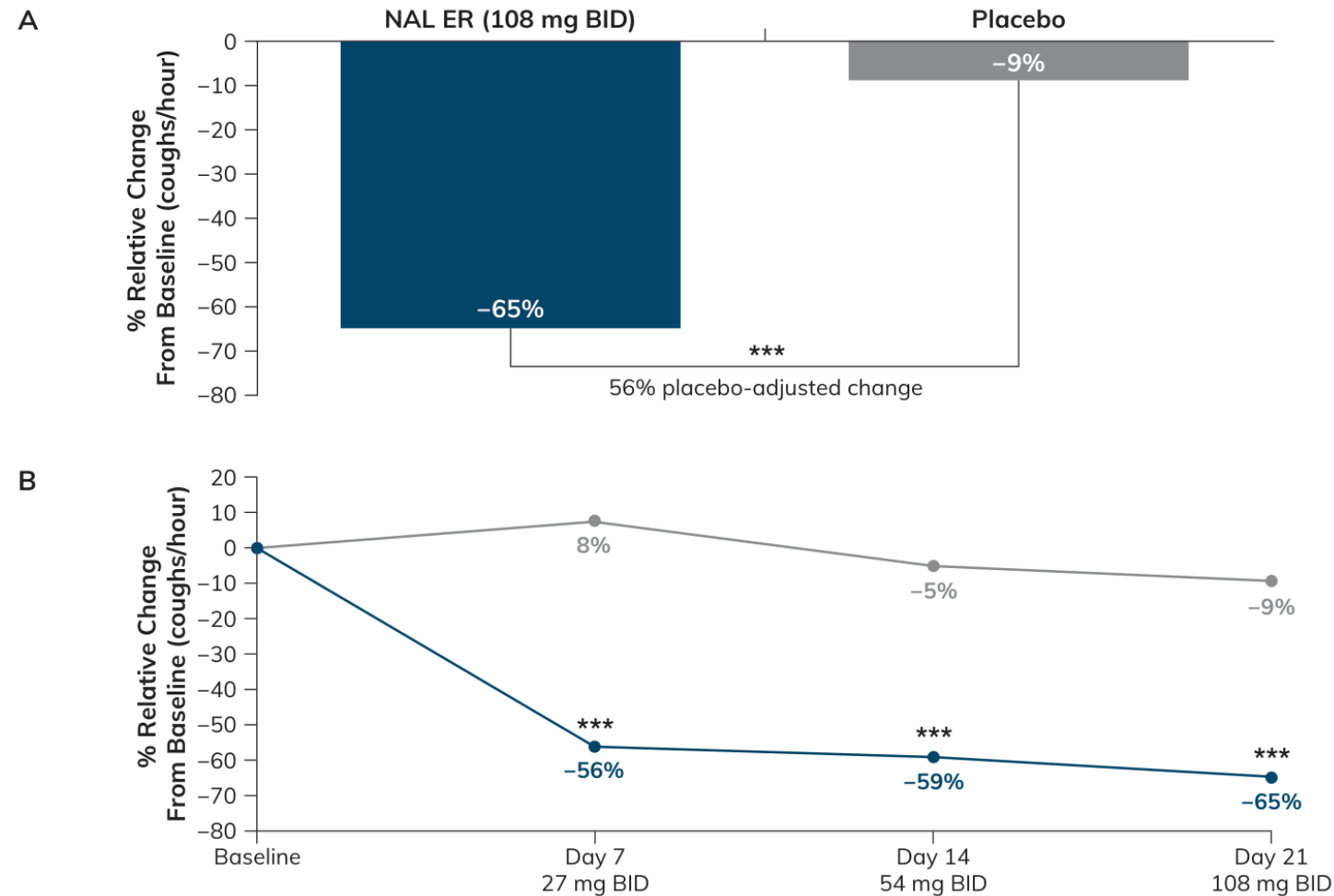
Nalbuphine: RIVER와 CORAL

항목	RIVER	CORAL
대상·설계	RCC 66명 교차시험, 각 21일	IPF 기침 165명 4군 병행시험, 6주
투여	최대 108 mg BID로 증량	27 / 54 / 108 mg BID
24h 기침빈도 기저 대비	-65% vs 위약 -9% Day 21, ERS 2025 포스터	-60.2% vs 위약 -16.9% 108 mg, Week 6
LCQ 반응자 ≥1.3점 개선	78.6% vs 25.5% ERS 2026 추가 분석	80.8% vs 35.7% 108 mg, Week 6
근거 수준	학회 포스터 PubMed 결과 본논문 미확인	정식 RCT 논문 JAMA 2026

CORAL 빈도: 위약군 극단값 1명 제외 분석. 서로 다른 시험 간 감소율 직접 비교 불가

Smith JA, ERS 2025 PA3593. Satia I, ERS 2026 RIVER LCQ poster. Molyneaux PL, JAMA 2026;335:1050-1059.

Figure 2. Relative Change From Baseline in 24-hour Cough Frequency



TEAE, %	NAL ER n=63	위약 n=59
Any	79.4	54.2
leading to treatment discontinuation	14.3	1.7
Constipation	28.6	6.8
Somnolence	25.4	0
Nausea	22.2	3.4
Dizziness	19.0	3.4
Serious TEAEs	0	0

*** $P < .0001$; NAL ER vs placebo.

Day 21: -65% vs -9%, $p < .0001$

CORAL (COugh Reduction in IPF with nALbuphine ER, phase 2b, 165 pts)

IPF + 만성기침 8주+ (실제 3-5년), CS-NRS ≥4; FVC ≥40%·DLCO ≥25%; 165명

Molyneaux PL, et al. CORAL Randomized Clinical Trial. JAMA 2026;335(12):1050-1059 (NCT05964335)

Table 1. Baseline Patient Characteristics

Characteristic	No. (%)			
	Nalbuphine ER twice daily			Placebo twice daily (n = 40)
	27 mg Twice daily (n = 42)	54 mg Twice daily (n = 43)	108 mg Twice daily (n = 40)	
Demographics				
Age, mean (SD), y	69.1 (7.0)	68.5 (7.3)	71.9 (7.0)	71.2 (7.7)
Sex				
Male	29 (69.0)	31 (72.1)	29 (72.5)	29 (72.5)
Female	13 (31.0)	12 (27.9)	11 (27.5)	11 (27.5)
Race and ethnicity ^a				
American Indian or Alaska Native	0	0	0	0
Asian	1 (2.4)	2 (4.7)	0	0
Black or African American	0	1 (2.3)	1 (2.5)	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	40 (95.2)	38 (88.4)	39 (97.5)	40 (100)
Not reported	1 (2.4)	2 (4.7)	0	0
Medical history				
Cough duration, mean (SD), y	3.0 (2.8)	4.1 (5.2)	5.4 (10.8)	4.4 (4.8)
Smoking history				
Past	24 (57.1)	20 (46.5)	22 (55.0)	21 (52.5)
Current	1 (2.4)	2 (4.7)	0	0
Gastroesophageal reflux disease ^b	13 (31.0)	19 (44.2)	17 (42.5)	17 (42.5)
Received supplemental oxygen at any time	6 (14.3)	5 (11.6)	5 (12.5)	6 (15.0)
Concomitant medications				
Antifibrotics	31 (73.8)	34 (79.1)	31 (77.5)	31 (77.5)
Nintedanib	17 (40.5)	22 (51.2)	21 (52.5)	24 (60.0)
Pirfenidone	14 (33.3)	12 (27.9)	11 (27.5)	7 (17.5)
Proton pump inhibitors	21 (50.0)	26 (60.5)	19 (47.5)	22 (55.0)
Physical findings				
BMI, mean (SD)	27.7 (3.3)	26.9 (3.8)	27.6 (3.9)	27.8 (4.6)
Pulmonary function tests				
Forced vital capacity, mean (SD), L	2.6 (0.9)	2.5 (0.7)	2.7 (0.9)	2.4 (0.9)
Forced vital capacity, mean (SD), % predicted of normal	77.2 (19.7)	73.4 (16.1)	79.1 (20.2)	76.8 (19.3)
Diffusing capacity of the lungs for carbon monoxide, mean (SD), % predicted	52.6 (14.8)	49.0 (12.3)	56.6 (21.4)	49.6 (16.2)
Oxygen saturation by pulse oximetry, mean (SD), %	96.0 (2.0)	95.5 (2.1)	96.0 (2.0)	95.4 (1.7)
PGI-S, mean (SD) ^c	2.3 (0.6)	2.4 (0.5)	2.1 (0.6)	2.1 (0.6)

Outcome	Nalbuphine ER			
	27 mg Twice daily (n = 42)	54 mg Twice daily (n = 43)	108 mg Twice daily (n = 40)	Placebo twice daily (n = 40)
Primary outcome				
Change from baseline in 24-h objective cough count at wk 6				
Absolute objective cough count at baseline, mean (SD) [No. of patients]	24.6 (19.2) [40]	28.0 (29.6) [42]	31.5 (29.3) [39]	29.4 (30.9) [38]
Absolute cough count at wk 6, mean (SD) [No. of patients], coughs/h	11.9 (11.0) [39]	14.9 (22.1) [34]	11.9 (18.6) [36]	28.1 (60.5) [35] ^a
Absolute cough count change from baseline at wk 6, mean (95% CI)	-12.3 (-16.7 to -7.9)	-14.5 (-20.4 to -8.6)	-18.5 (-24.6 to -12.4)	-2.0 (-14.9 to 11.0)
Relative change ^b in absolute cough count, mean (SD), %	-47.9 (38.5)	-53.4 (54.0)	-60.2 (36.7)	86.7 (623.7)
Relative change ^b in absolute coughs/h, mean (SD), % (extreme value excluded) ^c	-47.9 (38.5)	-53.4 (54.0)	-60.2 (36.7)	-16.9 (47.9)
Model-adjusted log-transformed relative change in coughs/h, LSM (SEM), coughs/h (extreme value excluded) ^{c,d}	-0.90 (0.16)	-1.27 (0.17)	-1.32 (0.17)	-0.3 (0.17)
P value ^e	.008	<.001	<.001	NA
Key secondary outcome				
Change from baseline in patient-reported cough frequency (E-RS: IPF cough subscale) at wk 6 ^f				
Absolute patient-reported cough frequency at baseline, scale score, mean (SD) [No. of patients] ^f	2.3 (0.7) [40]	2.6 (0.6) [41]	2.4 (0.6) [38]	2.6 (0.6) [39]
Absolute patient-reported cough frequency at wk 6, scale score, mean (SD) [No. of patients] ^f	1.5 (0.6) [40]	1.4 (0.6) [36]	1.4 (0.7) [37]	1.9 (0.6) [38]
Absolute patient-reported cough frequency, change from baseline, scale score, mean (95% CI) ^f	-0.8 (-1.0 to -0.6)	-1.2 (-1.5 to -0.9)	-1.0 (-1.3 to -0.8)	-0.7 (-0.9 to -0.4)
Relative patient-reported cough frequency, No. of patients at wk 6	38	34	35	37
Model-adjusted relative change from baseline, scale score, LSM (SEM), % ^{b,f}	-31.4 (4.6)	-40.6 (4.7)	-40.2 (4.7)	-21.9 (4.6)
Model-adjusted relative change from baseline, difference from placebo, scale score, LSM (95% CI), % ^{d,f}	-9.49 (-22.0 to 3.0)	-18.67 (-31.3 to -6.02)	-18.29 (-30.9 to -5.69)	NA
P value ^e	.14	.004	.005	NA

	Nalbuphine ER			
	27 mg Twice daily (n = 42)	54 mg Twice daily (n = 43)	108 mg Twice daily (n = 40)	Placebo twice daily (n = 40)
Serious adverse events ^b	1 (2.4)	0	1 (2.5)	4 (10.0)
Adverse event resulting in treatment discontinuation	0	6 (14.0)	1 (2.5)	2 (5.0)

Headache
Nausea
Dizziness

Nalbuphine: 후속 개발 현황

시험	대상·단계	투여기간	현황
OCEAN-1	IPF 기침 Phase 3	총 54주 적정 2주 포함	모집 중
OCEAN-2	IPF 기침 Phase 3	총 14주 적정 2주 포함	모집 전
LAKE	RCC Phase 2b	6주	모집 중

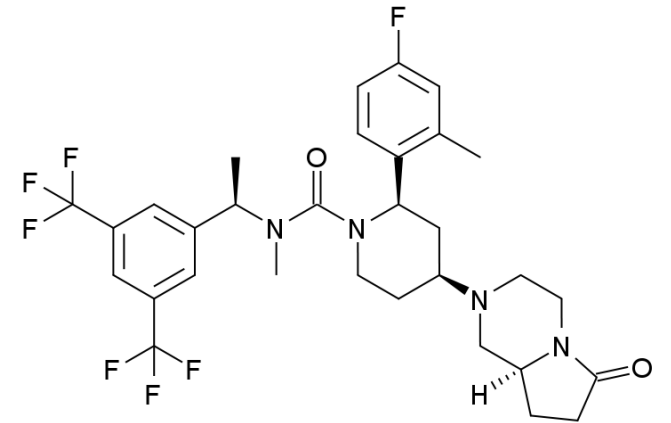
Orvepitant: 중추 NK-1 경로 차단

뇌투과성 NK-1 antagonist
Substance P 신호 억제

중독·호흡억제 없음, 1일 1회 경구 투여

환자보고 중증도·LCQ에서 개선 신호
객관적 기침빈도 개선 미달

피로, 어지럼, 졸음
장기 효능·안전성과 확증시험 결과는 미확립



Orvepitant: VOLCANO-2와 COMFORT의 평가변수

항목	VOLCANO-2	IPF COMFORT
대상·설계	RCC/UCC 315명 3용량, 12주 병행군	IPF 기침 80명 10/30 mg, 4주 교차
1차 평가변수	각성기 기침빈도	일일 기침중증도 NRS 주간 평균
주분석, 30 mg	위약 대비 비 0.92 p=.531	위약 대비 -0.58점 p=.054
객관적 24h 빈도	1차 평가변수는 각성기 빈도	위약 대비 비 1.04 p=.761
해석	객관적 빈도 NS	주관적 중증도 NS
출처	ERS 2019	ERS 2025

VOLCANO-2 (RCC/UCC, phase 2b)

Background: No proven therapies exist for refractory chronic cough (CC). Neurokinin(NK)-1 antagonists may modulate the central neural hypersensitivity causing CC. The NK-1 antagonist orvepitant was assessed in CC in a Phase 2b dose-ranging study.

Methods: A randomised, controlled, parallel group study recruited subjects with CC ≥ 1 yr and awake cough count > 10 /hr.

Subjects took placebo (PBO) or one of 3 orvepitant doses (10, 20 or 30mg) once daily for 12-wks. Primary endpoint was awake cough frequency (CF) at Wk-12, using a VitaloJAK ambulatory cough monitor. Other efficacy measures were the patient recorded outcomes (PROs): Leicester Cough Questionnaire (LCQ), Cough Severity (CS) & Urge-to-Cough (UTC) VASs, and global ratings of change (GRoC).

Results: 315 subjects were randomised and 275 were evaluable at Wk-12. Orvepitant 30mg resulted in clinically relevant and significant improvements in PROs in the full analysis set (FAS) at Wk 12: LCQ (PBO-corrected improvement 1.6, $p=0.009$), CS VAS (9.0mm, $p=0.034$) and UTC VAS (11.8mm, $p=0.005$). GRoC scores: for cough severity $p=0.054$, and frequency $p=0.124$. The CF endpoint was not significant in the FAS due to an exaggerated PBO response at Wk 12, most evident in the lower CF subjects. In a pre-defined sub-group of higher CF subjects ($\geq$ study median awake CF at baseline), a greater efficacy signal is evident with 30mg orvepitant in primary (geometric mean ratio vs PBO 0.71, $p=0.066$) and secondary efficacy endpoints (e.g. LCQ 1.9, $p=0.041$), with most being significant despite the study not being powered for sub-group analyses. Orvepitant was safe and well-tolerated.

IPF COMFORT (ORV-PF-01, phase 2)

We investigated orvepitant, a selective antagonist of the NK1 receptor, as a treatment for chronic cough in IPF.

This phase 2, randomised, double blind, placebo-controlled, 2-period cross-over study tested orvepitant 10 mg and 30 mg once daily in patients with confirmed IPF. Treatment periods were 4-wks with a wash-out of 3-wks. Eligible subjects had a mean score of ≥ 5 on a 0-10 cough severity numerical rating scale (NRS) in the last 7 days of screening. Assessments included daily and periodic patient-reported outcome measures and cough frequency monitoring for efficacy, and safety tests. The primary endpoint was weekly mean of the Daily Cough Severity NRS at wk 4.

80 patients were randomised. There was a significant period effect due to a marked placebo response in Period A, hence both cross over (XO) and additional by period (PB) analyses are presented. At wk 4, Daily Cough Severity NRS scores decreased with orvepitant 30mg compared to placebo in both XO (-0.58 pts, $p=0.054$) and PB (-1.17 pts, $p=0.009$) analyses. There were also reductions in the cough frequency verbal rating scale (XO: -0.23, $p=0.010$; PB: -0.35, $p=0.018$) and urge to cough NRS (XO: -0.46, $p=0.092$; PB: -0.84, $p=0.042$) scores. Wk 2 findings were similar. Leicester Cough Questionnaire QoL scores were improved (XO: 1.24, $p=0.025$; PB: 1.94, $p=0.015$) and more subjects reported their cough improved with orvepitant 30 mg (69%) than placebo (44%) on a global rating of change. The 10 mg dose was not different to placebo. Both doses were well tolerated with no safety concerns.

Orvepitant 30 mg once daily improved multiple patient-reported measures of cough burden in patients with IPF.

Taplucainium — 기전과 개요

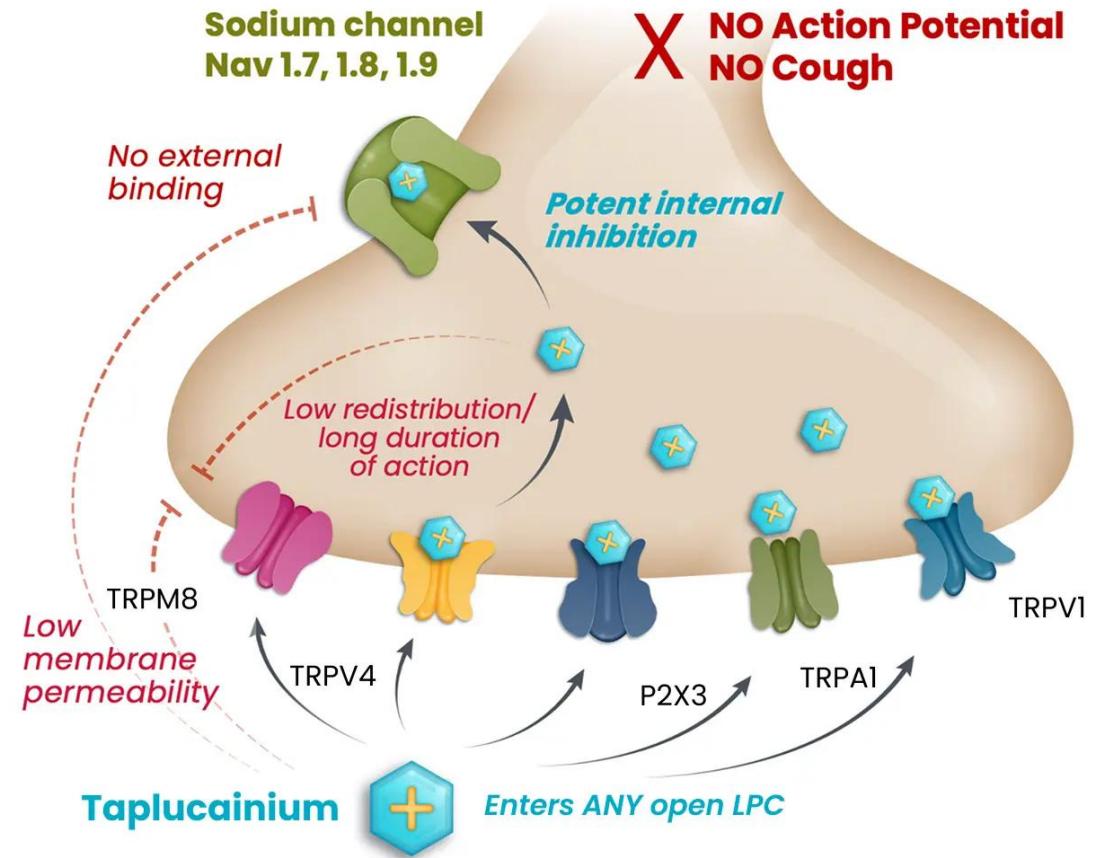
- Charged sodium-channel blocker(CSCB): 열린 large-pore channel을 통해 활성화된 감각신경에만 진입
- 세포 안쪽에서 Na^+ channel 차단 → 정상 신경 기능은 보존하는 국소 선택성
- 흡입 DPI(NOC-110) · 빠른 발현을 목표
- 현재 근거: 초기 임상/topline; 확증 효능·S/E 논문은 아직 없음



Taplucainium — CSCB 작동 원리 (차별점)

- 1 자극으로 TRPV1/TRPA1/P2X3 등 large-pore channel 개방
- 2 양전하 약물이 활성화된 신경 내부로만 유입
- 3 세포 안쪽 Na^+ channel 차단 → 과흥분성 신호 억제

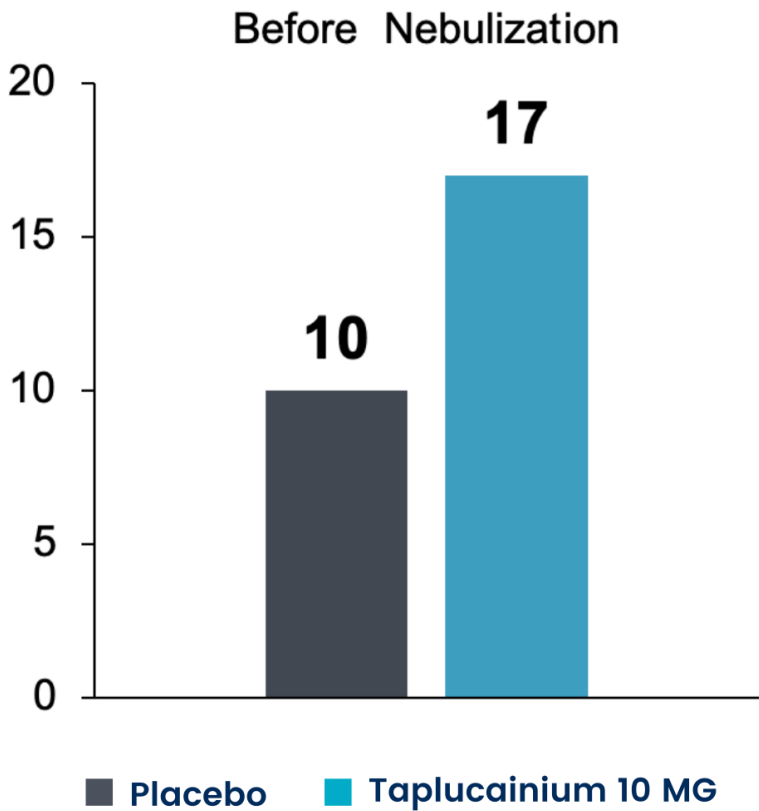
광범위 통로 억제가 아니라 “활성화된 신경” 선택



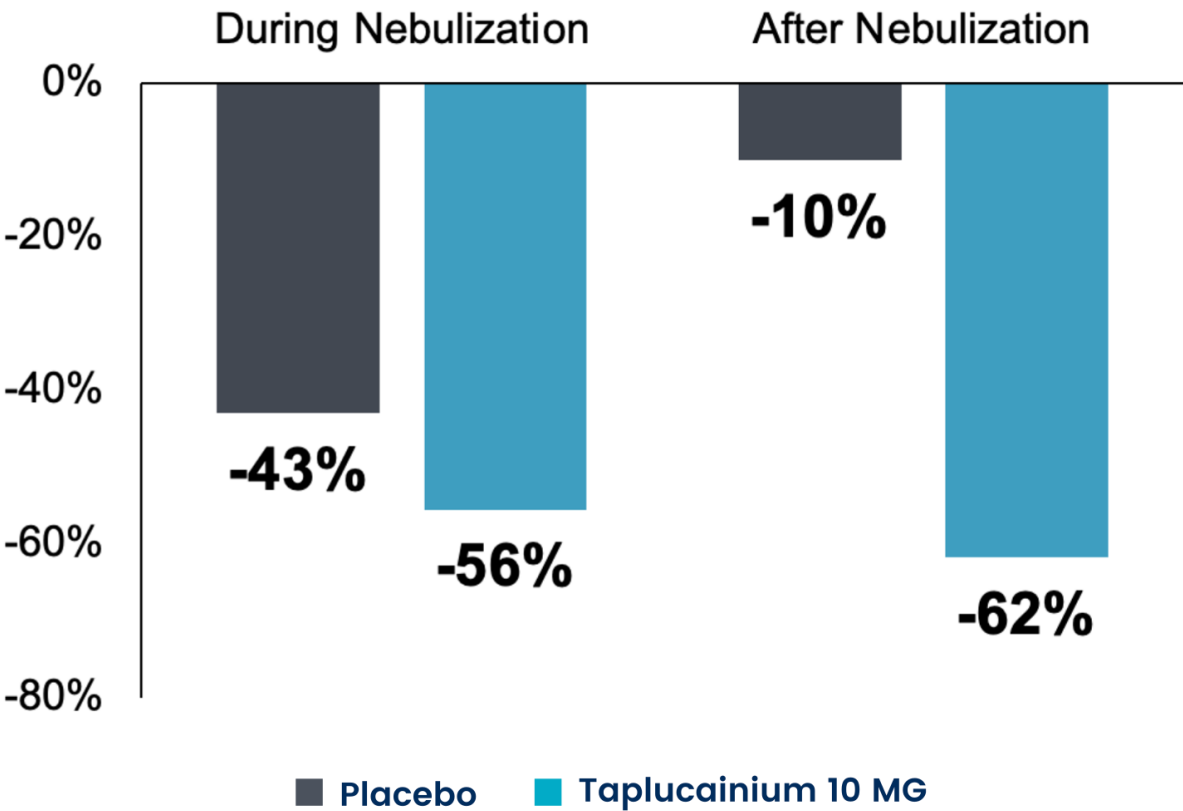
Taplucainium: Phase 2b Aspire study

회사 공개 Phase 2a 자료, 만성기침 41명, nebulized 10 mg, 무작위 교차시험

Median baseline cough counts (#)



% change from pre-nebulization



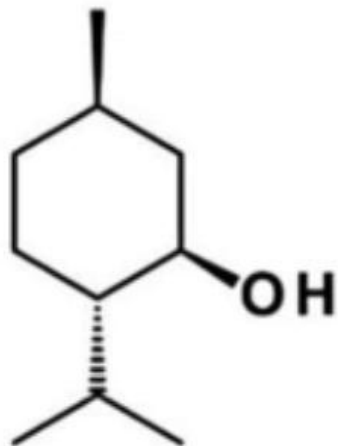
Taplucainium: ASPIRE phase 2b

항목	ASPIRE, NCT06504446
설계	무작위·이중눈가림·위약대조, 4주
대상	RCC/UCC, 회사 발표 기준 240명 등록 완료
투여	DPI 1 / 3 / 6 mg 또는 위약, 1일 1회
1차 평가변수	24시간 객관적 기침빈도 변화
주요 2차·안전성	각성기 빈도, VAS, LCQ, PGI-I, S/E
공개 현황	2026년 3분기 topline 예정, 결과 공개 미확인

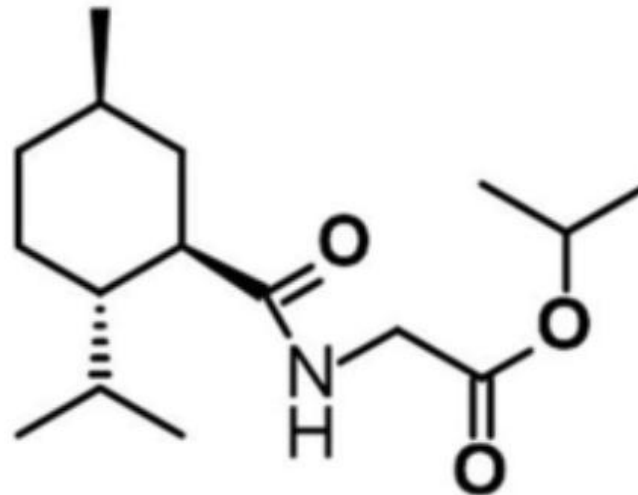
NCT05628740은 이전 bridging 시험. ASPIRE 결과와 분리

TRPM8 작용제 AX-8

A



B.



- orally disintegrating tablet— menthol cooling-like counter-irritant
- selective TRPM8 agonist: 구강·인두의 cooling sensation을 활성화
- Cooling/counter-irritation과 sensory gating을 통해 과민해진 기침 감각신호를 억제
(정확한 중추·말초 작용기전은 아직 미확립)

TRPM8 작용제 AX-8

- 23` Abstract만.. 대규모 다기관 RCT로 장기 유효성·안전성·최적용량 확인 필요

Background: The treatment of refractory or unexplained chronic cough (RCC/UCC) remains a significant unmet need. Although P2X3 antagonists have demonstrated efficacy in recent trials, other therapies targeting neuronal mechanisms have not. We performed a 2-week, randomized double-blind, placebo-controlled, crossover study that evaluated the efficacy and safety of AX-8, a TRPM8 agonist, in patients with RCC/UCC. Methods: Participants had RCC/UCC diagnosis ≥ 1 yr, cough severity visual analogue scale (VAS) score ≥ 40 mm and 24h cough frequency ≥ 10 coughs/hour at screening. They received two doses of AX-8 (40mg orally dispersible tablet) or placebo 8 hours apart. The primary endpoint was 8h cough frequency on day 1 although as this was a proof of concept study the duration of action was uncertain and the endpoints chosen were exploratory. Results: 51 participants were treated and analyses done on the per-protocol set, i.e. 47 participants (79% female, mean age 60.5yrs, mean cough duration 13.5yrs). On day 1, AX-8 reduced cough frequency within 15min, and more than placebo over 2h and 4h ($p < 0.09$) but not 8h ($p = 0.4$). In participants with baseline throat discomfort VAS score ≥ 55 mm (median value), reduction in cough frequency vs. placebo was significant over 24h with a maximum reduction compared to placebo of 43% over two hours ($p < 0.005$). Over 14 days, AX-8 significantly improved patient-reported outcomes and the safety profile was good with no serious adverse events. Conclusions: This data suggests TRPM8 agonism shows potential for control of RCC/UCC as an alternative or adjunct to other therapies, especially in those patients complaining of cough driven by throat sensations.

감사합니다