Response In Patient-Reported Cough Severity in SOOTHE, A Phase 2b Trial of Camlipixant in Refractory Chronic Cough

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American Thoracic Society Meeting
21 May 2023

Disclosure to Learners

Financial relationships with relevant companies within the past 24 months:

- Dr McGarvey reports grants, personal fees and non-financial support from Merck, grants and personal fees from Bellus Health, grants and personal fees from Shionogi, grants from Bayer, grants and personal fees from Chiesi, personal fees from Nocion, personal fees from Genentech, personal fees from Reckitt Benkiser, personal fees from Astra Zeneca, personal fees from GSK outside the submitted work

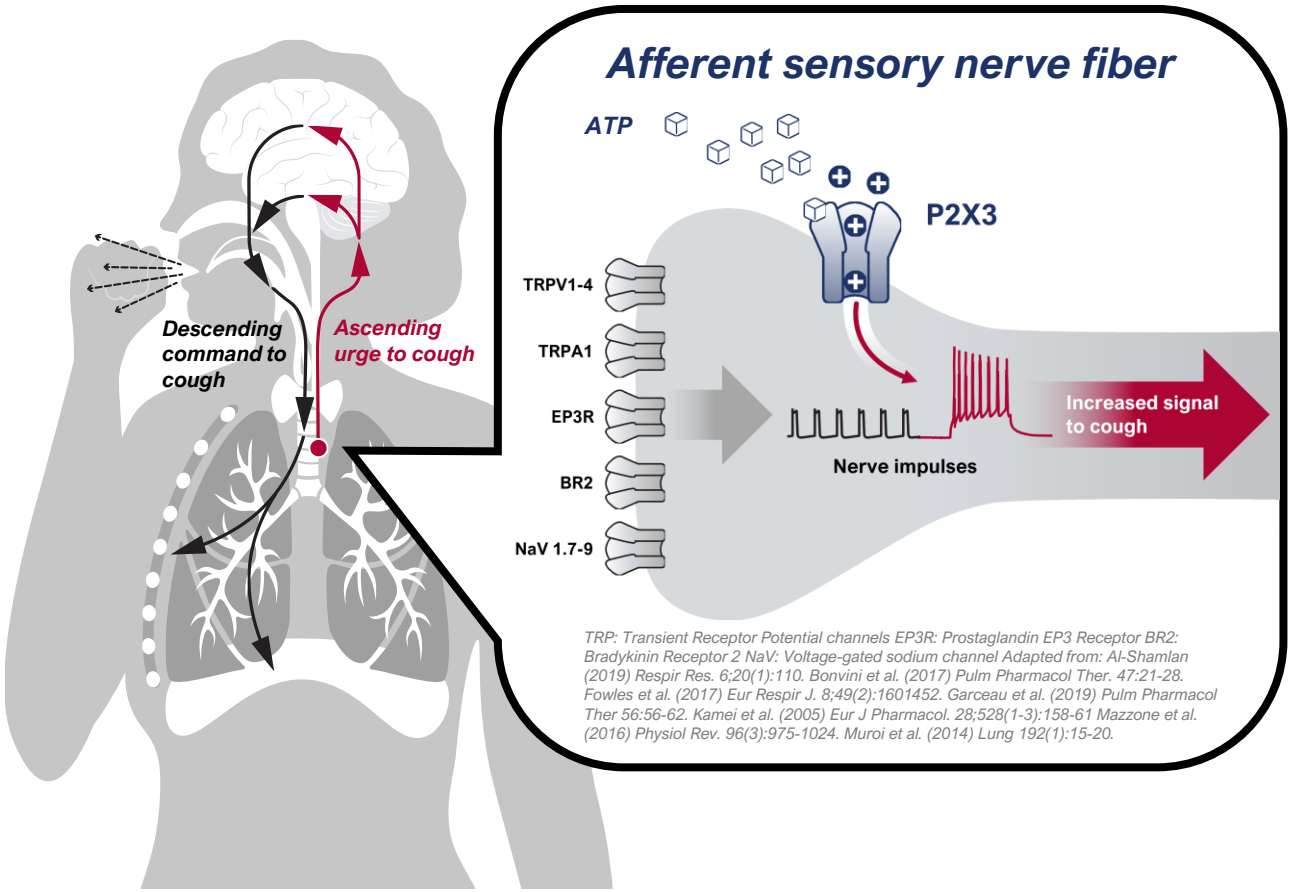
Refractory Chronic Cough

- **Refractory Chronic Cough (RCC)** manifests as a cough lasting > 8 weeks that does not respond to treatment of conditions commonly associated with cough or without a discernable cause following comprehensive evaluation[1]

- **Dysfunction of the neuro-respiratory pathways** controlling cough contributes to the disease pathology[2]
  - Current options for treatment of RCC are not approved by the FDA and some are associated with serious side effects or the risk of addiction[2]

- **Camlipixant (BLU-5937)**, selectively inhibits P2X3 receptors, which are expressed on sensory neurons considered important in the pathophysiology of RCC[3]
  - Camlipixant is in development for the treatment of RCC

Model Of P2X3 In Cough Signaling



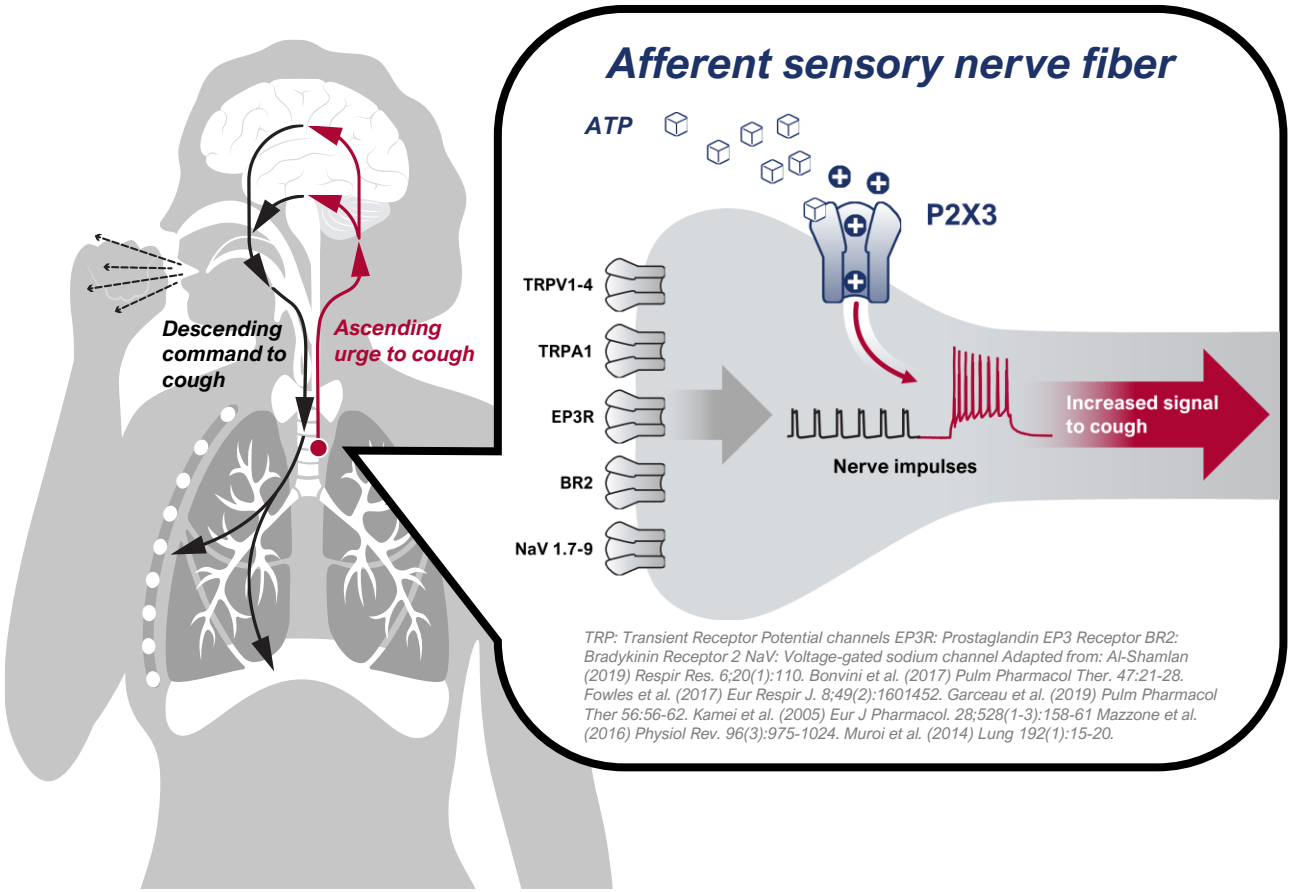
1. Irwin et al, (2018) CHEST 153 (1): 196-209. 2. Chung et al (2022) Nat Rev Dis Primers 8(1):45.
3. Garceau et al. (2019) Pulm Pharmacol Ther 56:56-62.

Severity of Refractory Chronic Cough

- **Impact on quality of life can be severe and heterogeneous** [1-6]
  - Social isolation
  - Interference with normal conversations
  - Anxiety
  - Depressive symptoms
  - Cough-related incontinence
  - Negative impact on sleep
  - Severe physical outcomes (fractures, syncope, etc)

- **Frequency** and **intensity** of the cough also impact the overall severity of cough experienced by patients[7]

Model Of P2X3 In Cough Signaling



TRP: Transient Receptor Potential channels EP3R: Prostaglandin EP3 Receptor BR2: Bradykinin Receptor 2 NaV: Voltage-gated sodium channel Adapted from: Al-Shamlan (2019) Respir Res. 6;20(1):110. Bonvini et al. (2017) Pulm Pharmacol Ther. 47:21-28. Fowles et al. (2017) Eur Respir J. 8;49(2):1601452. Garceau et al. (2019) Pulm Pharmacol Ther 56:56-62. Kamei et al. (2005) Eur J Pharmacol. 28;528(1-3):158-61 Mazzone et al. (2016) Physiol Rev. 96(3):975-1024. Muroi et al. (2014) Lung 192(1):15-20.

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Assessing the Severity of Refractory Chronic Cough

- The **Cough Severity Visual Analog Scale** (VAS) is a straightforward measurement of the patient-experienced severity of cough[1]

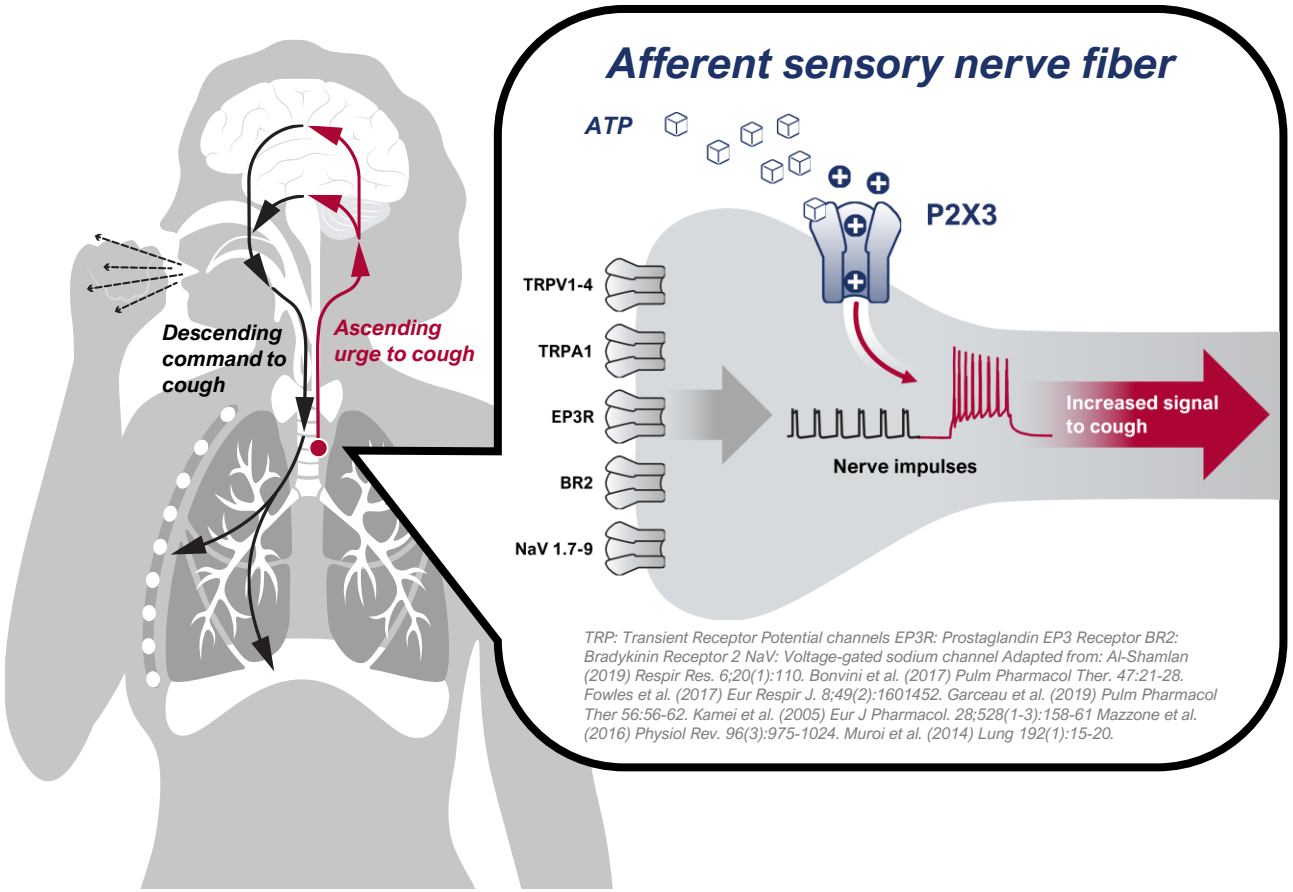
How severe has your cough been over the last 1 week?

0 mm — ***No cough***

100 mm — ***Worst cough imaginable***

- Recently validated in RCC[2]
  - Clinically meaningful change: **≥ 30 mm**
  - Minimal clinically meaningful change: **≥ 20 mm**

Model Of P2X3 In Cough Signaling

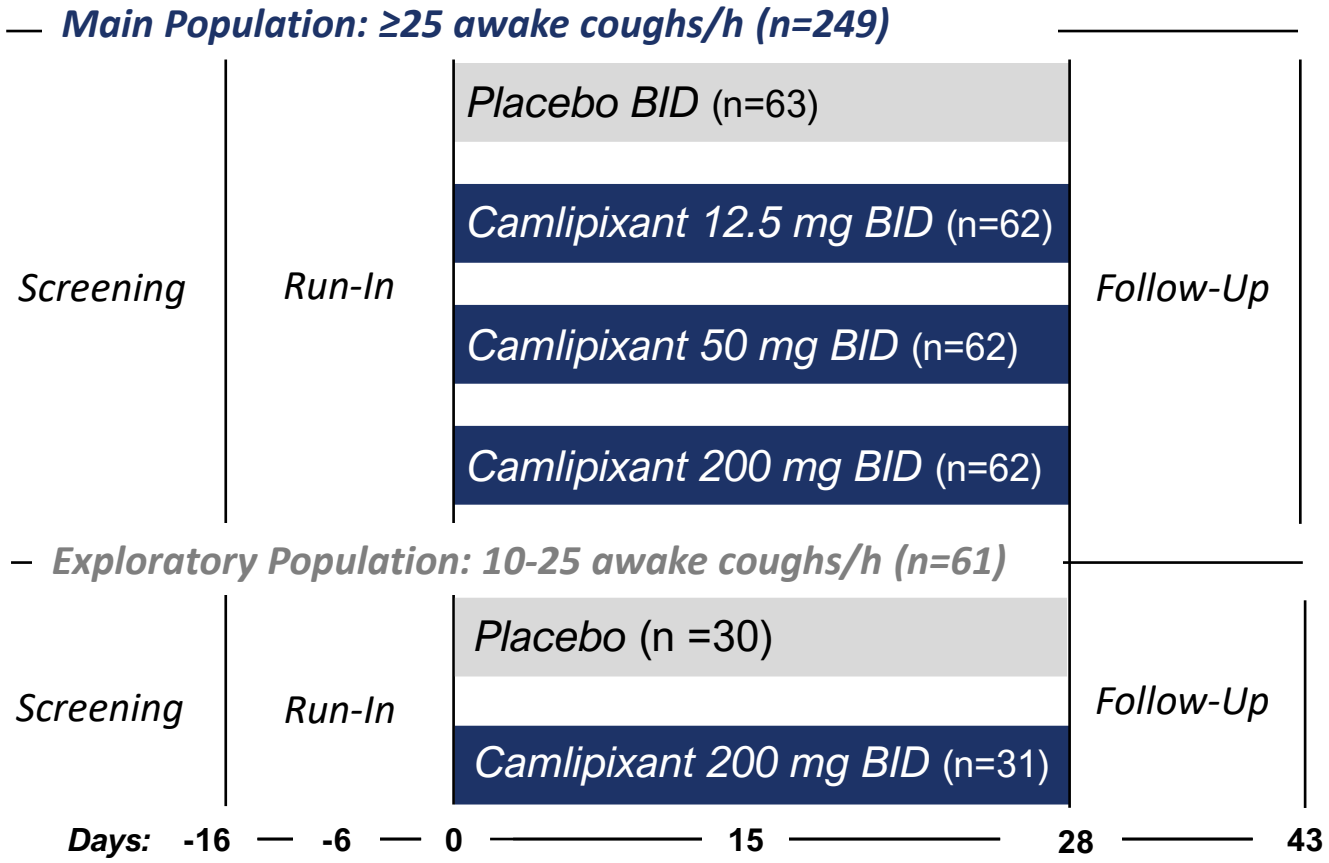


1. Kelsall et al. (2008) Eur Respir J 32(1):175-9. 2. Nguyen et al. (2021) Ther Adv Respir Dis 15:17534666211049743.

SOOTHE: Phase 2b Trial of Camlipixant in Refractory Chronic Cough

SOOTHE - NCT04678206

- Randomized, double-blind, placebo-controlled, parallel arm dose-finding study
- Primary endpoint: change in objective cough frequency*
- Improvement in patient-reported cough severity assessed by the Cough Severity VAS
- Main population enrolled:
  - *Refractory chronic cough for ≥1 year*
  - *Screening / baseline awake cough frequency: ≥25 coughs/h*
  - *Baseline Cough Severity VAS ≥40 mm*



** Measured over a 24H period, calculated as the log-transformed geometric means ratio*

Baseline Characteristics

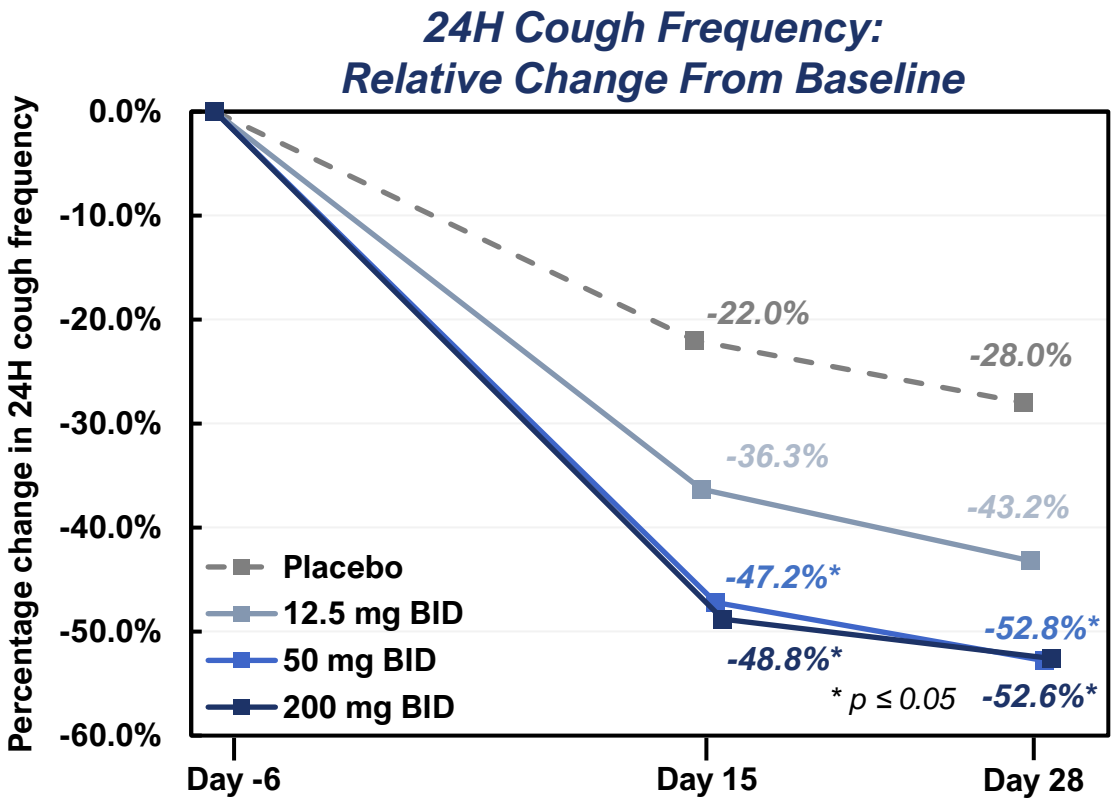
- The Main Population randomized in SOOTHE was representative of RCC
- Demographics and clinical characteristics were generally well-balanced across arms

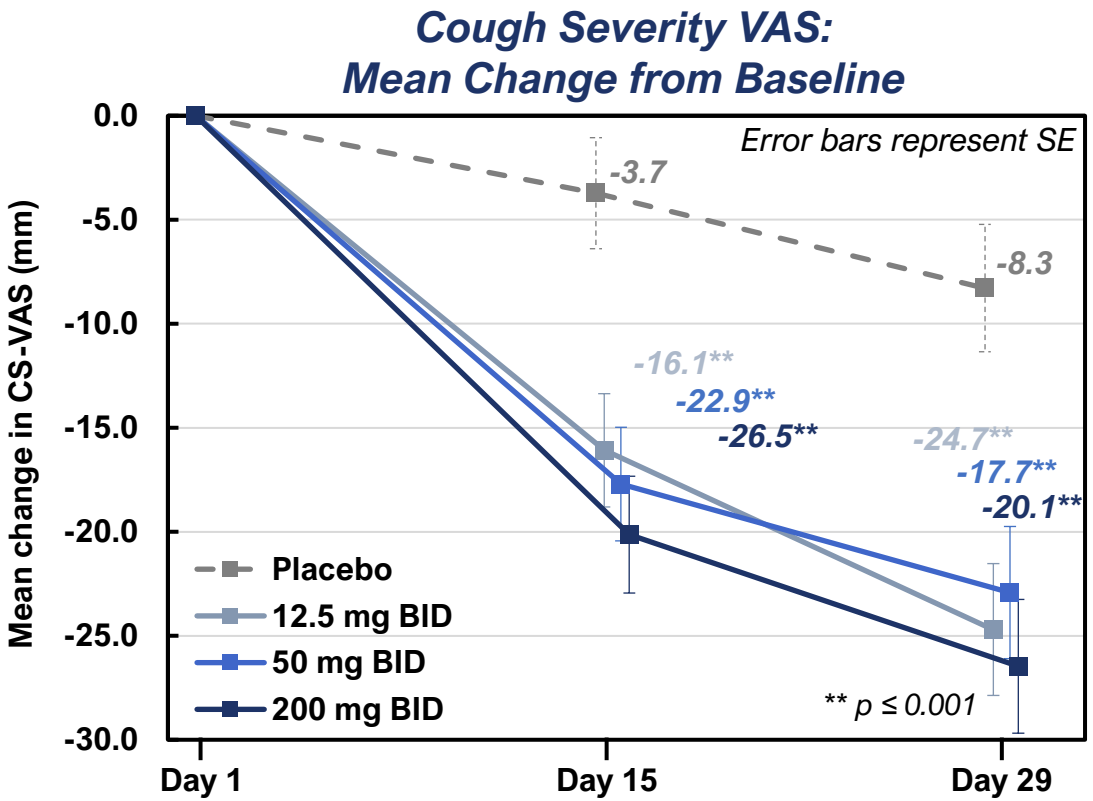
	Placebo (BID)	Camlipixant (BID)			Total
		12.5 mg	50 mg	200 mg	
Number of subjects, n	63	62	62	62	249
Female, n (%)	49 (78%)	48 (77%)	52 (84%)	55 (89%)	204 (82%)
Age (years), mean (SD)	61.4 (11.3)	60.7 (10.1)	61.6 (9.6)	59.7 (11.4)	60.9 (10.6)
BMI (kg/m^2), mean (SD)	27.9 (5.6)	28.1 (5.3)	28.6 (7.3)	27.9 (5.7)	28.1 (6.0)
FEV_1/FVC, mean (SD)	0.77 (0.07)	0.77 (0.07)	0.76 (0.07)	0.77 (0.08)	0.77 (0.07)
Cough Characteristics					
Duration of cough (years), mean (SD)	11.1 (9.7)	11.9 (9.1)	13.5 (11.5)	10.3 (9.1)	11.7 (9.9)
24H cough frequency (coughs/h)**, $mean_{geo}$	39.6	41.3	39.9	35.2	38.9
Cough Severity VAS* (mm), mean (SD)	73.9 (14.9)	71.7 (14.5)	74.0 (14.4)	72.0 (15.6)	72.9 (14.8)
Leicester Cough Questionnaire*, mean (SD)	10.4 (3.1)	10.7 (3.0)	10.0 (3.1)	11.4 (3.0)	10.6 (3.1)

** Measured at Day –6*
***Measured at Day 1*

Change From Baseline in 24H Cough Frequency And Cough Severity

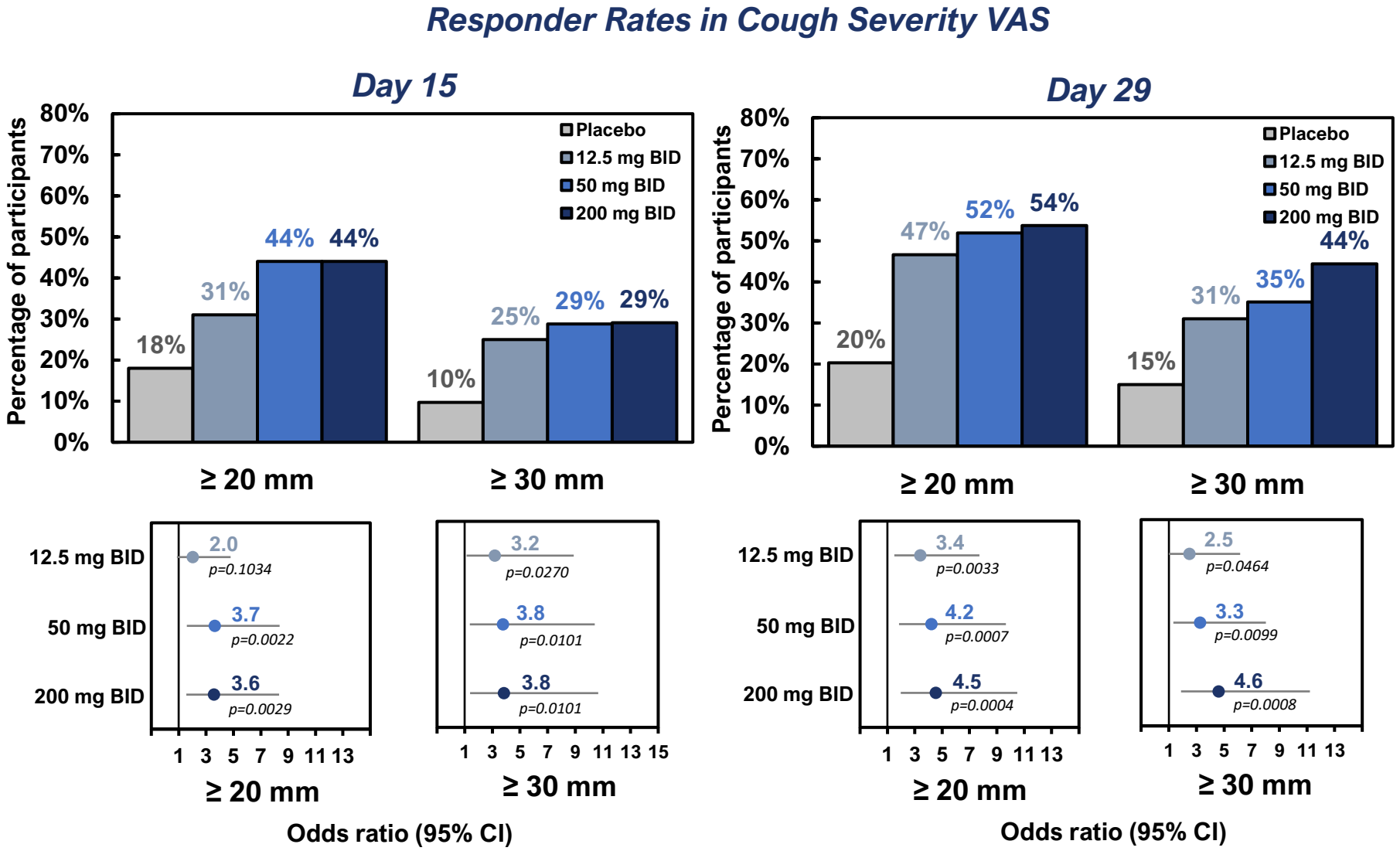
- Rapid and sustained concurrent improvements in cough frequency and patient-reported cough severity
- All treatment groups demonstrated highly statistically significant improvements in CS-VAS over placebo (p≤ 0.001)





Cough Severity VAS Responder Analyses

- For all doses, a greater proportion of participants experienced meaningful improvements compared to placebo.
- At day 29 all doses show significant ($p \leq 0.05$) odds ratio over placebo to achieve either a response of at least 20 or 30 mm.



Conclusions

- SOOTHE demonstrated the potential for camlipixant to improve both objective cough frequency and patient-reported cough severity in a RCC population enriched for higher baseline cough frequency.
- More participants reported meaningful improvements in cough severity after 15 and 29 days of treatment with camlipixant than with placebo

Supplemental Slides

Safety And Tolerability

Overall Safety And Tolerability

- Similar incidence of treatment emergent adverse events (TEAE) reported for placebo and camlipixant
- No treatment emergent serious adverse events (TESAE)
- One discontinuation on placebo and 2 discontinuations on camlipixant 200 mg BID due to possibly-treatment related AEs*

Taste Disturbance Adverse Events

- Taste disturbance adverse events ≤ 6.5% for any group
- No complete nor partial loss of taste at any dose
- No discontinuations due to taste disturbances

	Placebo (BID) (n= 63)	Camlipixant (BID) 12.5 mg (n= 62)	Camlipixant (BID) 50 mg (n= 62)	Camlipixant (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

** As deemed by investigator. Placebo: worsening of cough; BLU-5937 200 mg BID: worsening of cough, dry mouth*