Safety And Efficacy of BLU-5937 In the Treatment of Refractory Chronic Cough from the Phase 2b SOOTHE Trial

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Disclosure to Learners

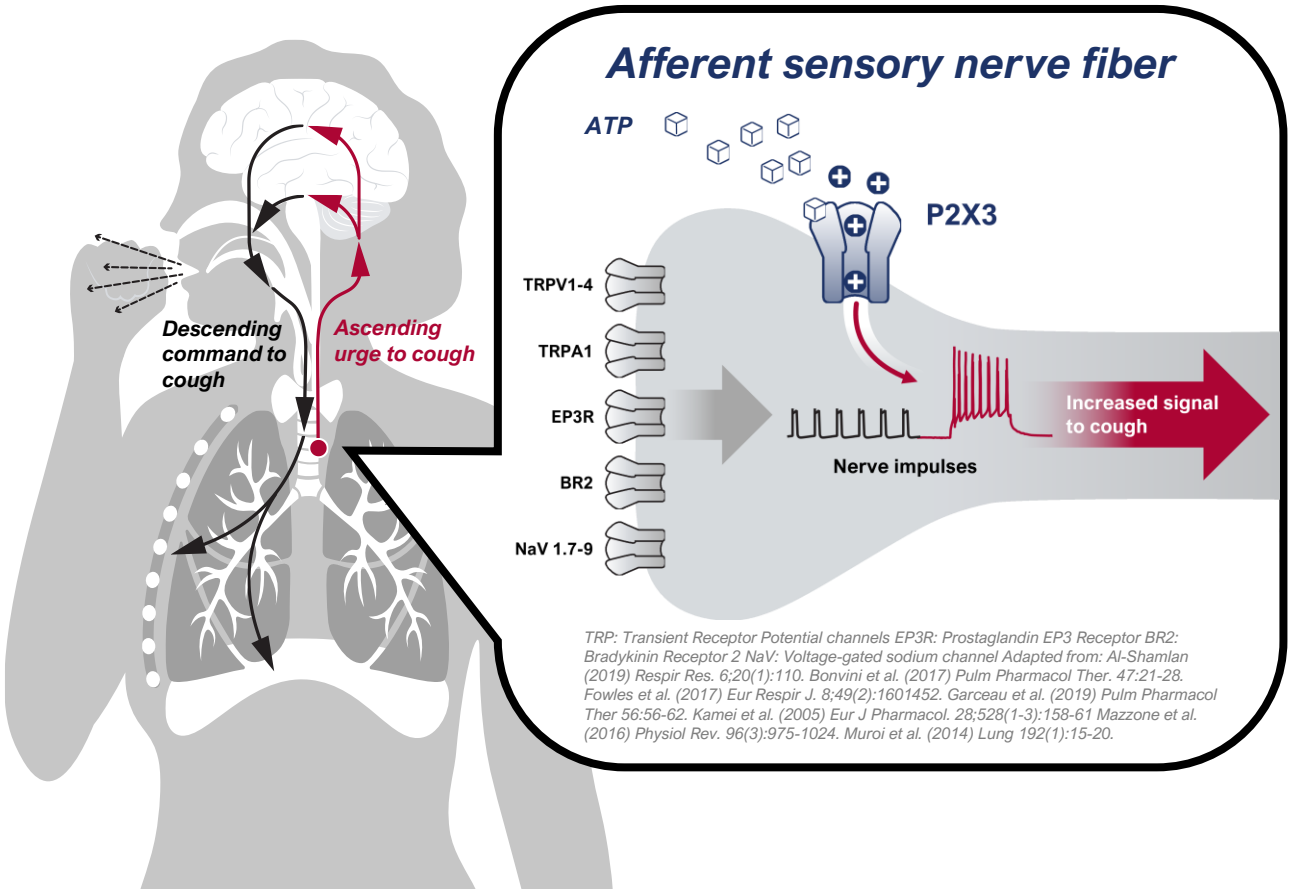
- **Financial relationships with relevant companies within the past 24 months:**
  - *Bellus Health, Advisory committee, Research - industry initiated ; Merck, Advisory committee, Research - industry initiated and grant funding, Speaker/faculty – non-promotional activity; Nocion, Research - industry initiated, Advisory committee; Bayer, Research - industry initiated, Advisory committee; Axalbion, Consultant, Research - industry initiated, Algernon, Consultant; Shionogi, Advisory committee; AstraZeneca, Consultant.*
  - *Vitalograph Ltd, Royalties paid to the hospital in which I work.*

Refractory Chronic Cough

Refractory Chronic Cough

- Cough lasting ≥ 8 weeks that does not respond to treatment of possible associated diseases or without associated disease[1]
- Current treatment options are not approved by the FDA and suffer from serious side effects or the risk of addiction[2]
- Hypersensitization of cough signaling pathways, including the P2X3 receptor, is thought to play a key role in RCC[3]
- P2X3 antagonists have shown promise in RCC clinical trials[4]
  - Identification of optimal population, management of the placebo effect and high incidence of taste disturbance have presented challenges

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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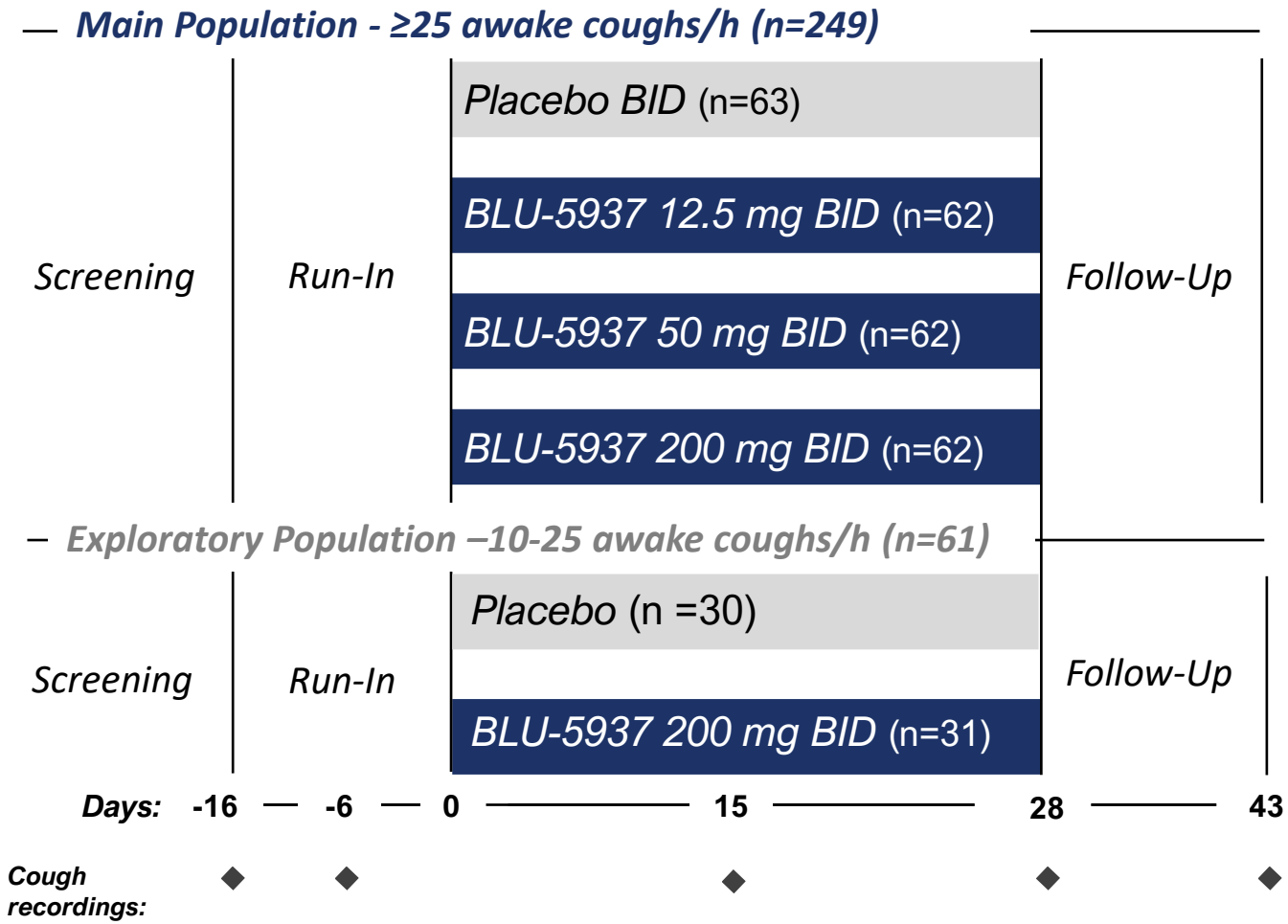
SOOTHE Phase 2b Trial

BLU-5937

- P2X3 antagonist with high selectivity vs P2X2/3
- Selectivity suggests the possibility to maintain efficacy with lower incidence of taste disturbances

SOOTHE Trial *(NCT04678206)*

- Randomized, double-blind, placebo-controlled parallel arm dose finding study
- Primary endpoint: change in objective cough frequency*
- Main population enrolled:
  - *Refractory chronic cough for ≥1 year*
  - *Screening / baseline awake cough frequency: ≥25 coughs/h*



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

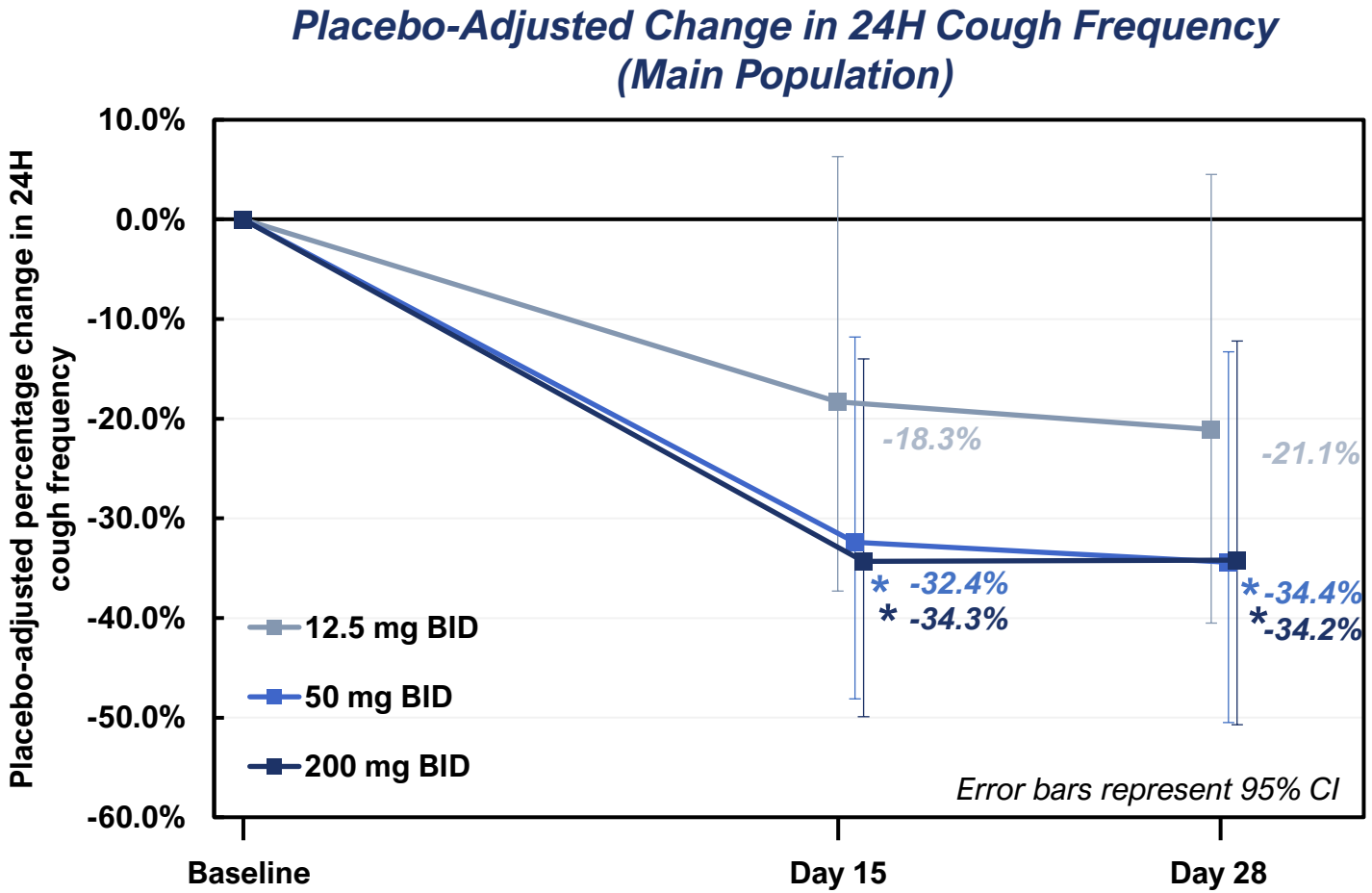
SOOTHE Baseline Characteristics

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

		Placebo (BID)	BLU-5937 (BID)		
			12.5 mg	50 mg	200 mg
Number of subjects, n		63	62	62	62
Female, n (%)		49 (78%)	48 (77%)	52 (84%)	55 (89%)
Age (years), 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)
Race, n (%)	White	62 (98%)	58 (94%)	60 (97%)	60 (97%)
	Asian	1 (2%)	3 (5%)	0	0
	Black	0	0	1 (2%)	2 (3%)
	American Indian/ Alaska Native	0	1 (2%)	1 (2%)	0
24H cough frequency (coughs/h), mean$_{geo}$		39.6	41.3	39.9	35.2

SOOTHE Primary Efficacy Endpoint
Placebo-Adjusted Change From Baseline in 24H Cough Frequency

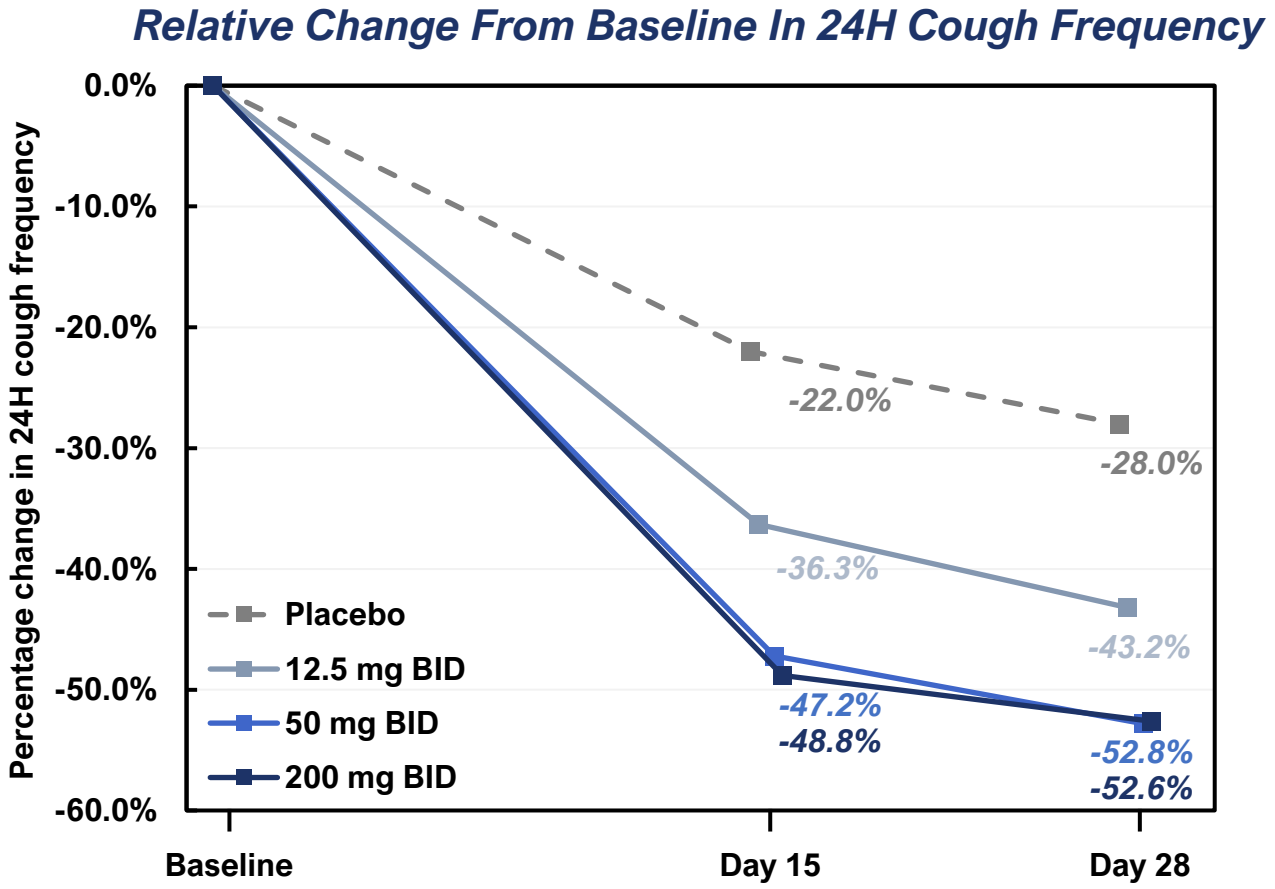
- Statistically significant and clinically meaningful reductions in 24H cough frequency over placebo
- Day 28: Reductions over placebo of 34.4 and 34.2% at 50 and 200 mg BID doses respectively
- Significant reductions observed as early as Day 15



* $p \leq 0.005$, two-sided

SOOTHE Change From Baseline in 24H Cough Frequency

- Rapid reductions from baseline in cough frequency sustained over 4 weeks
- Day 28: Reductions over placebo of 52.8 and 52.6% at 50 and 200 mg BID doses respectively
- Reduction in cough frequency from baseline of 28.0% in the placebo group



SOOTHE Dose-Finding Trial: BLU-5937 Dose Response

SOOTHE *(NCT04678206)*

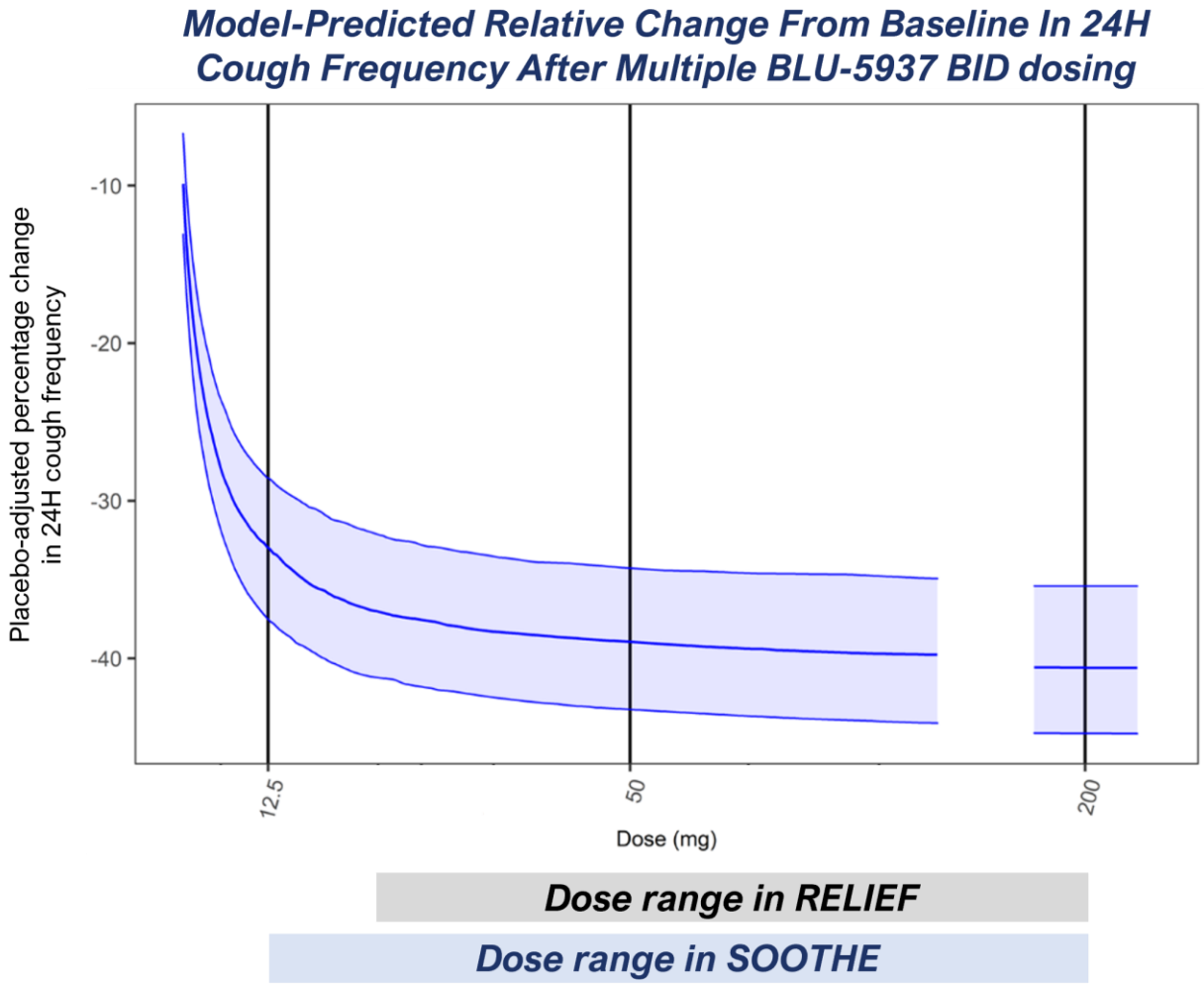
- Dose response observed between 12.5 and 50 mg BID
- No dose response between 50 and 200 mg BID

RELIEF *(NCT03979638)*

- No dose response between 25 and 200 mg BID in forced dose escalation trial

DOSE RESPONSE MODELLING

- PD modelling of response based on SOOTHE data
- Confirms dose response between 12.5 and 50 mg BID
- Percent of maximum effect:
  - 91.3% for 25 mg BID
  - 96.3% for 50 mg BID



SOOTHE: Safety And Tolerability

Overall Safety And Tolerability

- Similar incidence of treatment emergent adverse events (TEAE) reported for placebo and BLU-5937
- No treatment emergent serious adverse events (TESAE)
- One discontinuation on placebo and 2 discontinuations on BLU-5937 200 mg BID due to possibly-treatment related AEs*

Taste Disturbance Adverse Events

- Taste disturbance adverse events ≤ 6.5% for any BLU-5937 group
- No complete nor partial loss of taste at any dose
- No discontinuations due to taste disturbances

	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

Bellus HEALTH

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

SOOTHE: Conclusions

- SOOTHE demonstrated the efficacy of 3 doses of BLU-5937 as measured by objective cough monitoring in a population enriched for baseline cough frequency.
- Design of the study identified patients most likely to demonstrate benefit from treatment with a P2X3 antagonist and mitigated the potential impact of the placebo effect.
- Important reductions in cough frequency and a favorable safety profile support the continued development of P2X3 antagonists with a high selectivity versus P2X2/3.