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

Smith J[1], McGarvey L[2], Birring S.S[3], Morice A.H[4], Sher M[5], Dicpinigaitis P[6], Blaiss M[7], Lanouette S[8], Harvey L[8], Yang R[9], Shaw J[9], Garin M[9], Bonuccelli C[9]

1.University of Manchester, Manchester, UK 2.Queen's University Belfast, Belfast, UK 3.King's College London, London, UK 4.Hull York Medical School, Cottingham, UK 5.Center for Cough, Largo, USA 6.Albert Einstein Hosp, Bronx, NY, USA 7.Medical College of Georgia, Augusta, GA, USA 8.Bellus Health Inc., Laval, Canada 9.Bellus Health Inc., Wilimington, USA

Bellus HEALTH

Introduction

- Refractory Chronic Cough (RCC) is a cough that persists for 8 weeks or more despite adequate treatment of all identifiable associated diseases or without identifiable cause[1,2].
- The current lack of approved treatment exacerbates the significant physical, psychological, and social burdens RCC imposes on patients.

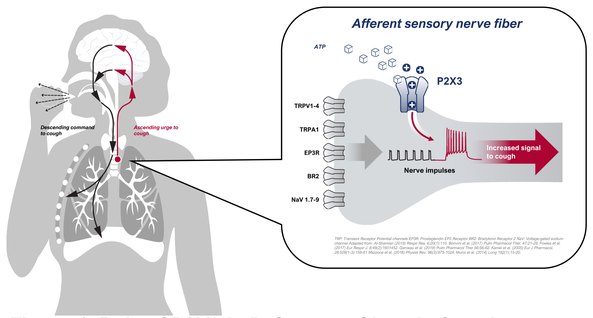

Figure 1. Role of P2X3 in Refractory Chronic Cough

- The ATP-gated ion channel P2X3 is suggested to play a role in the pathophysiology of RCC (Fig 1.), and P2X3 antagonists have shown promise as a treatment for RCC[3-5].
- We report the primary efficacy and safety results from a Phase 2b study of BLU-5937 in RCC, a highly selective P2X3 antagonist, for the treatment of RCC.

Methodology

- SOOTHE (NCT04678206) was a multi-center Phase 2b, randomized, placebo-controlled, parallel arm, clinical dose-finding study in participants diagnosed with RCC for ≥1 year.

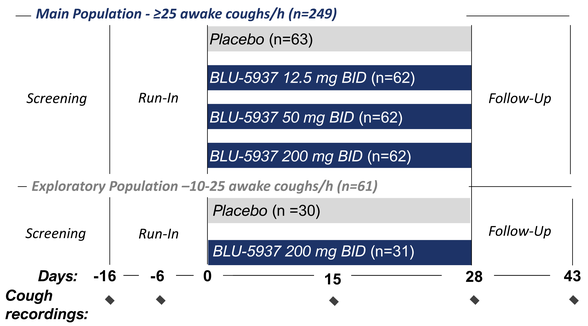

Figure 2. SOOTHE Study Design

- The primary endpoint was the change from baseline in 24H cough frequency.
- Following a single-blind run-in period, 249 participants who had maintained a baseline awake cough frequency ≥25 coughs/h were randomized 1:1:1:1 to the three active treatment arms of BLU-5937 (12.5, 50 and 200 mg BID) or placebo for 4 weeks of double-blind treatment.

Baseline Characteristics

- The Main Population in SOOTHE, enriched for higher baseline cough frequency, displayed demographic and clinical characteristics typical of RCC[3-6].
- Demographics and clinical characteristics were generally well-balanced across arms.

TABLE 1. SOOTHE Participants Baseline Characteristics

		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/m²), 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

Efficacy: Primary Endpoint

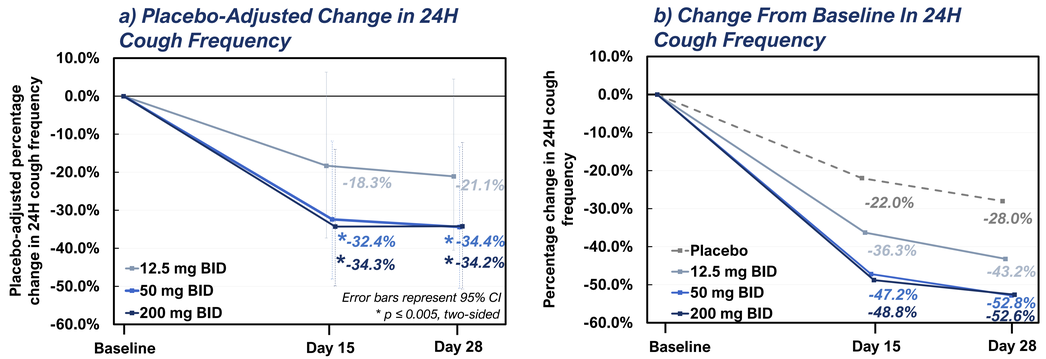

FIGURE 3. Change In 24H Cough Frequency

- Statistically significant and clinically meaningful reductions over placebo were observed for 50 and 200 mg BID at Days 15 and 28 (Fig 3a).
  - Reductions over placebo of 34.4 and 32.4% at 50 and 200 mg BID doses, respectively.
- Reductions from baseline in cough frequency occurred rapidly and were sustained over 4 weeks.(Fig 3b).
  - Reductions of 52.8 and 52.6% from baseline at 50 and 200 mg BID doses at Day 28, respectively.
  - Placebo effect remained moderate, with reduction in cough frequency from baseline of 28.0% in the placebo group at Day 28.

Safety & Tolerability

Overall Safety And Tolerability

- A similar incidence of treatment emergent adverse events (TEAEs) was reported for placebo and BLU-5937.
- There were no treatment emergent serious adverse events (TESAE).
- The rate of discontinuations due to possibly-treatment-related AEs was low: one on placebo and 2 on BLU-5937 200 mg BID.

Taste Disturbance Adverse Events

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

TABLE 2. Incidence of Treatment-Emergent AEs

	Placebo (BID) (n= 63)	BLU-5937 (BID) 12.5 mg (n= 62)	50 mg (n= 62)	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

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 features of the study, including a run-in period and the requirement to demonstrate persistent severity and frequency of cough, identified patients most likely to demonstrate benefit from treatment with a P2X3 antagonist and mitigated the 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.

References

1. Morice et al. *Eur Respir J*. (2020) 55(1):1901136.
2. Irwin et al. *Chest*. (2018) 153(1):196-209.
3. McGarvey et al. *Lancet*. (2022) 99(10328):909-923
4. Morice et al. *Eur Respir J*. (2021) 58(5):2004240.
5. Niimi et al. *Eur Respir J*. (2021) 2100725.
6. Chamberlain et al. *Lung*. (2015) 193(3):401-8.