Efficacy in SOOTHE, A Phase 2b Trial of BLU-5937 In Refractory Chronic Cough, Was Not Dependent of Taste Disturbance Adverse Events

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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.

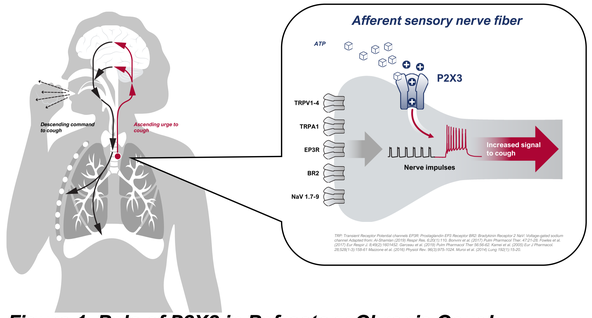


Figure 1. Role of P2X3 in Refractory Chronic Cough

- The ATP-gated ion channel homotrimeric P2X3 receptor is suggested to play a role in the pathophysiology of RCC (Fig 1). The closely related heterotrimeric receptors P2X2/3 receptors are suggested to have a role in taste function[3].

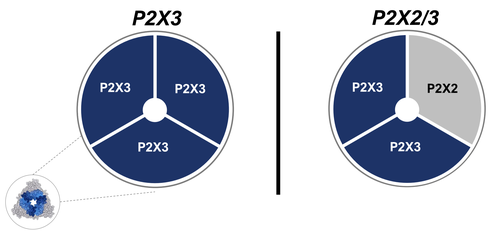


Figure 2. Homotrimeric P2X3 And Heterotrimeric P2X2/3 receptors

- P2X3 antagonists have been validated in clinical trials as a treatment option for RCC, but many have been associated with a significant incidence of taste disturbances, including taste loss, attributed to the inhibition of P2X2/3[4-6].
- Taste disturbances may also potentially unblind participants to treatment, possibly confounding measurement of efficacy.
- Here we characterize the taste disturbance adverse events and their impact on efficacy in SOOTHE, a Phase 2b trial of BLU-5937, a P2X3 antagonist with a >1500-fold selectivity vs. P2X2/3, for the treatment of RCC.

Methods

- SOOTHE (NCT04678206) was a multi-center Phase 2b, randomized, placebo-controlled, parallel arm, clinical dose-finding study in adults diagnosed with RCC for ≥1 year.
- The primary endpoint was the change from baseline in 24H cough frequency calculated on the log scale.
- 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.
- Taste disturbance adverse events (TDAE) reports were collected through routine capture, in a similar fashion to all other adverse events. Participants who reported a TDAE were asked to characterize how bothersome they found the disturbance.
- A post-hoc analysis assessed the change from baseline on the log scale in 24H cough frequency, calculated in participants that did not report TDAEs, to characterize the impact of TDAE reporting on the assessment of BLU-5937 efficacy in SOOTHE

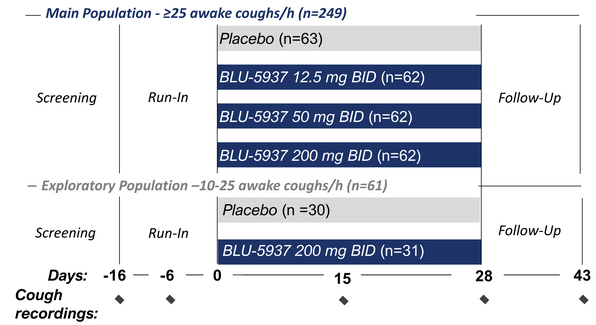


Figure 3. SOOTHE Study Design

Results

TABLE 1. Taste Disturbance Adverse Events

	Placebo (BID) (n= 63)	BLU-5937 (BID) 12.5 mg (n= 62)	50 mg (n= 62)	200 mg (n= 62)
Subjects with TDAE leading to discontinuation, n (%)	0	0	0	0
Incidence of 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
Description of Taste Disturbance Adverse Events				
Not bothersome	0	0	1 (1.6%)	0
Slightly bothersome	0	3 (4.8%)	1 (1.6%)	3 (4.8%)
Moderately bothersome	0	0	2 (3.2%)	0
Severely bothersome	0	0	0	0
Extremely bothersome	0	0	0	0

† No TDAE reported in the exploratory population

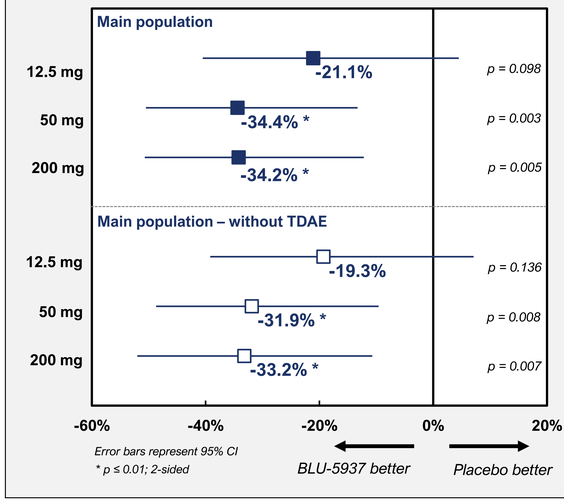
Characterization of Taste Disturbance Adverse Events

- Treatment-emergent TDAEs were reported by 4.8, 6.5, 4.8 and 0% of participants in the 12.5, 50, 200 mg BID and placebo groups, respectively (Tab.1).
- No complete nor partial loss of taste were reported at any dose (Tab.1).
- No discontinuations due to taste disturbances occurred in any group (Tab.1).
- All TDAEs resolved either during treatment or by the end of the follow-up period.
- Nine events were characterized as "mild" and one as "moderate"; none were considered "severe".
- Most TDAE were described as "not" or "slightly" bothersome, with two described as moderately bothersome. No participant reported a severely or extremely bothersome TDAE (Tab.1).

Taste Disturbance Adverse Events vs Efficacy

- Changes in 24H cough frequency over placebo of -21.1, -34.4, and -34.2% were observed in the main population after 28 days of BLU 5937 treatment at 12.5, 50, and 200 mg BID, respectively.
- Participants who did not report TDAEs saw similar placebo-adjusted reductions in 24H cough frequency of -19.3, -31.9, and -33.2%.

Figure 4. Placebo-adjusted 24H cough frequency change from baseline at Day 28



Conclusions

- SOOTHE demonstrated the efficacy of 2 doses of BLU-5937 as measured by objective cough monitoring in a population enriched for baseline cough frequency.
- Incidence of taste disturbances at any dose was ≤6.5%, with no reported loss of taste. Overall, most of these taste disturbances were mild in nature.
- The limited incidence and mild nature of TDAEs reported during treatment with BLU-5937 in SOOTHE does not appear to have significantly confounded assessment of treatment effect as measured by change from baseline in 24H cough frequency, as suggested by post-hoc analyses.

References

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