Improvements In Awake Cough Frequency In Participants Treated With BLU-5937 In A Phase 2b Trial of BLU-5937 in Refractory Chronic Cough

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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 ATP-gated ion channel P2X3 is suggested to play a role in the pathophysiology of RCC (Fig 1.).

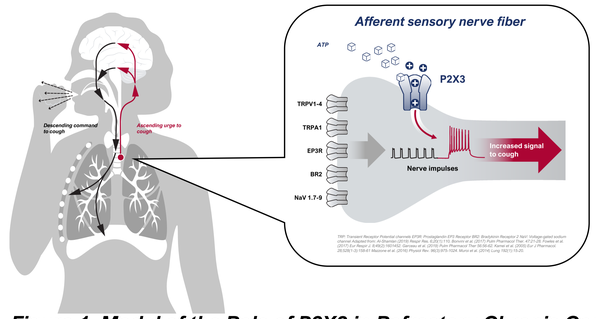


Figure 1. Model of the Role of P2X3 in Refractory Chronic Cough

- There are currently no approved medications outside of Japan and Switzerland for RCC. P2X3 antagonists have been validated in clinical trials as a potential option for the management of RCC[3-5].
- Cough frequency in clinical trials has been reported over either 24H or awake periods. In SOOTHE, a Phase 2b study of BLU-5937 in RCC, the primary endpoint was the change from baseline in 24H cough frequency. We report here the change in awake cough frequency, assessed as a secondary endpoint

Methods

- 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.

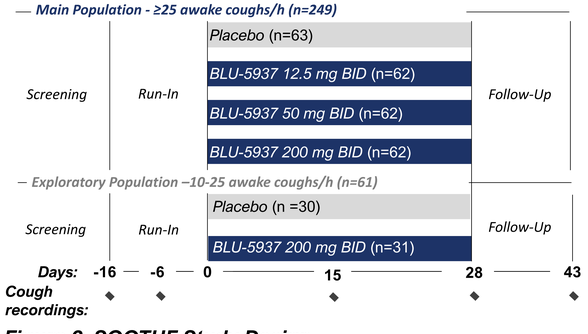
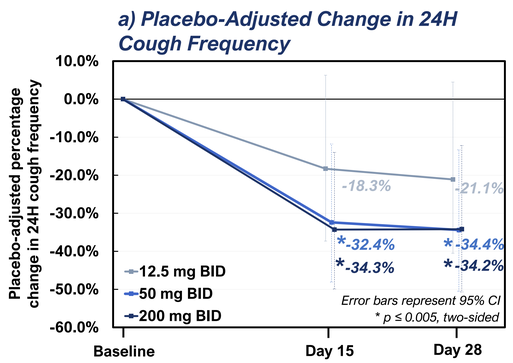


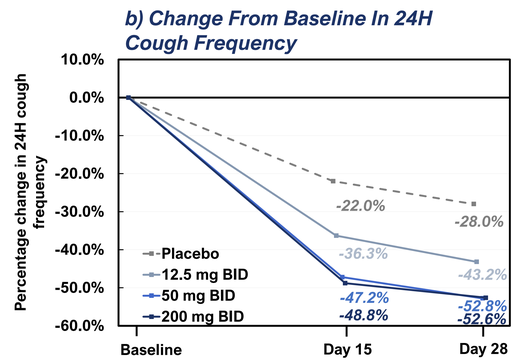
Figure 2. SOOTHE Study Design

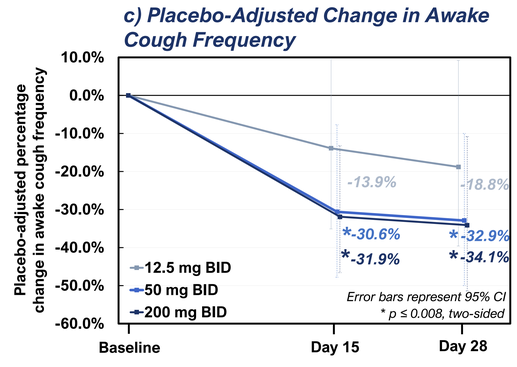
- Following a single-blind run-in period, 249 participants who had maintained a baseline awake cough frequency ≥25 coughs/h were randomized 1:1:1:1 to the three active treatment arms of BLU-5937 (12.5, 50 and 200 mg BID) or placebo for 4 weeks of double-blind treatment.

Results

- Overall baseline cough frequency was balanced between treatment groups (Tab 1).
- The primary efficacy analysis showed reductions in 24H cough frequency over placebo at Day 28 of -21.1%, p=0.098, -34.4%, p=0.003 and -34.2%, p=0.005, at 12.5, 50, and 200 mg BID respectively; reductions of 44.0%, 52.8% and 52.6% from baseline were observed in the 12.5, 50 and 200 mg BID treatment groups, respectively (Fig 3a and 3b).
  - Statistically significant and clinically meaningful reductions over placebo were observed for 50 and 200 mg BID at Days 15 and 28 (Fig 3a).
- Reductions in awake cough frequency were observed as early as after 15 days of treatment and were maintained through the end of the treatment period. Participants in the 12.5, 50 and 200 mg groups showed awake frequency improvements over placebo of -13.9% p=0.300, -30.6% p=0.012 and –31.9% p=0.010, respectively at Day 15 (Fig 3c).
- Placebo-adjusted improvements in awake cough frequency at Day 28 were -18.8%, p=0.167 -32.9%, p=0.008 and -34.1%, p=0.007, at 12.5, 50, and 200 mg BID respectively (Fig 3c).
  - Reductions from baseline in awake cough frequency of -53.8% and -54.6% for 50 and 200 mg BID at Day 28 were also observed, while the placebo group experienced an average reduction of 31.1% (Fig 3d).
- The proportion of participants experiencing a ≥30% reduction in awake frequency at Day 28 was numerically greater for all doses of BLU-5937 compared to placebo (Fig 4).







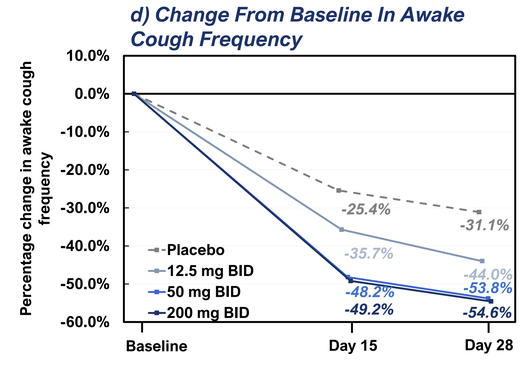


FIGURE 2. Change In 24H And Awake Cough Frequency

TABLE 1. Participant Cough Frequency at Baseline

	Placebo (BID)	BLU-5937 (BID)		
		12.5 mg	50 mg	200 mg
Number of particpants, n	63	62	62	62
24H cough frequency (coughs/h), $mean_{geo}$	39.6	41.3	39.9	35.2
Awake cough frequency (coughs/h), $mean_{geo}$	56.9	58.4	55.8	49.7

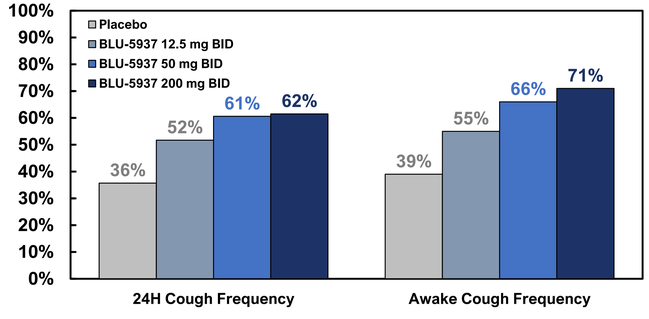


Figure 4. Proportion of Participants With A ≥30% Reduction In Cough Frequency at Day 28 by treatment

Conclusions

- The SOOTHE Phase 2b study demonstrated the efficacy of 3 doses of BLU-5937 as measured by objective cough monitoring in a population enriched for baseline cough frequency.
- Improvements in awake cough frequency with BLU-5937during awake hours closely align with improvements observed over a 24-hour period.
- These results demonstrate clinically meaningful reductions in cough frequency during waking hours after treatment with BLU-5937, the period during which RCC patients experience most of their cough.

References

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