Design of SOOTHE, a phase 2b dose finding study with BLU-5937, a selective P2X3 antagonist, in refractory chronic cough

Bonuccelli C[1], Smith J[2], Birring S. S.[3], Blaiss M[4], Dicpinigaitis P[5], Sher M[6], Garceau D[1], Chauret N[1], Garin M[1], Harvey L[1], Carroll K J[7], Shaw J E[1]

1. Bellus Health Inc. 2. University of Manchester, Manchester, UK 3. King's College London, London, UK 3.Hull York Medical School, Cottingham, UK 3. 4. Medical College of Georgia at Augusta University, Augusta, USA 5. Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, USA 6. Center for Cough, Largo, USA 7. KJC Statistics Ltd, Cheshire, UK

Bellus HEALTH

Introduction

- Refractory Chronic Cough (RCC) is a cough lasting more than 8 weeks that does not respond to optimal treatment of identifiable etiologies[1].
- RCC causes significant physical, psychological, and social burdens, exacerbated by the lack of currently approved treatments[1].
- Inhibition of P2X3 has shown promise in the treatment of the cough reflex hypersensitivity underlying RCC [2].
- As in other similar trials, a proof-of-concept study of the P2X3 antagonist BLU-5937 (RELIEF; NCT03979638) demonstrated a greater treatment effect in subjects with higher baseline cough frequency[2,4-7].
- Those findings justified the use of higher frequency entry criteria in future clinical trials to enrich the study population for those most likely to show benefit from treatment.
- Here, we present the design of SOOTHE, a phase 2b study on the safety and efficacy of BLU-5937 in a RCC population enriched using cough frequency.

Study design

- SOOTHE (NCT04678206) is a multi-center phase 2b, randomized, placebo-controlled, parallel arm dose-finding study in participants diagnosed with RCC for ≥1 year.
- Following a single-blind run-in period, participants with a baseline awake cough frequency ≥25 coughs/h (n=240) are randomized 1:1:1:1 to the active treatment arms of BLU-5937 (12.5, 50 and 200 mg BID) or matching placebo for 4 weeks of double-blind treatment (**fig. 1**).
- The effect in a lower cough frequency population is assessed in an exploratory cohort (n=60) with baseline awake cough frequencies between 10 and 25 coughs/h. Participants are randomized 1:1 to BLU-5937 200mg BID or matching placebo for 4-weeks of double-blind treatment (**fig. 1**).
- Change in 24H cough frequency relative to placebo is the primary efficacy endpoint (**tab. 1**) in both cohorts.
- All participants are followed up 14 days after the completion of the 4-week treatment period.

FIGURE 1. SOOTHE study design

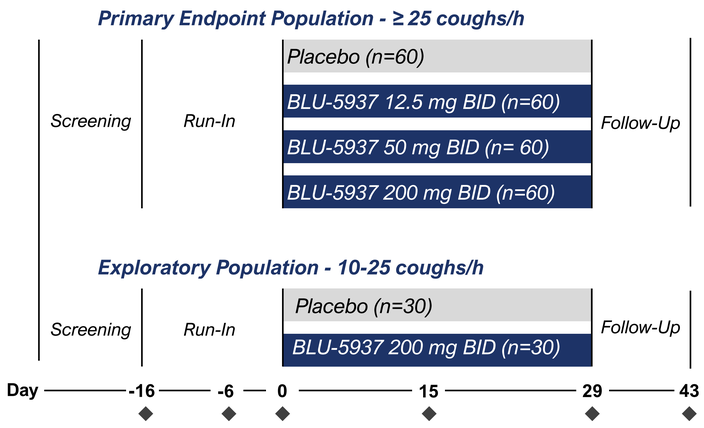


TABLE 1. Efficacy Endpoints

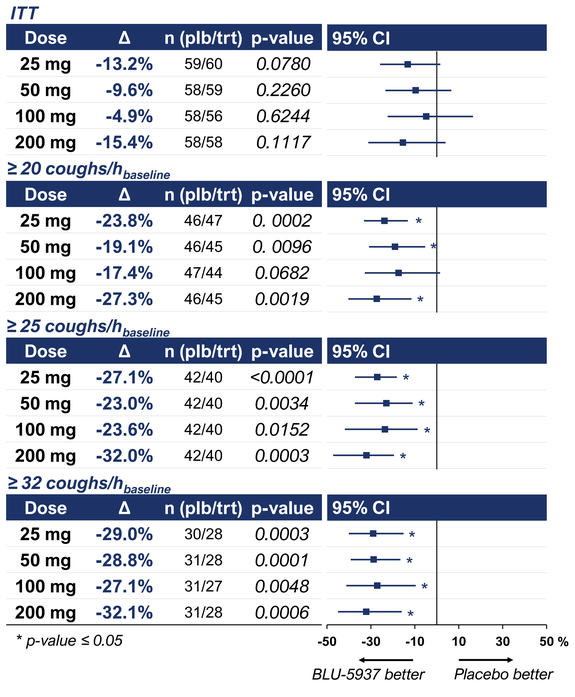
Primary Efficacy Endpoint
Change from baseline in 24H cough frequency
Secondary Endpoints – Objective Cough Frequency
Change from baseline in awake cough frequency
Change from baseline in nighttime cough frequency
Percentage of participants with a reduction from baseline in 24-hour cough frequency of ≥ 30%, 50% and 70%
Secondary Endpoints – Patient Reported Outcomes
Change from baseline in Leicester Cough Questionnaire (LCQ)
Percentage of participants with a LCQ Increase from baseline of ≥ 1.3
Change from baseline in cough severity Visual Analogue Scale
Patient Global Impression of Change (PGI-C)
Patient Global Impression of Severity (PGI-S)
Safety Endpoints
Incidence and grade of AEs, serious AEs and treatment emergent AEs
Discontinuation of treatment due to an AE

Rationale

Population enrichment

- In RELIEF, participants (≥10 coughs/h) were randomized to 16-day treatment (25, 50, 100, 200 mg BID) or placebo, with dose escalation every 4 days. After washout, they were crossed over to the other regimen[7].
- Because a significant interaction between treatment effect and baseline cough frequency has been demonstrated for BLU-5937, the SOOTHE population is enriched for higher baseline cough frequency.
- Nominally significant (p <0.05) reductions in cough frequency in RELIEF were seen in pre-specified subgroups with baseline awake cough frequencies ≥20 or 32 coughs/h (**fig. 2**)
- These results suggested that requiring a minimum baseline awake cough frequency between 20 and 32 coughs/h would be an appropriate enrichment strategy for future trials with BLU-5937.
- RELIEF participants with baseline awake cough frequencies between 20 and 25 coughs/h demonstrated little response to BLU-5937 (*not shown*).
- Subsequent post-hoc analysis of the subgroup with baseline awake cough frequency ≥25 coughs/h (**fig. 2**) confirmed a consistent improvement in those subjects.
- This data suggests that a cut-off value of 25 coughs/h to enrich the population of SOOTHE by awake cough frequency offers the widest range with consistent treatment effect.
- To ensure a balanced distribution of participants with the highest cough frequencies, randomization is stratified by baseline awake cough frequency (above and below 45 coughs/h).

FIGURE 2. Placebo-adjusted changes from baseline in 24-hour cough frequency in RELIEF



Dose selection

- All active doses included in RELIEF were predicted to achieve ≥80% estimated receptor occupancy.
- No clear dose response was observed for any subgroup (**fig. 2**).
- The RELIEF trial design did not allow for differentiation of effects due to increasing dose versus that due to increasing treatment duration.
- Three doses were selected to cover a broader range of predicted P2X3 occupancy in SOOTHE: 12.5, 50 and 200 mg BID.

Statistical power & sample size

- The primary endpoint will be assessed using the back-transformed least square means analysis of log transformed 24H cough frequency data using a mixed model repeated measures (MMRM) analysis.
- The design of SOOTHE allows for >80% power to detect a 25% difference in placebo-adjusted 24H cough frequency change from baseline (1-sided 5% significance level) for the primary analysis population. This assumes a standard deviation of 0.6 on the log scale.
- A blinded sample size re-estimation (SSRE) will be performed when between 30 and 50% of planned patients have completed 4 weeks of treatment. Following the blinded SSRE, a subsequent administrative interim analysis will be performed when 50% of the expected randomized population has completed the primary endpoint in order to assess the likelihood of dose effectiveness to assist. The latter is solely to aid decision making external to the trial and will have no bearing on ongoing trial conduct.

Conclusion

- The SOOTHE study will assess the safety and efficacy of 3 doses of BLU-5937 in an enriched RCC population as measured by ambulatory cough monitoring and patient reported outcome measurements.
- The inclusion of a run-in period and of enrichment and stratification by baseline cough frequency in SOOTHE are expected to address challenges in RCC trials, including the influence of the baseline on the treatment effect and important placebo responses.
- Results from the SOOTHE trial will help determine optimal therapeutic doses of BLU-5937 in the treatment of RCC to support the design of future clinical studies.

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