Update on the development of BLU-5937 for the treatment of refractory chronic cough

Catherine M Bonuccelli, MD

Chief Medical Officer

Bellus Health, Inc

American Cough Conference

12 June 2021

Disclosures

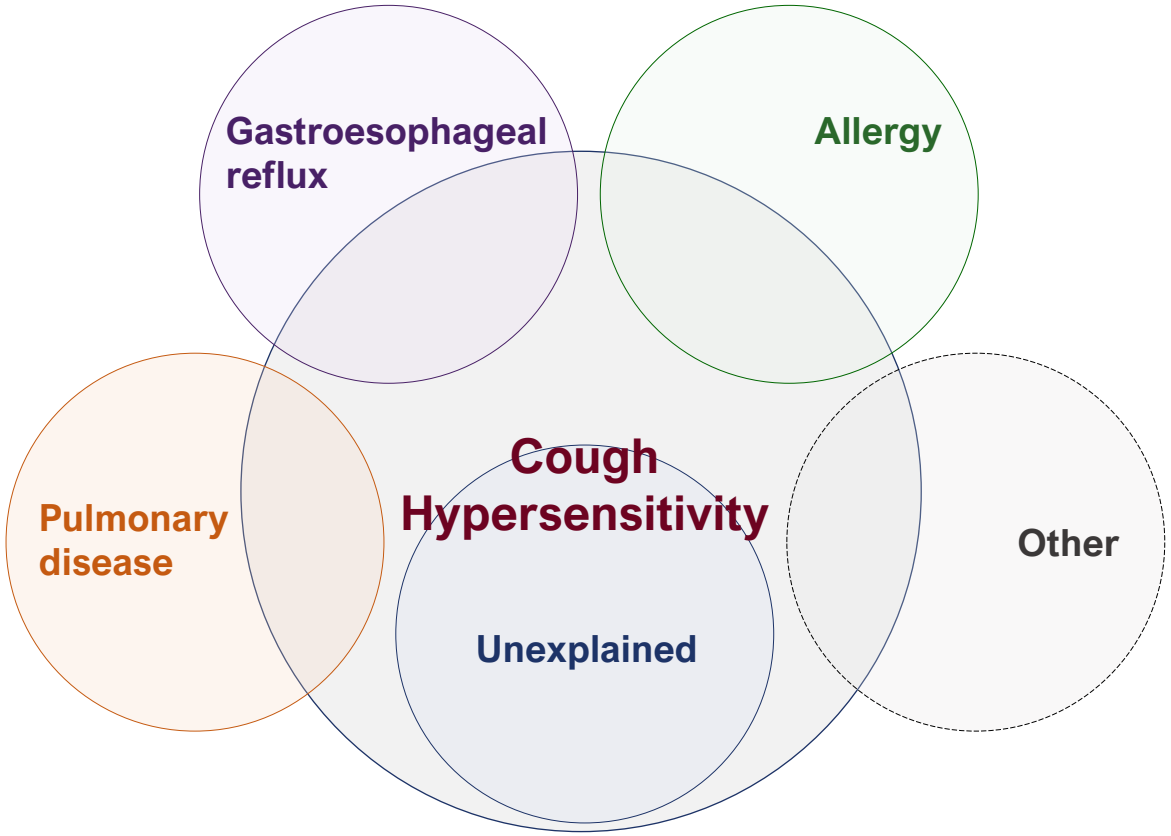
The presenter is a fulltime employee of Bellus Health Inc.

Bellus HEALTH

Cough hypersensitivity in chronic cough

- Refractory or Unexplained Chronic Cough (RCC) is often associated with hypersensitization of the cough reflex[1-3]
- One of the key mediators of this sensitization is the P2X3 ATP-gated ion channel[4]
- P2X3 antagonists are being investigated for the treatment of cough hypersensitivity in RCC

Cough hypersensitivity overlaps with common etiologies of chronic cough



1. Chung et al. (2013) Lancet Resp. Med. 1(5) 414-22. 2. Morice et al. (2014) Eur. Resp. J. 44(5) 1132-48. 3. Song et al. (2017) Allerg. Asthma Immun. Res. 9(5) 394-402
4. Ford et al. (2014) Front Cell Neurosci 19(7) 267.

BLU-5937: a selective P2X3 antagonist

BLU-5937 is being investigated for the treatment of RCC

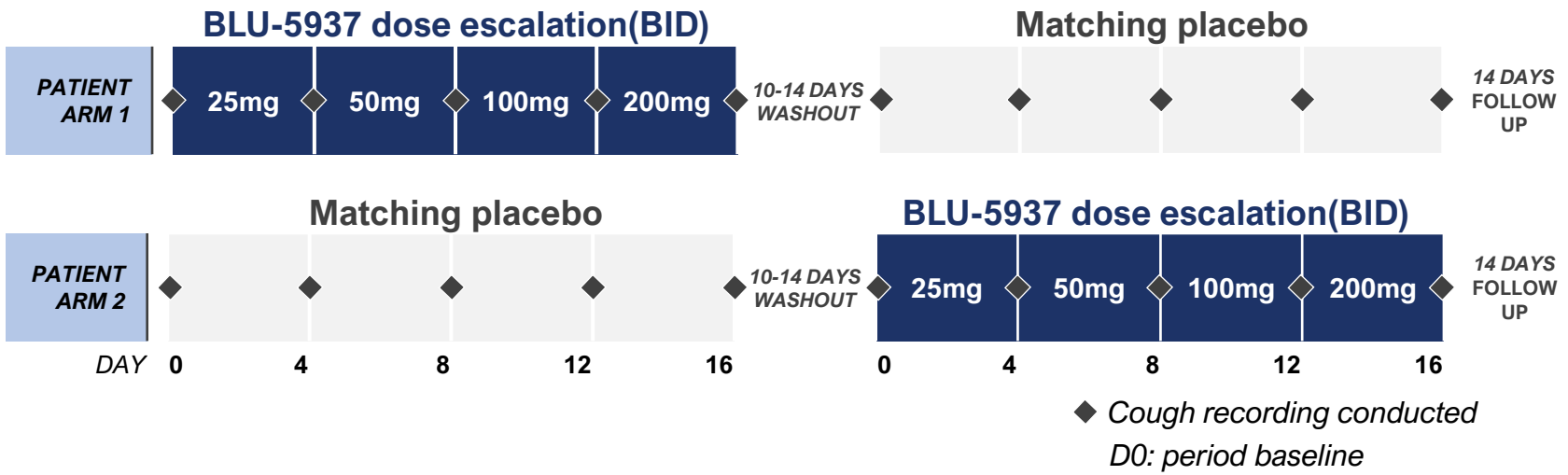
- Potent, non-competitive blocker of the P2X3 receptor
- >1500-fold selectivity for hP2X3 over hP2X2/3[1]
- Good oral bioavailability and does not cross blood-brain barrier
- Linear PK and BID dosing[2]
- No significant food interaction[2]
- Eliminated primarily through hepatic metabolism[2]

1. Garceau et al. (2019) Pulm Pharmacol Ther. 56:56-62. 2. Garceau et al. (2019) Am. J. Resp Crit Care Med. 199 A7395 P556

The RELIEF Study

A Randomized, Double-blind, Placebo-Controlled, Crossover, Dose Escalation Study of BLU-5937 in Subjects with Unexplained or Refractory Chronic Cough

- The proof of concept, phase 2, RELIEF study (NCT03979638) assessed the safety, tolerability and efficacy of BLU-5937 in adult subjects with refractory or unexplained chronic cough
- Two-period placebo-controlled crossover with doses of 25, 50, 100 and 200 mg BID, with forced dose escalation every 4 days
- Primary endpoint: placebo-adjusted change in awake cough frequency



Bellus HEALTH

Cough frequency as a marker of response to P2X3 antagonism

Why focus on cough frequency?

- *Cough hypersensitivity has been shown to be associated with higher cough frequencies*[1-3]
- *Previous studies with a P2X3 antagonist had reported a statistically significant interaction between the cough frequency at baseline and treatment effect*[4-6]

Cough frequency in RELIEF

- **Key inclusion criteria**
  - Awake cough frequency ≥ 10 coughs/h at screening
- **Prespecified analyses**
  - Assessment of an interaction between baseline cough frequency and treatment effect
  - Assessment of efficacy in two subgroups defined by baseline awake cough frequency:
    - ≥ or < baseline median (32.4 coughs/h)
    - ≥ or < 20 coughs/h

Bellus HEALTH

1. Kelsall et al. (2009) Thorax 64(5): 393-8 2. Decalmer et al. (2007) Thorax 62(4): 329-34 3. Birring et al. (2006) Resp Med. 100(6): 1105-9
4.Abdulqawi et al. (2015) Lancet 385(9974):1198-205. 5. Smith et al. (2020) Eur Respir J . 55(3):1901615. 6. Ishihara et al. (2020) Eur Respir J 56: Suppl. 64, 2271

Baseline characteristics

Demographics and baseline characteristics of safety set and prespecified subgroups in RELIEF[1]

	Safety set	32 coughs/h		20 coughs/h	
		≥	<	≥	<
n *(% of ITT population)*	68 (100%)	34 (50%)	34 (50%)	54 (79%)	14 (21%)
Sex *m/f, n (%)*	10/58 (15/85%)	1/33 (3/97%)	9/25 (27/73%)	6/48 (11/89%)	4/10 (29/71%)
Age*, years - mean (SD)*	64.0 (10.5)	65.4 (8.5)	62.6 (12.2)	65.0 (9.3)	60.2 (14.3)
BMI*, Kg/m^2 – mean (SD)*	28.8 (6.1)	28.4 (6.6)	29.2 (5.6)	28.2 (5.9)	31.0 (6.5)
FEV$_1$/FVC*, %*	73.7 (7.4)	71.5 (6.6)	76 (7.7)	72.5 (6.7)	78.7 (8.6)
Cough Duration*, years – mean (SD)*	14.7 (9.9)	17.4 (11.2)	12.1 (7.7)	16.1 (10.3)	9.6 (6.2)
Leicester Cough Questionnaire - mean score (SD)	**10.7 (3.4)**	**10.1 (3.5)**	**11.3 (3.2)**	**10.2 (3.3)**	**12.6 (3.1)**
Cough Severity VAS - mean (SD)	**71.1 (17.9)**	**78.6 (15.4)**	**63.6 (17.3)**	**72.8 (16.8)**	**64.6 (21.2)**

- Burden of cough is moderately higher in higher frequency subgroups but still significant in lower frequency subgroups

1. Birring et al. (2021) Am J Respir Crit Care Med 203:A2357

Change in awake cough frequency in ITT and pre-specified subgroups

- In the ITT, differences favored BLU-5937 at all doses, but did not achieve statistical significance over placebo at any dose
- BLU-5937 showed statistically significant and clinically meaningful reductions in cough frequency in populations with baseline awake cough frequency ≥ 20 coughs/h

Placebo-adjusted awake cough frequency change from baseline[1]

ITT

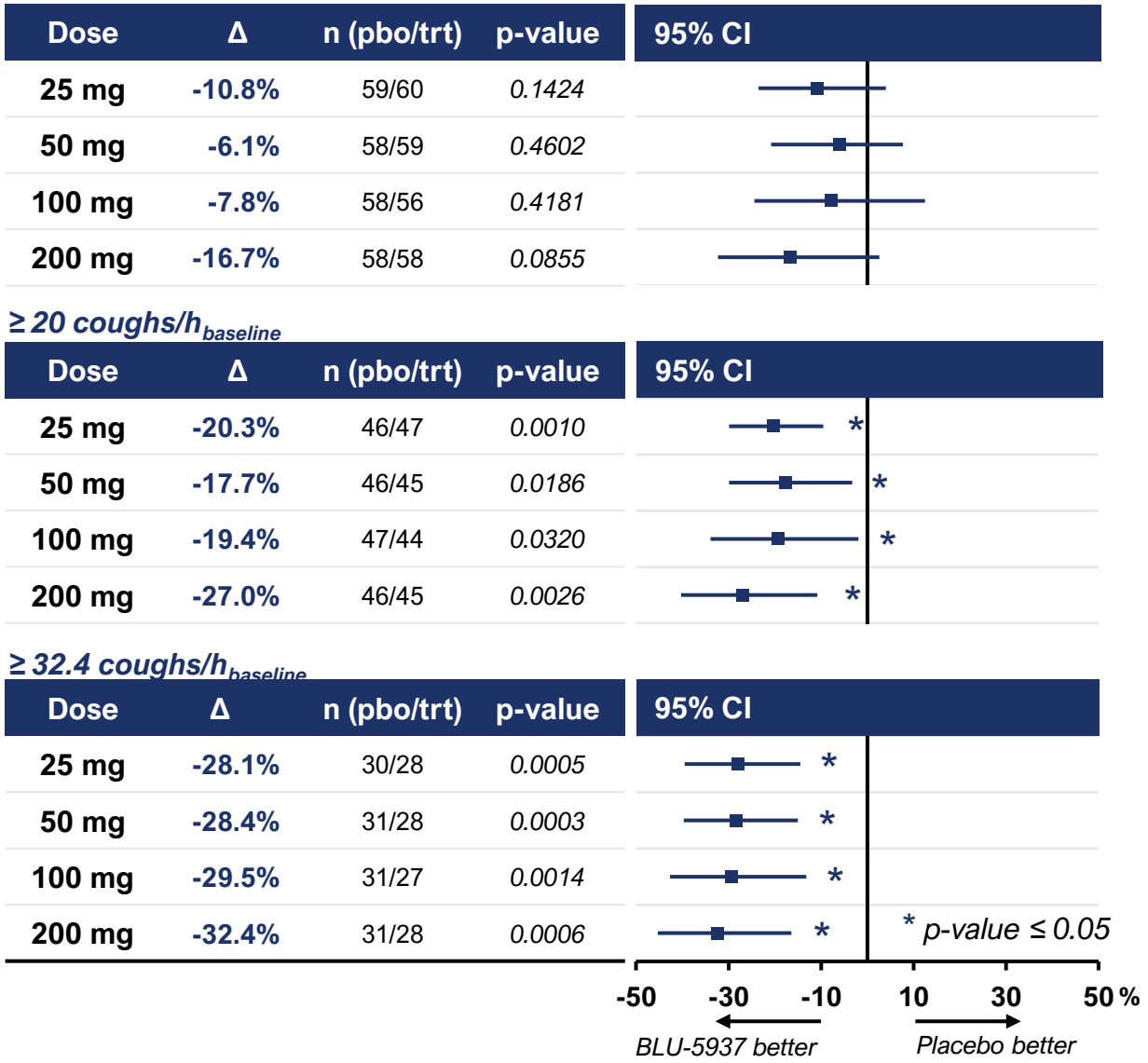
Dose	Δ	n (pbo/trt)	p-value
25 mg	-10.8%	59/60	*0.1424*
50 mg	-6.1%	58/59	*0.4602*
100 mg	-7.8%	58/56	*0.4181*
200 mg	-16.7%	58/58	*0.0855*

≥ 20 coughs/h$_{baseline}$

Dose	Δ	n (pbo/trt)	p-value
25 mg	-20.3%	46/47	*0.0010*
50 mg	-17.7%	46/45	*0.0186*
100 mg	-19.4%	47/44	*0.0320*
200 mg	-27.0%	46/45	*0.0026*

≥ 32.4 coughs/h$_{baseline}$

Dose	Δ	n (pbo/trt)	p-value
25 mg	-28.1%	30/28	*0.0005*
50 mg	-28.4%	31/28	*0.0003*
100 mg	-29.5%	31/27	*0.0014*
200 mg	-32.4%	31/28	*0.0006*



1. Smith et al. (2021) Am J Respir Crit Care Med 203:A1019

Change in 24-hour cough frequency in ITT and pre-specified subgroups

- In the same subgroups, similar reductions were observed in awake and 24-hour cough frequencies

Placebo-adjusted 24-hour cough frequency change from baseline

ITT

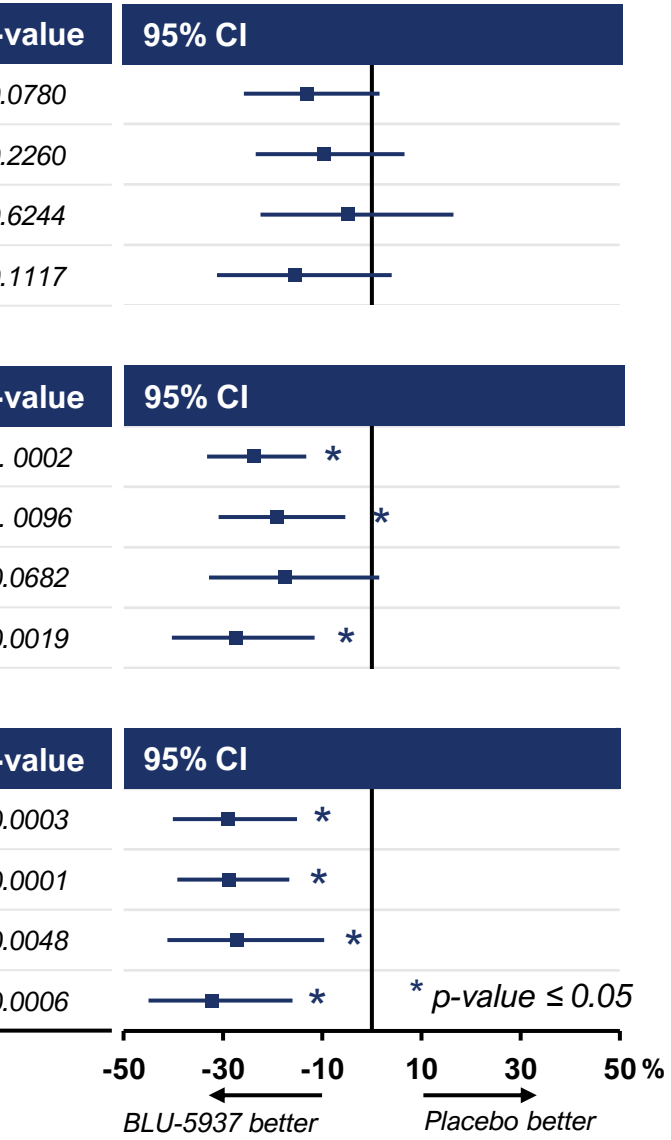
Dose	Δ	n (pbo/trt)	p-value
25 mg	-13.2%	59/60	*0.0780*
50 mg	-9.6%	58/59	*0.2260*
100 mg	-4.9%	58/56	*0.6244*
200 mg	-15.4%	58/58	*0.1117*

≥ 20 coughs/h$_{baseline}$

Dose	Δ	n (pbo/trt)	p-value
25 mg	-23.8%	46/47	*0. 0002*
50 mg	-19.1%	46/45	*0. 0096*
100 mg	-17.4%	47/44	*0.0682*
200 mg	-27.3%	46/45	*0.0019*

≥ 32.4 coughs/h$_{baseline}$

Dose	Δ	n (pbo/trt)	p-value
25 mg	-29.0%	30/28	*0.0003*
50 mg	-28.8%	31/28	*0.0001*
100 mg	-27.1%	31/27	*0.0048*
200 mg	-32.1%	31/28	*0.0006*



1. Smith et al. (2021) Am J Respir Crit Care Med 203:A1019

Safety and tolerability of BLU-5937

*Study Treatment Emergent Adverse Events**	Placebo (N=61)	BLU-5937 (N=61)
n of subjects (%) with TEAEs	**41 (67.2%)**	**42 (68.9%)**
Serious TEAEs	**0**	**0**
Most Common TEAEs (≥5% of subjects)		
Headache	7 (11.5%)	6 (9.8%)
Back pain	6 (9.8%)	5 (8.2%)
Dysgeusia	2 (3.3%)	5 (8.2%)
Diarrhea	3 (4.9%)	4 (6.6%)
URTI	3 (4.9%)	4 (6.6%)
Dizziness	2 (3.3%)	4 (6.6%)
Oropharyngeal pain	0	3 (4.9%)

AEs of special interest*	Placebo (N=61)	BLU-5937 (N=61)
n of Subjects (%) with taste disturbance events		
Taste disturbances (total) **	**3 (4.9%)**	**6 (9.8%)**
Dysgeusia	2 (3.3%)	5 (8.2%)
Hypogeusia	1 (1.6%)	2 (3.3%)
Ageusia	0	0
n of Subjects (%) with other AEs of special interest		
Oral Paresthesia	1 (1.6%)	1 (1.6%)
Oral Hypoesthesia	0	1 (1.6%)

* *Events which started during one period and continued into another are counted in both*

** *One subject reported both dysgeusia & hypogeusia during the same period at all dose levels*

- No dose-related pattern of AEs or TDAEs was seen
- There were no discontinuations for taste disturbance
- No treatment-related serious adverse events were reported
  - One non-related serious adverse event was reported after the study was completed (colorectal cancer, 5 months after patient's last visit)
- There were no clinically significant effects on vital signs, ECG, or laboratory measures

Bellus HEALTH

Learnings from RELIEF on RCC trial design

- Selection of patients with high likelihood of cough hypersensitivity is key to assessing the efficacy of P2X3 antagonists
  - *Cough frequency at baseline is correlated with treatment response*
  - *Enrichment for higher cough frequency at baseline is a key strategy for patient selection*

- In RELIEF, patients above an awake cough frequency of at least **20 coughs per hour** at baseline experienced better response to P2X3 antagonism
  - *Suggests that the percentage of patients with cough hypersensitivity may be enriched above these CFs*
  - *Patients below this threshold also reported a high burden of cough and may also benefit from treatment*

- Reductions in awake and 24-hour cough frequency were highly correlated, and showed similar shifts in treatment effect in higher cough frequency subgroups
  - *Enriching refractory chronic cough populations based on awake cough frequency at baseline is a valid approach in clinical trials using 24-hour cough frequency as primary outcome*

SOOTHE: a phase 2b design in a population enriched for cough frequency

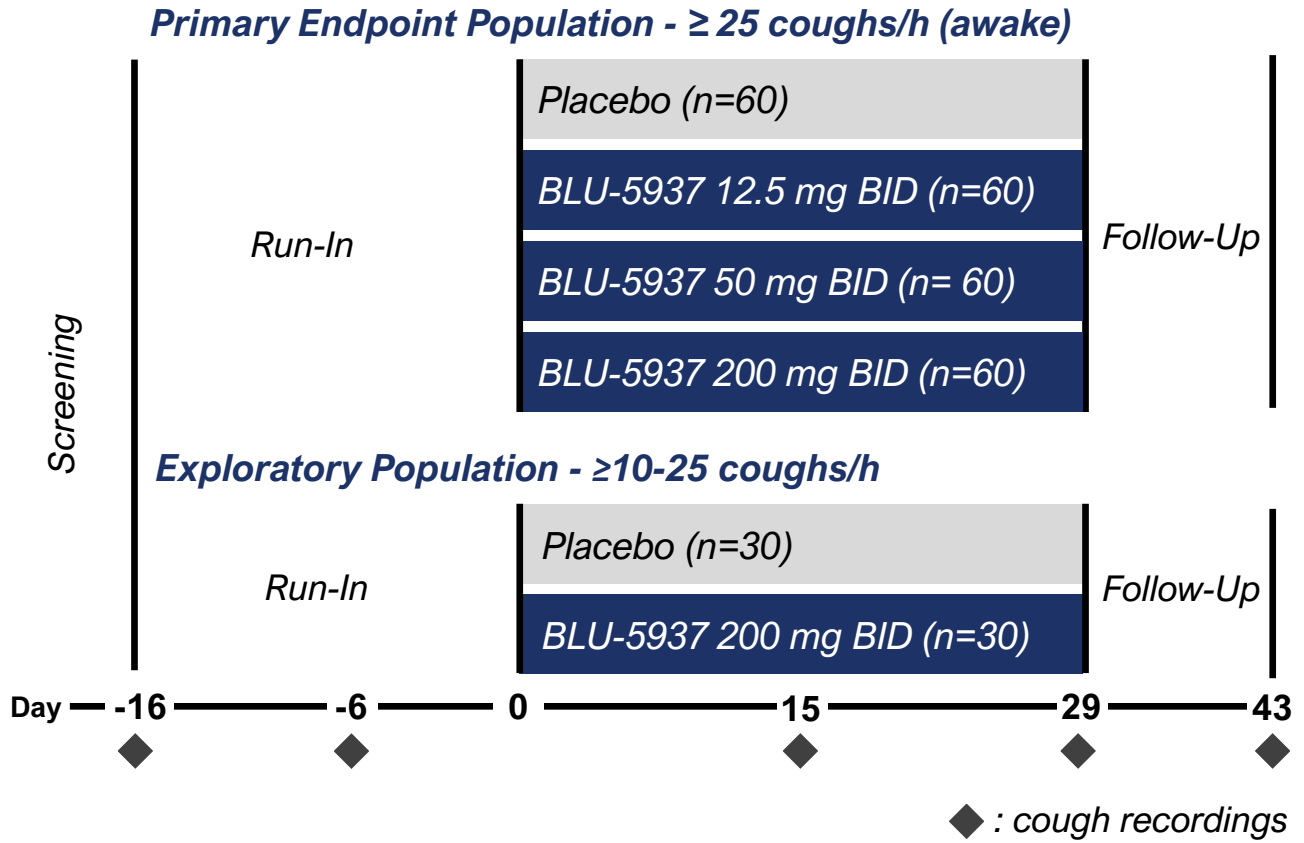
- SOOTHE (NCT04678206) is a multi-center phase 2b, randomized, placebo-controlled, parallel-arm dose-finding study in participants diagnosed with RCC for ≥1 year.

Primary endpoint population

- ≥ 25 coughs/h

Exploratory population

- ≥10-25 coughs/h



1. Bonuccelli et al. (2021) Am J Respir Crit Care Med 203:A2356

SOOTHE: a phase 2b design enriched for cough frequency

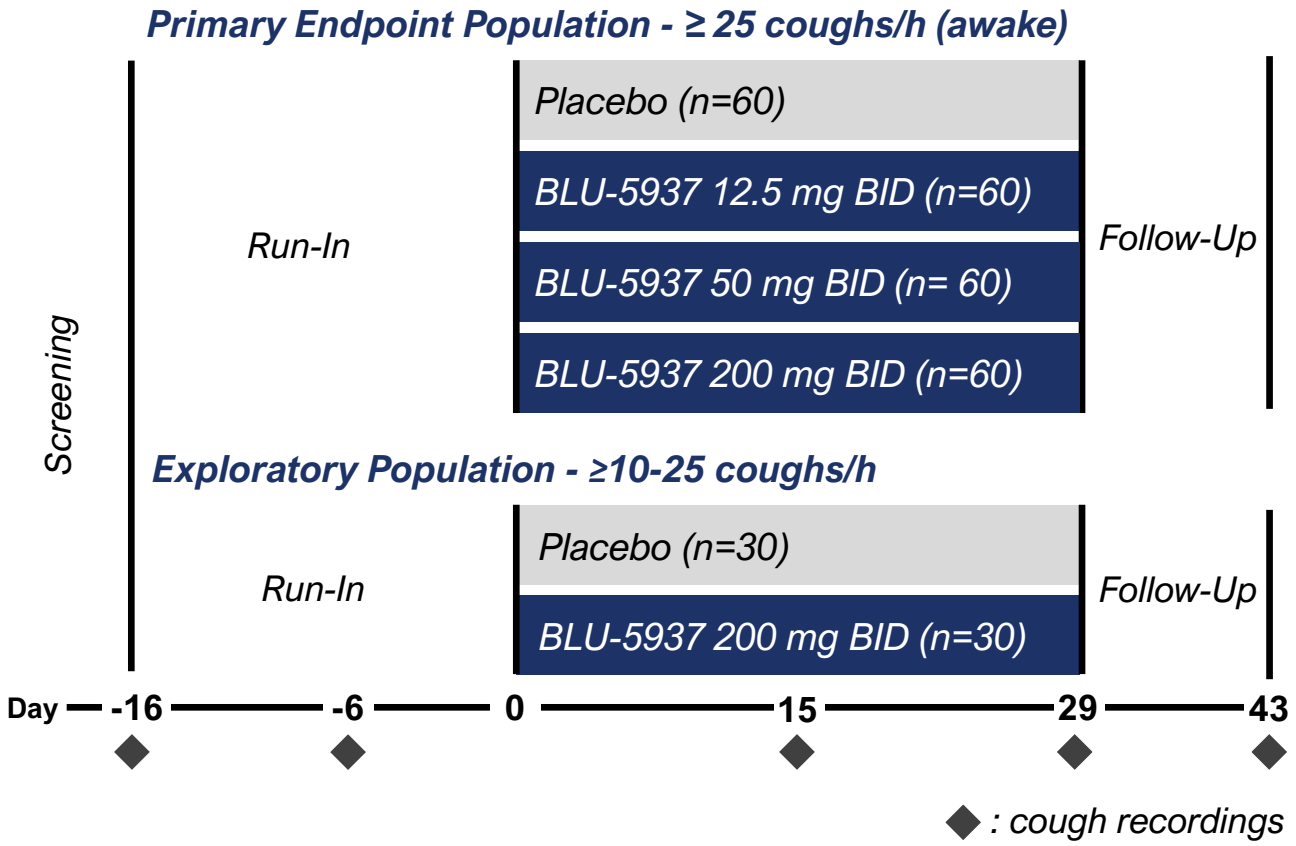
- SOOTHE (NCT04678206) is a multi-center phase 2b, randomized, placebo-controlled, parallel arm dose-finding study in participants diagnosed with RCC for ≥1 year.

Primary efficacy endpoint

- Change from baseline in 24-hour cough frequency

Secondary endpoints

- Change from baseline in awake cough frequency
- Change from baseline in nighttime cough frequency
- Change from baseline in LCQ score
- Change from baseline in Cough Severity VAS
- Patient Global Impression of Change



1. Bonuccelli et al. (2021) Am J Respir Crit Care Med 203:A2356

Conclusions

- Building on the findings from RELIEF, the SOOTHE trial assesses the safety and efficacy of 3 doses of BLU-5937 in an enriched RCC population

- The design of SOOTHE incorporates elements intended to help address key challenges in RCC trials, including
  - Influence of the baseline cough frequency on the treatment effect
  - Placebo response

- Results from the SOOTHE trial will help determine optimal therapeutic dose(s) of BLU-5937 to support the design of future RCC clinical trials