Development of BLU-5937 for the Treatment of Refractory Chronic Cough

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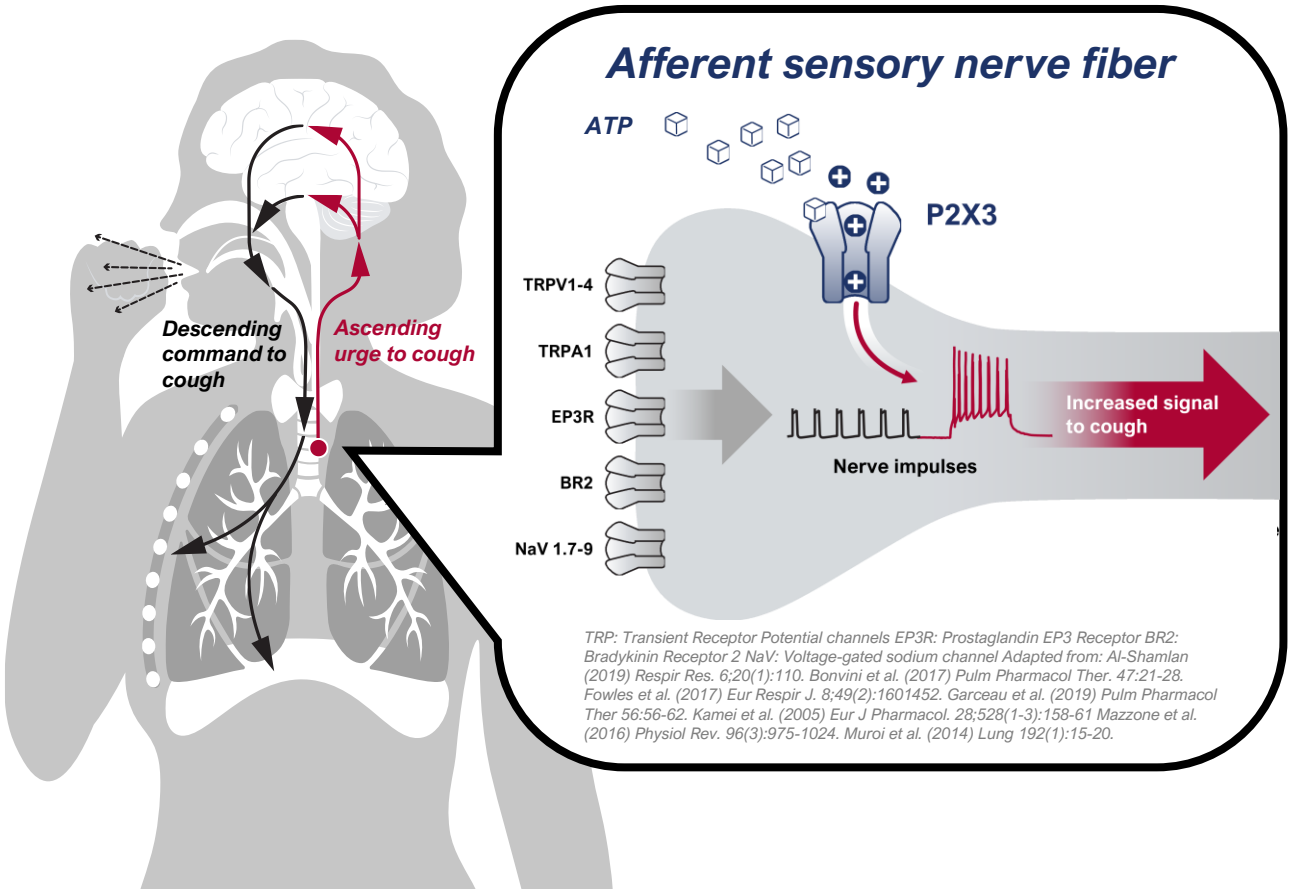
Refractory Chronic Cough

Refractory Chronic Cough

- Cough lasting ≥ 8 weeks that does not respond to treatment for associated diseases or without associated disease identified[1]
- Current treatment options are not approved by the FDA and suffer from undesirable side effects or the risk of addiction[2]
- Hypersensitization of cough signaling pathways, including the P2X3 receptor, is thought to play a key role in RCC[3]
- P2X3 antagonists have shown promise in RCC clinical trials[4]
  - Identification of optimal population, management of the placebo effect and high incidence of taste disturbance have presented challenges

Model Of P2X3 In Cough Signaling



TRP: Transient Receptor Potential channels EP3R: Prostaglandin EP3 Receptor BR2: Bradykinin Receptor 2 NaV: Voltage-gated sodium channel Adapted from: Al-Shamlan (2019) Respir Res. 6;20(1):110. Bonvini et al. (2017) Pulm Pharmacol Ther. 47:21-28. Fowles et al. (2017) Eur Respir J. 8;49(2):1601452. Garceau et al. (2019) Pulm Pharmacol Ther 56:56-62. Kamei et al. (2005) Eur J Pharmacol. 28;528(1-3):158-61 Mazzone et al. (2016) Physiol Rev. 96(3):975-1024. Muroi et al. (2014) Lung 192(1):15-20.

1. Irwin RS et al, (2018) CHEST 153 (1): 196-209. 2. Ryan NM, (2018) Expert Opin Pharmacother 19(7): 687-711. 3. Chung et al. (2016) Lancet Respir Med. 2016 Dec;4(12):934-935. 4. Abdulqawi et al. (2015) Lancet 385(9974):1198-205.

BLU-5937: A Highly Selective P2X3 Antagonist

- High potency for the human P2X3 receptor (IC50 = 15 nM*)
- High selectivity for human P2X3 vs human P2X2/3 (1500 X)[1]
- No evidence of food interaction[2]
- No evidence of blood brain barrier permeability[1]
- Linear pharmacokinetic profile over range studied to date

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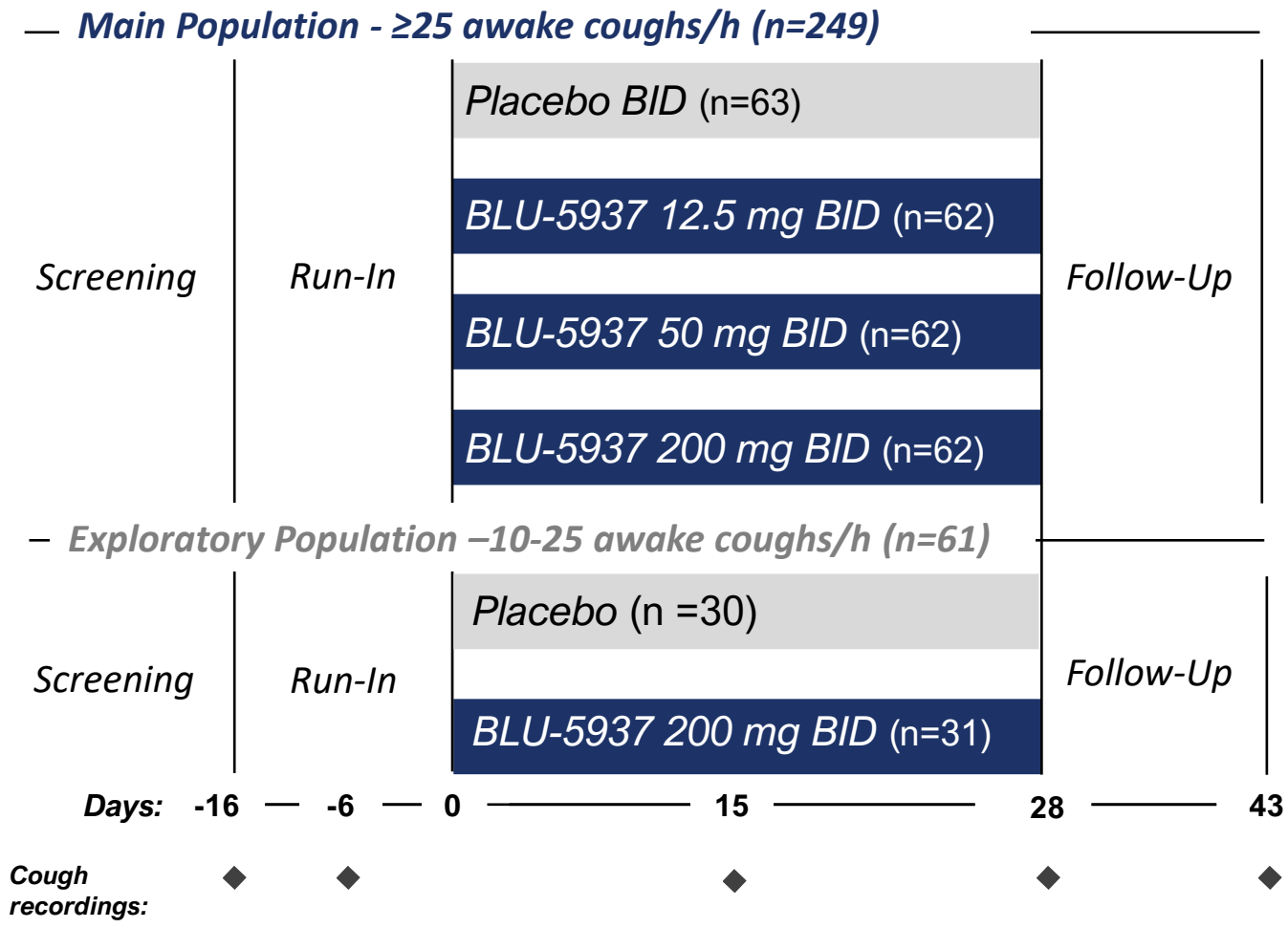
* Calculated from nine replicate experiments (FLIPR-Ca assays) conducted between 2019-2021

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

SOOTHE Phase 2b Trial

SOOTHE Trial *(NCT04678206)*

- Randomized, double-blind, placebo-controlled parallel arm dose finding study
- Primary endpoint: change in objective cough frequency*
- Main population enrolled:
  - Refractory chronic cough for ≥1 year
  - Cough Severity VAS ≥40 mm
  - Screening / baseline awake cough frequency: ≥25 coughs/h
- Exclusion
  - Diagnosis of COPD, bronchiectasis, IPF
  - FEV1/FVC < 60%
  - Prohibited medications
    - *Anti-tussive therapy*
    - *Gabapentin, pregabalin, baclofen, tricyclics*
    - *Systemic corticosteroids*
    - *ACE inhibitors*



* *Measured over a 24H period in the main population, calculated as the log-transformed geometric means ratio*

Learnings From Previous Trials in RCC For The SOOTHE Design

Use of cough frequency for patient selection

- In RELIEF and other early trials of P2X3 antagonists, an interaction between baseline cough frequency and treatment effect was observed[1-4]
- Cough sensitivity has been shown to be associated with higher cough frequencies[5-7]

Placebo response in cough clinical trials

- High and variable placebo responses have been observed in refractory chronic cough trials[8-10]
- In RELIEF, higher placebo responses were observed in participants with lower cough frequencies[4]

1.Abdulqawi et al. (2015) Lancet 385(9974):1198-205. 2. Smith et al. (2020) Eur Respir J . 55(3):1901615. 3. Ishihara et al. (2020) Eur Respir J 56: Suppl. 64, 2271 4. Smith J et al. (2021) AJRCCM 203:A1019 5. Kelsall et al. (2009) Thorax 64(5): 393-8 6. Decalmer et al. (2007) Thorax 62(4): 329-34 7. Birring et al. (2006) Resp Med. 100(6): 1105-9 8. McGarvey et al. (2022) Lancet 399(10328):909-923. 9. Niimi et al. (2022) Eur Respir J 59(6):2100725. 10. Morice et al. (2021) *Eur Respir J* 58(5):2004240.

SOOTHE Baseline Characteristics

- The Main Population randomized in SOOTHE was representative of RCC
- Demographics and clinical characteristics were generally well-balanced across arms

		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/m^2), 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

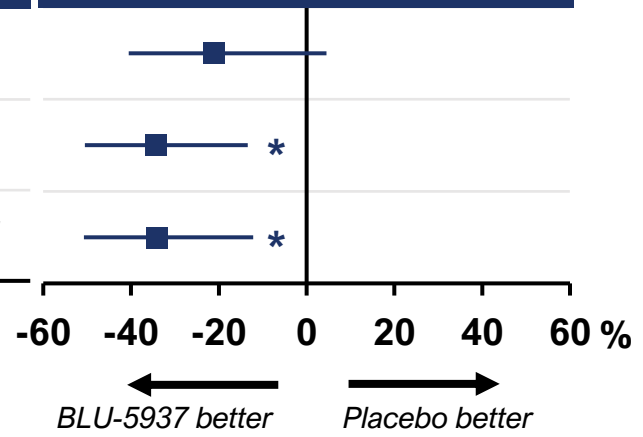
SOOTHE Primary Efficacy Endpoint
Placebo-Adjusted Change From Baseline in 24H Cough Frequency

- Statistically significant reductions in placebo-adjusted change in 24H cough frequency
  - *Reductions of 34% at 50 and 200 mg BID doses*
- Reduction in cough frequency from baseline of 53% for 50 and 200 mg BID doses at D28
- Dose response established between 12.5 mg and 50 mg BID
  - *Similar treatment effect between 50 mg and 200 mg is in line with previous results from the RELIEF phase 2a trial*

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

Main Population (n=249)

Dose	Δ	p-value	95% CI
12.5 mg	-21.1%	0.098	
50 mg	-34.4%	0.003	*
200 mg	-34.2%	0.005	*



*** p ≤ 0.005; 2-sided***

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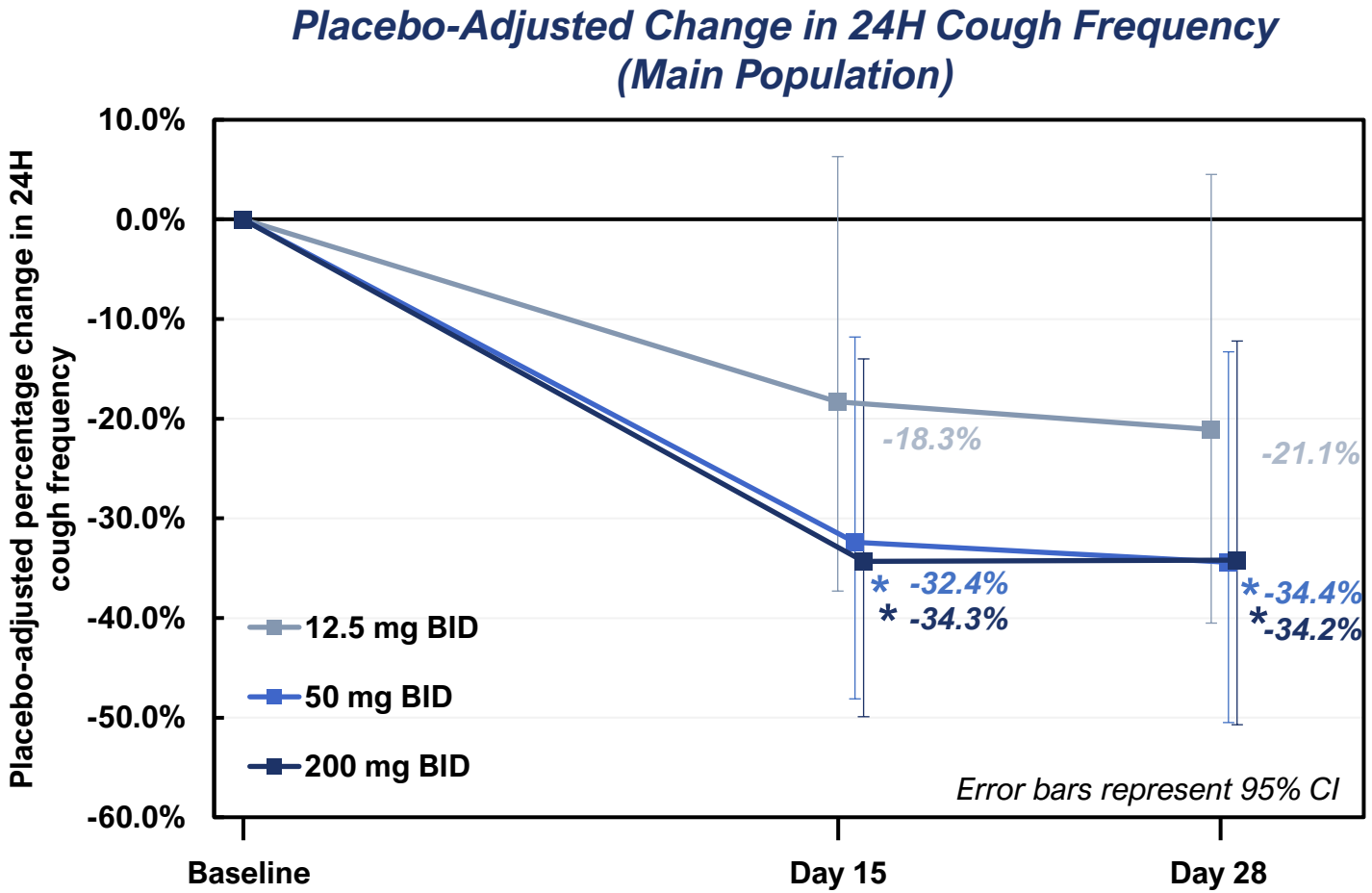
SOOTHE Primary Efficacy Endpoint
Placebo-Adjusted Change From Baseline in 24H Cough Frequency

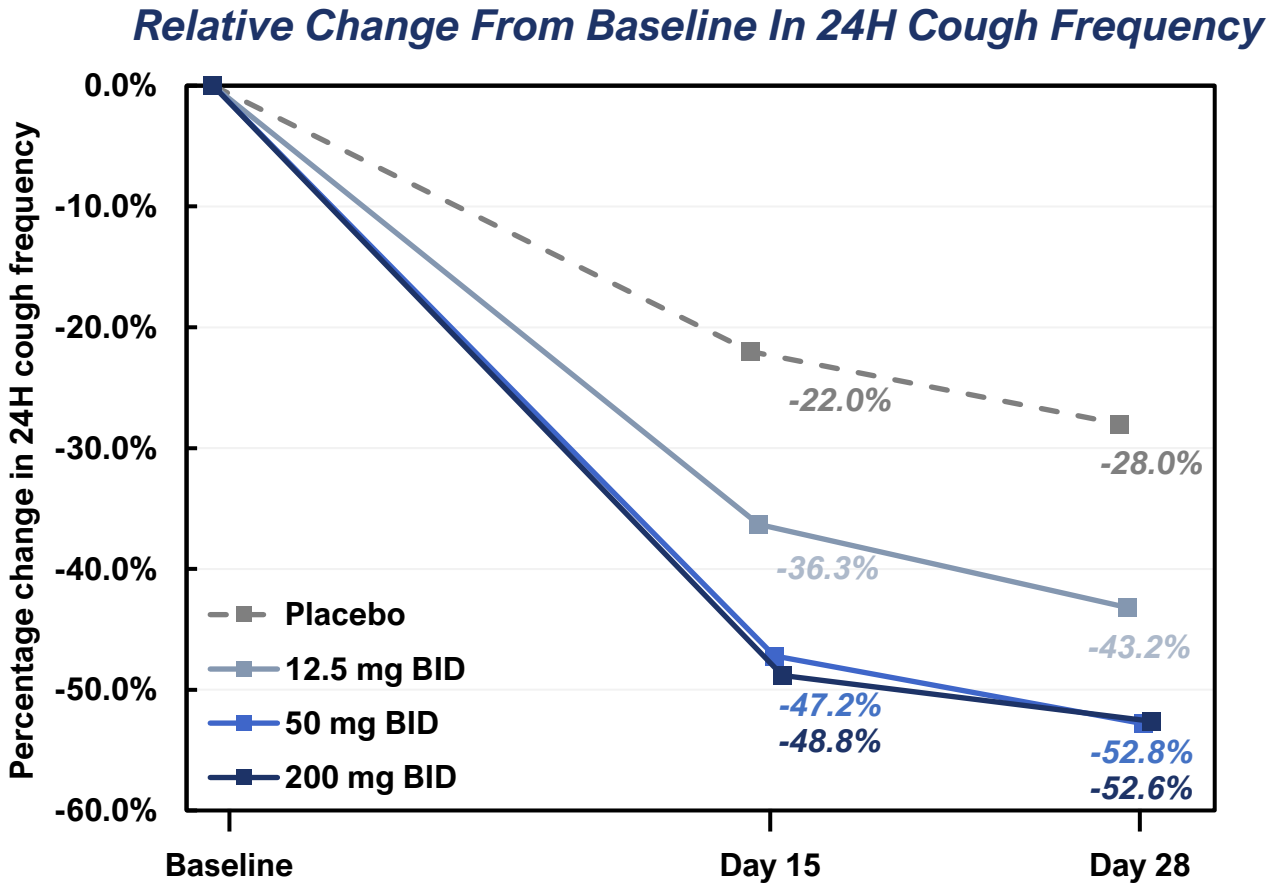
- Significant reductions observed as early as D15
- Rapid reductions from baseline in cough frequency sustained over 4 weeks



* $p \leq 0.005$, two-sided

SOOTHE Change From Baseline in 24H Cough Frequency

- D28: Reductions over placebo of 52.8% and 52.6% at 50 and 200 mg BID doses respectively
- Reduction in cough frequency from baseline of 28.0% in the placebo group



SOOTHE Dose-Finding Trial: BLU-5937 Dose Response

SOOTHE *(NCT04678206)*

- Dose response observed between 12.5 and 50 mg BID
- No dose response between 50 and 200 mg BID

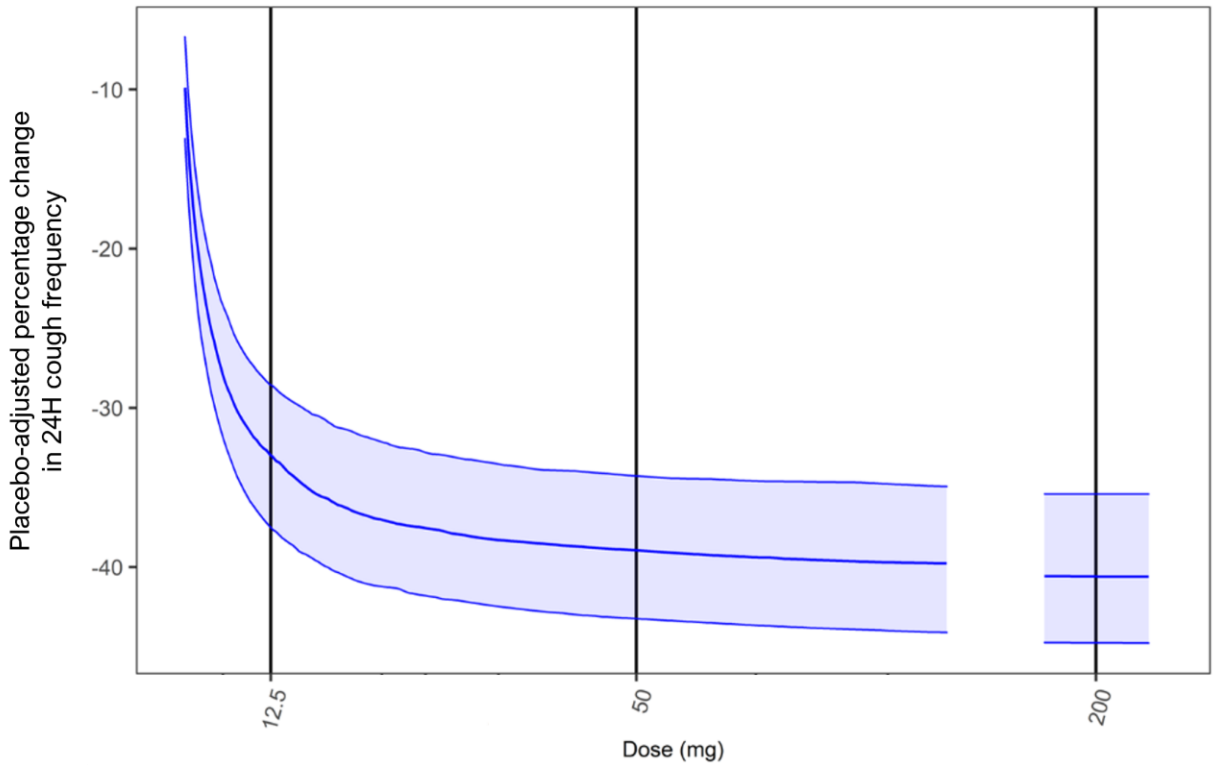
RELIEF *(NCT03979638)*

- No dose response between 25 and 200 mg BID in forced dose escalation phase 2a trial

DOSE RESPONSE MODELLING

- PD modelling of response based on SOOTHE data
- Confirms dose response between 12.5 and 50 mg BID
- Percent of maximum effect:
  - 91.3% for 25 mg BID
  - 96.3% for 50 mg BID

Model-Predicted Relative Change From Baseline In 24H Cough Frequency After Multiple BLU-5937 BID dosing

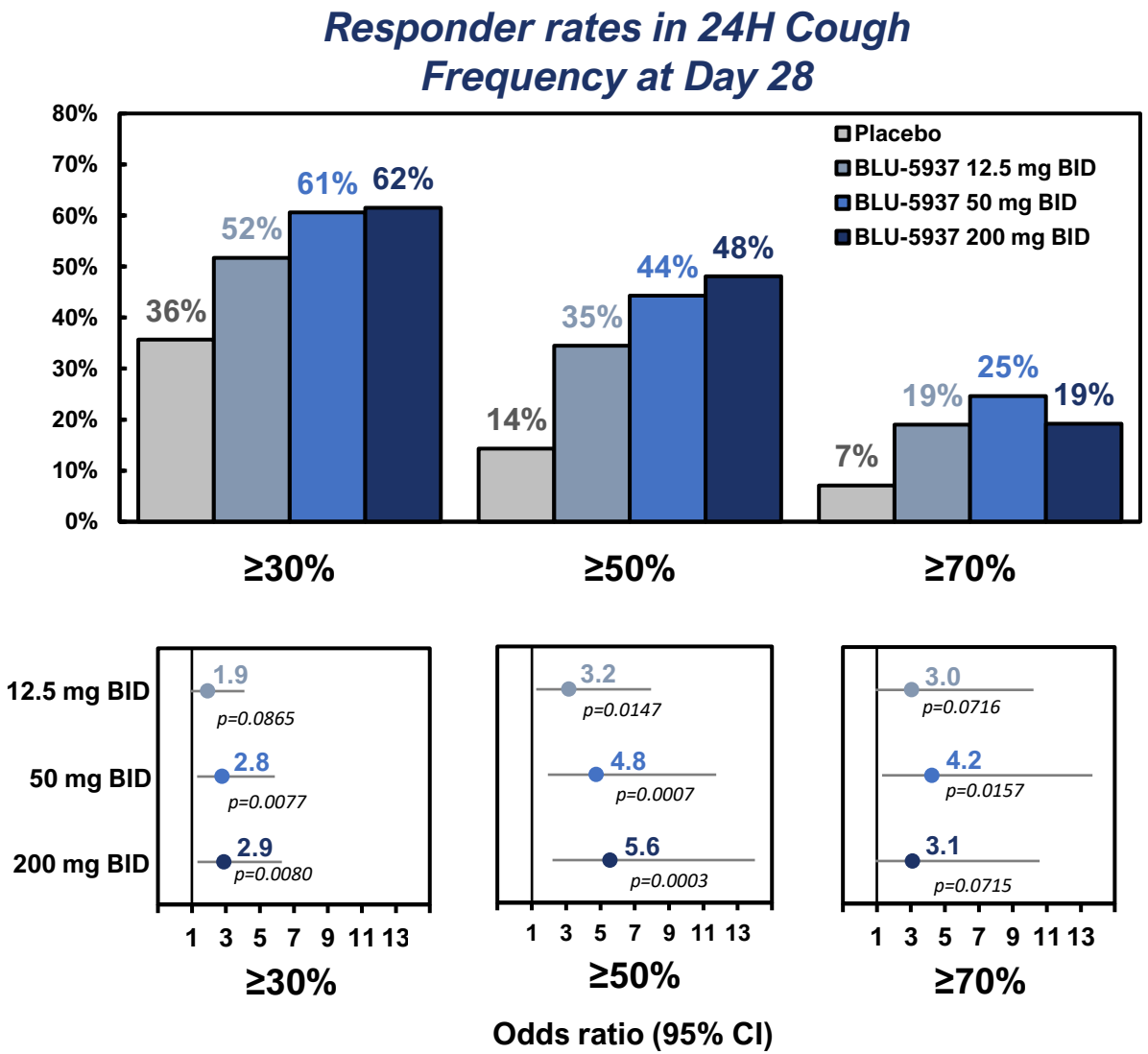


Responder Rates In 24H Cough Frequency

- A greater proportion of participants experienced at least 30%, 50% or 70% reduction in 24H cough frequency when treated with BLU-5937 than with placebo

- D28: odds ratios for achieving a clinically meaningful cough frequency reduction numerically favored treatment at every dose of BLU-5937 over placebo

- Participants treated with BLU-5937 are more likely to:
  - Experience a clinically meaningful change in cough frequency (30%)[1]
  - Experience more important reductions in cough (50, 70%)



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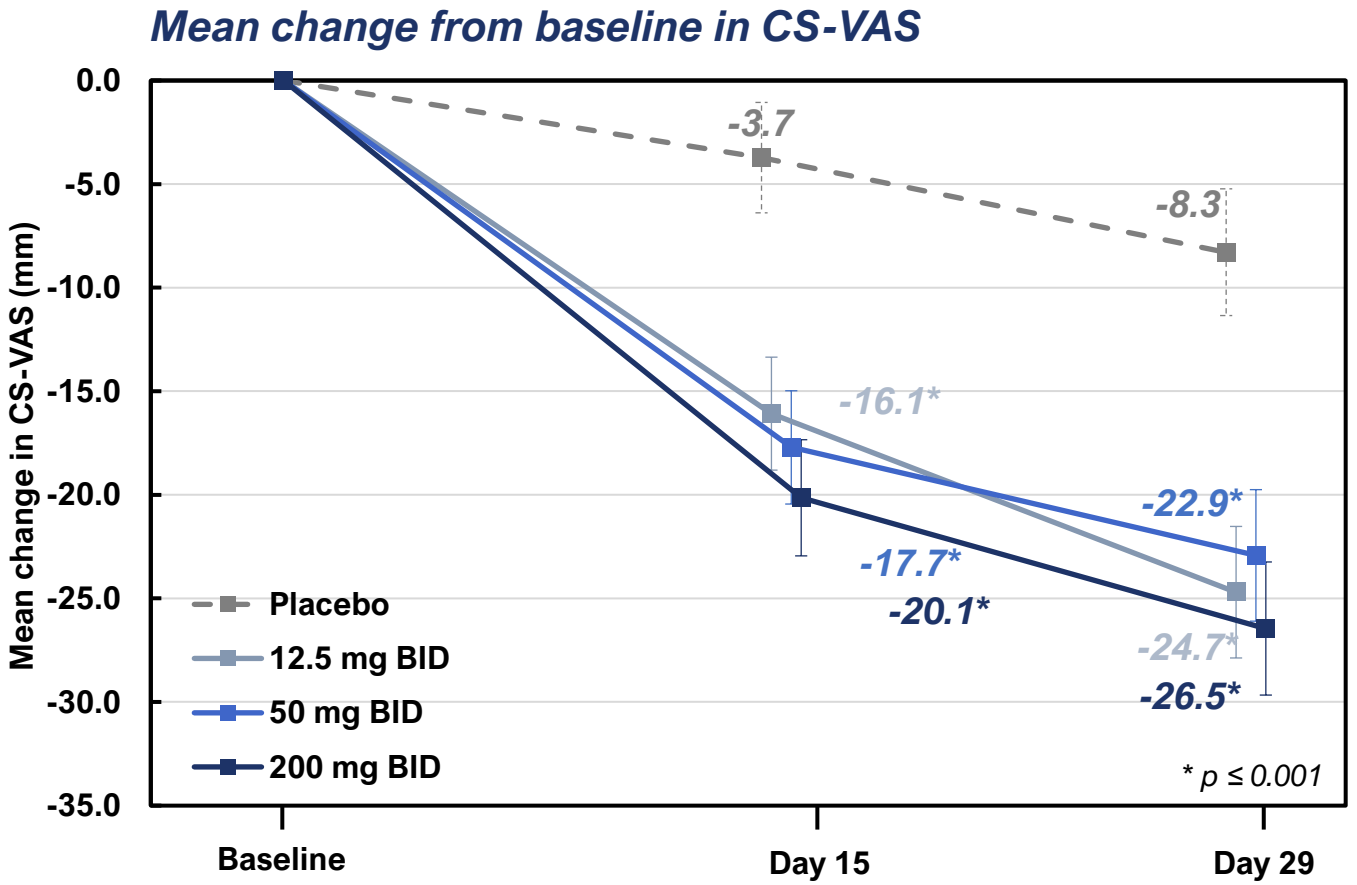
1. Nguyen et al. (2019) JACI 143(2) AB169:P516

Patient-Reported Outcomes: Cough Severity Visual Analog Scale

- Cough Severity Visual Analogue Scale (CS-VAS) scores range from 0 to 100mm: 0 mm representing no cough and 100 mm the worst imaginable cough.
- SOOTHE was not powered to observe a difference in CS-VAS.
- Clear separation from placebo ($p \leq 0.001$) as early as D15 at all doses.
- Highly statistically significant vs placebo reductions from baseline at all doses at D29



Error bars represent SE

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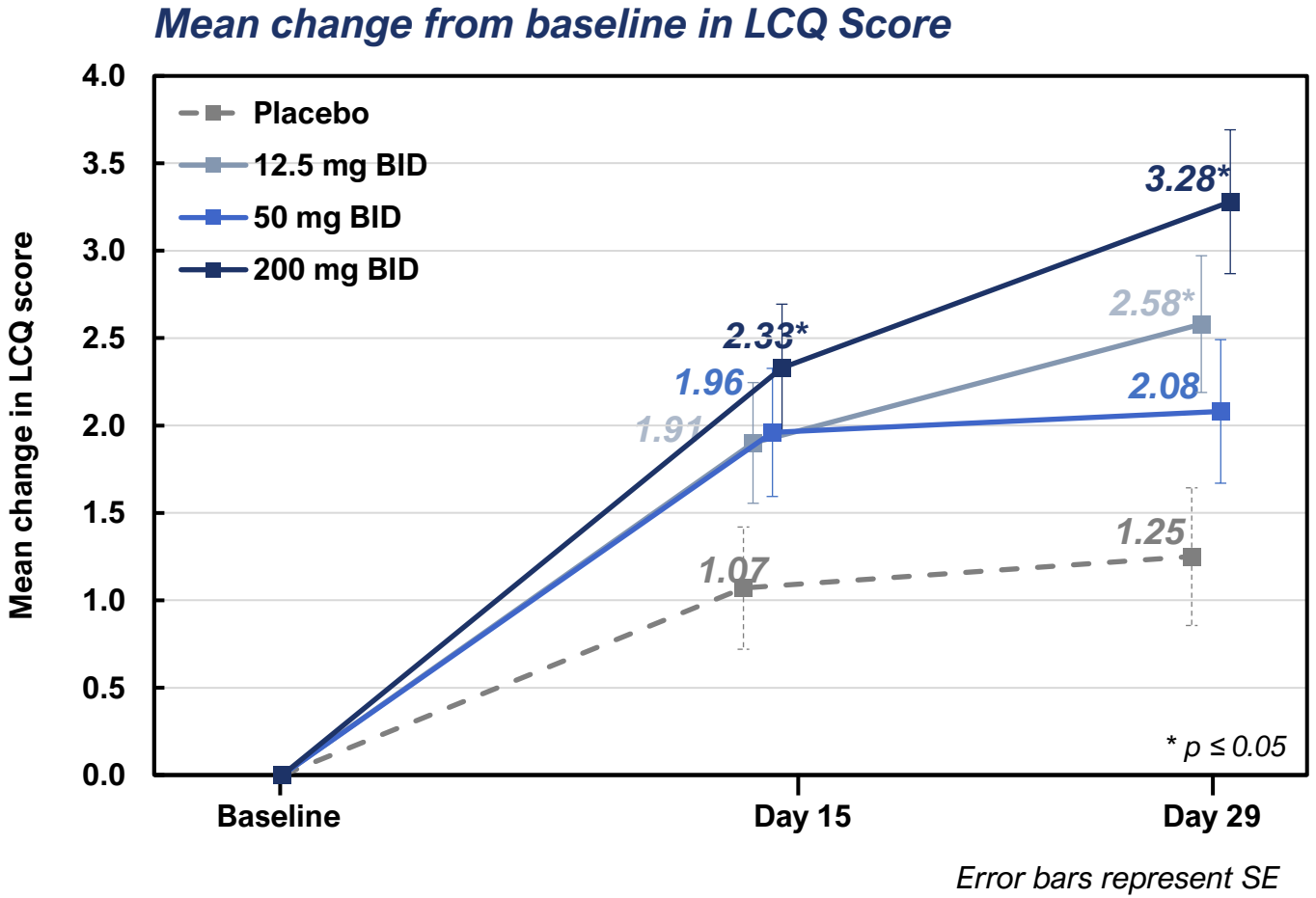
Patient-Reported Outcomes: Leicester Cough Questionnaire

- The Leicester Cough Questionnaire (LCQ) reflects the impact of cough on quality of life on a scale from 3 to 21
  - *Higher scores → better quality of life*
- SOOTHE was not powered to observe a difference in LCQ scores
- Significant difference from placebo for 200 mg BID at D15 and D29 and for 12.5 mg BID at D29



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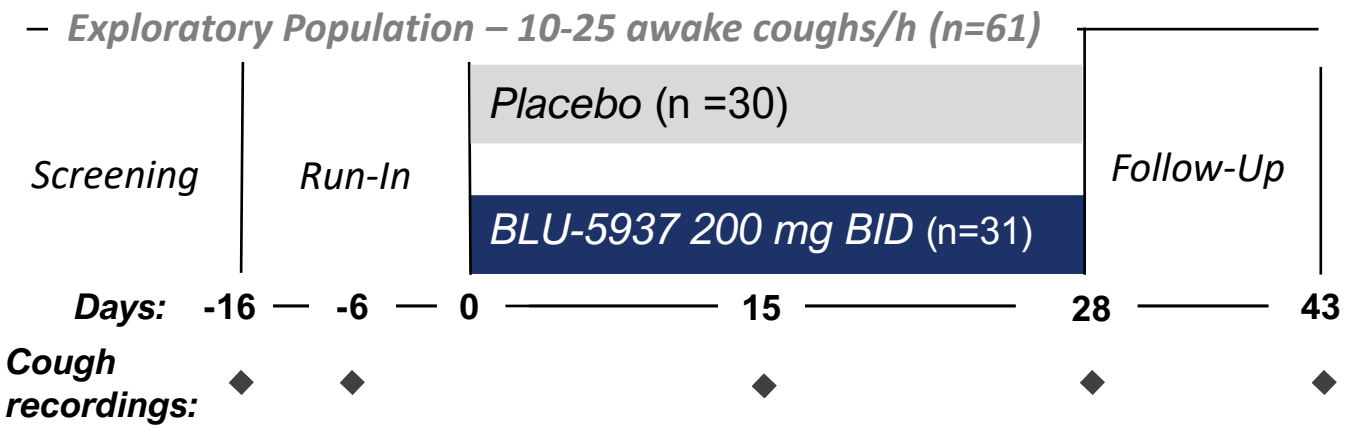
SOOTHE: Exploratory Population

- Exploratory analysis to generate additional data in a population with baseline cough frequency between 10 and 25 coughs/h
  - Not powered to observe a statistically significant response over placebo
  - 200 mg BID dose only
- Results in exploratory population:
  - No treatment effect of BLU-5937 (p=0.560)
  - Large placebo response and high variability
  - Statistical trend of interaction between baseline cough frequency and treatment effect (p= 0.077)



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SOOTHE: Safety And Tolerability

Overall Safety And Tolerability

- Similar incidence of treatment emergent adverse events (TEAE) reported for placebo and BLU-5937
- No treatment emergent serious adverse events (TESAE)
- One discontinuation on placebo and 2 discontinuations on BLU-5937 200 mg BID due to possibly-treatment related AEs*

Taste Disturbance Adverse Events

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

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

† No TEAE reported with an incidence ≥5% in the exploratory population
† † No TDAE reported in the exploratory population

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** As deemed by investigator. Placebo: worsening of cough; BLU-5937 200 mg BID: worsening of cough, dry mouth*

Conclusions

- SOOTHE demonstrated the efficacy of 3 doses of BLU-5937 as measured by objective cough monitoring and patient-reported outcomes in a population enriched for baseline cough frequency.
- BLU-5937 demonstrated a favorable safety and tolerability profile, with an incidence of reported taste disturbances ≤6.5%.
- Outcomes of the SOOTHE phase 2b trial support the continued development of BLU-5937 for the treatment of refractory chronic cough.