Results of RELIEF, a phase 2a study with BLU-5937 in refractory chronic cough

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Disclosures

The presenter is a fulltime employee of Bellus Health Inc.

BLU-5937 background

- BLU-5937 is a P2X3 antagonist with a high selectivity for P2X3 over P2X2/3 (>1500 fold)[1]
- Soluble, not predicted to cross blood-brain barrier, and low potential for drug-drug interactions
- Phase 1 showed linear PK at BID dosing and no food interaction[2]
- Eliminated primarily through hepatic metabolism (~20% renal)[2]
- Predicted receptor occupancy ≥ 85% for dosing of 50 mg BID and above[2]

Development of BLU-5937 was advanced to a phase 2a, proof-of-concept study in refractory chronic cough (RCC)

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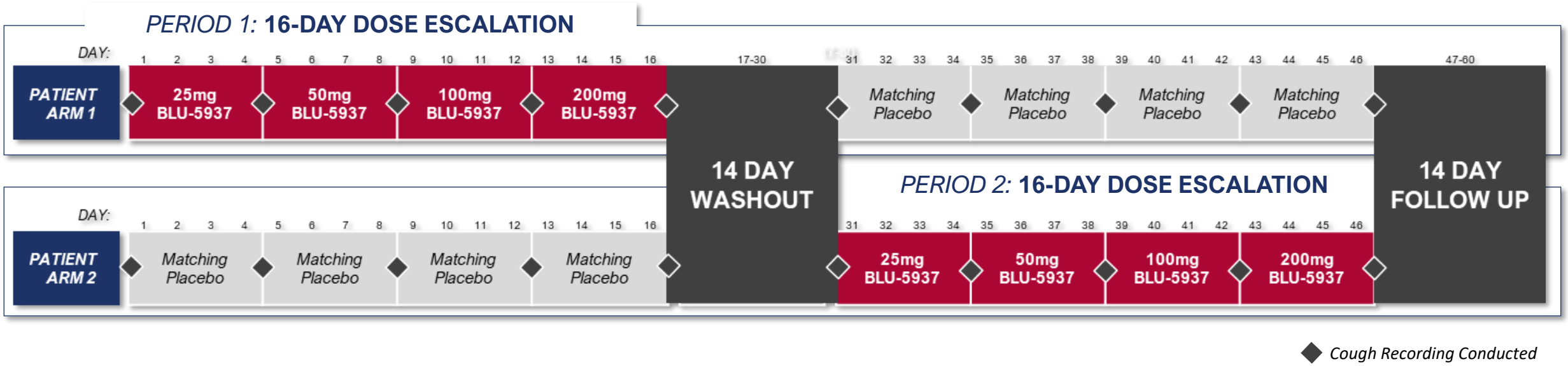
1. Garceau et al. (2019) Pulm Pharmacol Ther. 56:56-62. 2. Garceau et al. (2019) Am. J. Resp Crit Care Med. 199 A7395 P556

The RELIEF Study

*A **R**andomize**e**d, Doub**l**e-bl**i**nd, Plac**e**bo-Controlled, Crossover, Dose Escalation Study of BLU-5937 in Subjects with Unexplained or Re**f**ractory Chronic Cough*

- The RELIEF study (NCT03979638) assessed the safety, tolerability and efficacy of BLU-5937 in 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



Key entry criteria

KEY INCLUSION CRITERIA

- Refractory or unexplained chronic cough for ≥ 1 year
- Awake cough frequency ≥ 10 coughs/h, at screening
- Score ≥ 40 mm on cough severity - VAS at screening

KEY EXCLUSION CRITERIA

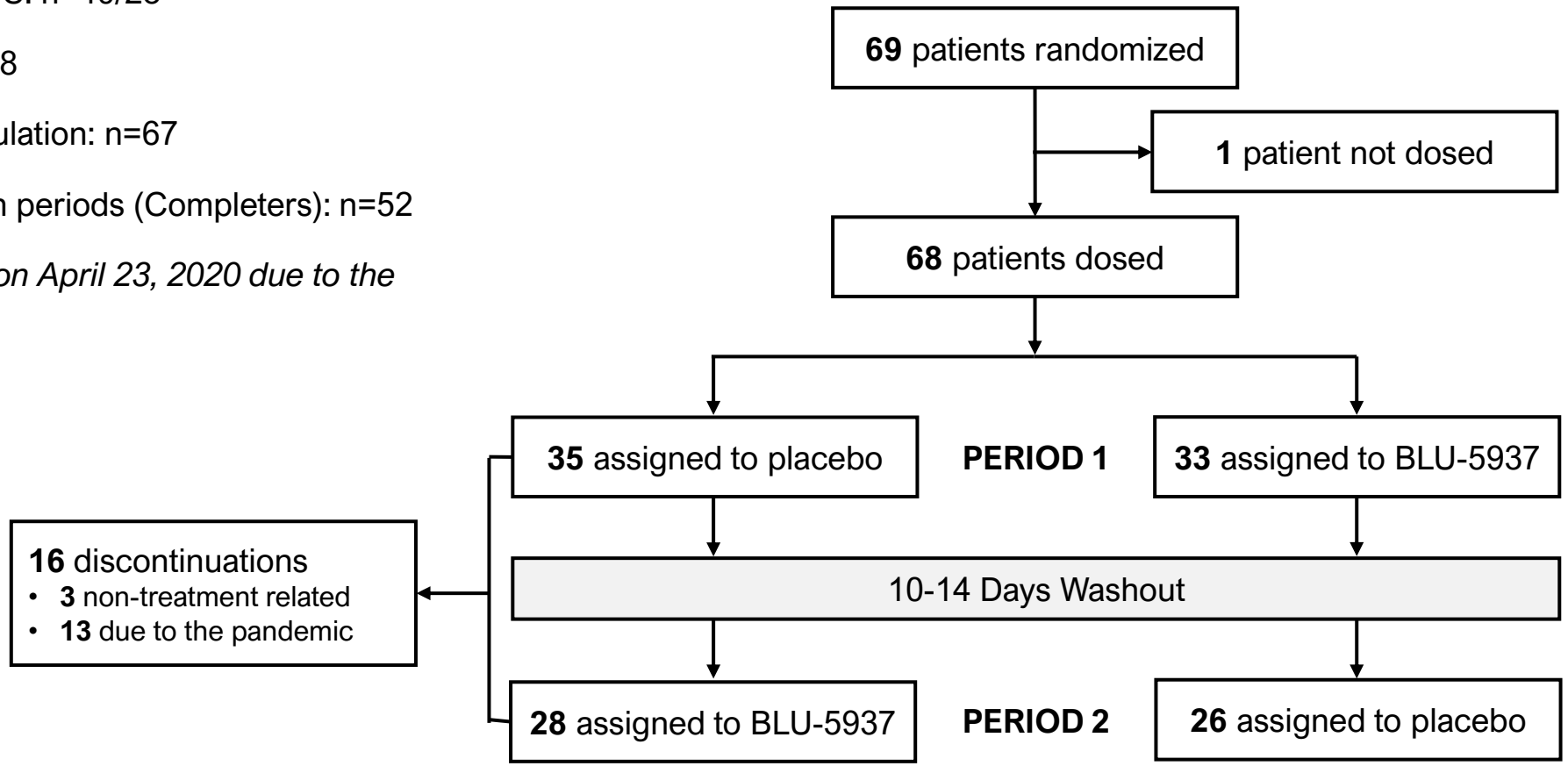
- Diagnosis of COPD, bronchiectasis, IPF
- Current/former smoker (within 6 months)
- $FEV_1/FVC < 60\%$
- History of upper respiratory tract infection or recent significant change in pulmonary status within 4 weeks of baseline

PROHIBITED MEDICATIONS

- Anti-cough medications; (dextromethorphan, gabapentin, pregabalin, opioids)
- Long-term oral steroids (prednisone)
- Medications to treat underlying disease/allergies (inhaled steroids, antihistamines) must be on stable doses for at least 8 weeks prior to screening visit

Patient disposition

- 16 sites – 8 in UK, 8 in US: n=40/28
- Safety Analysis Set: n=68
- Intent-to-treat (ITT) population: n=67
- Patients completing both periods (Completers): n=52
- *RELIEF was terminated on April 23, 2020 due to the COVID-19 pandemic*



Baseline characteristics

Safety analysis set		Patient Arm 1 BLU-5937 → PL (n=33)	Patient Arm 2 PL→ BLU-5937 (n=35)
Sex	Male n (%)	5 (15%)	5 (14%)
	Female n (%)	28 (85%)	30 (86%)
Age, mean (years) ±SD		64.3 ±11.5	63.7 ±9.7
BMI (kg/m^2) mean ±SD		29.2 ±6.4	28.4 ±5.8
Country	UK n (%)	23 (70%)	17 (49%)
	US n (%)	10 (30%)	18 (51%)
Smoking status	Never n (%)	21 (64%)	23 (66%)
	Former n (%)	12 (36%)	12 (34%)
FEV_1/FVC ratio ±SD		73.0 ±6.1	74.3 ±8.6
Duration of cough, mean (years) ±SD		14.6 ±11.4	14.9 ±8.5
Baseline awake cough frequency, (geo mean) (c/h)		31.2	31.8

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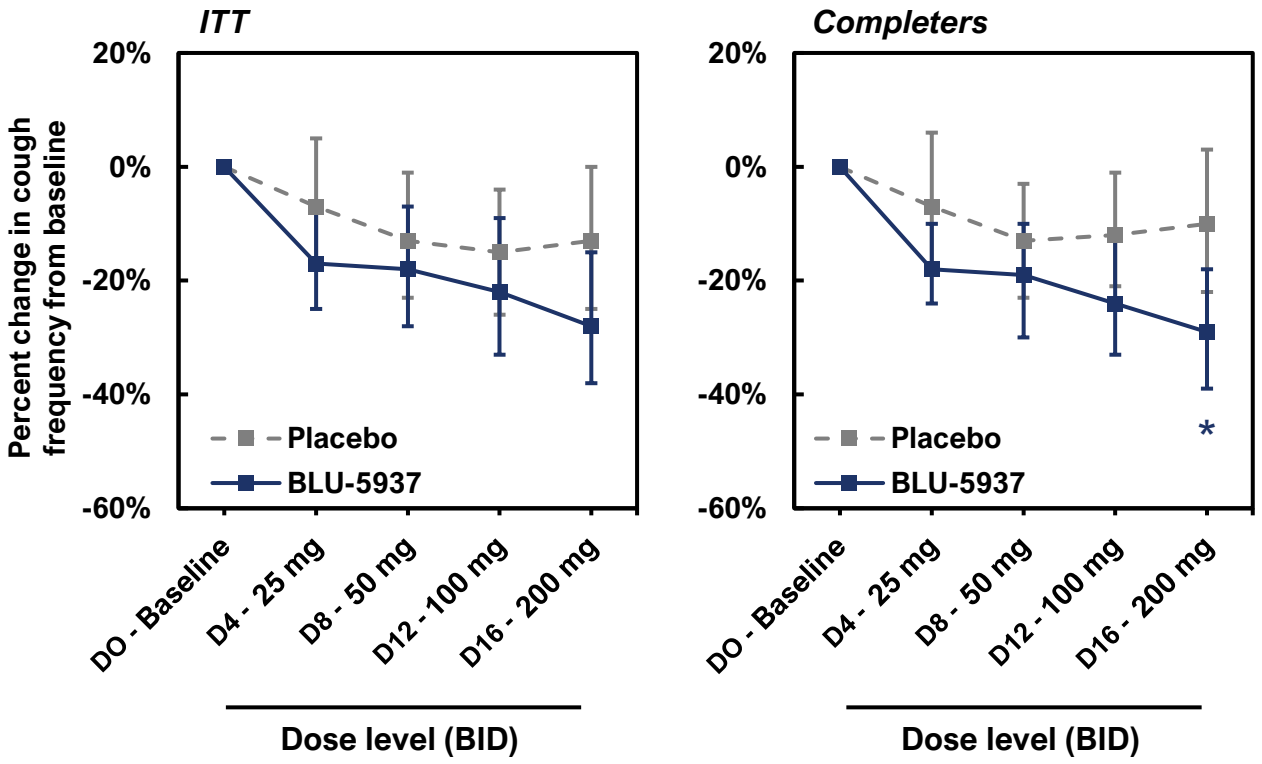
Change in awake cough frequency – ITT and Completers

Awake cough frequency change from baseline



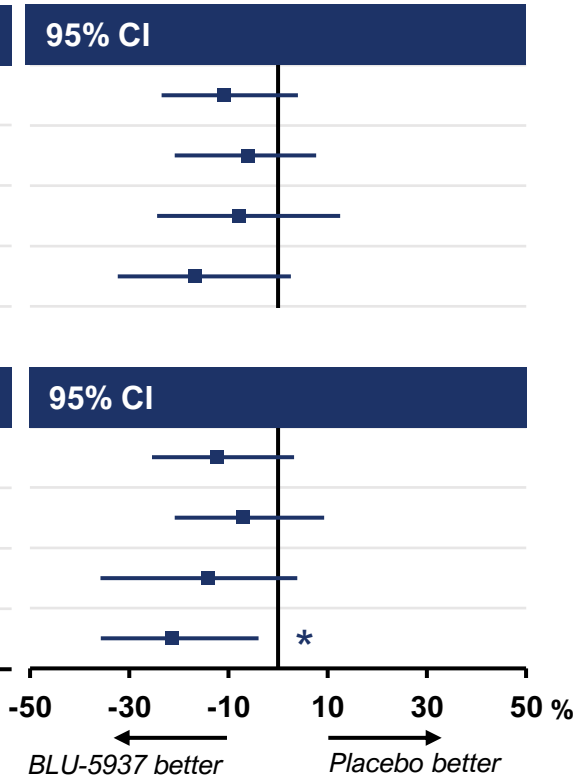
Placebo-adjusted awake cough frequency change from baseline

ITT

Dose	Δ	p-value
25 mg	-10.8%	*0.1424*
50 mg	-6.1%	*0.4602*
100 mg	-7.8%	*0.4181*
200 mg	-16.7%	*0.0855*

Completers

Dose	Δ	p-value
25 mg	-12.3%	*0.1113*
50 mg	-7.0%	*0.3737*
100 mg	-14.0%	*0.1160*
200 mg	-21.4%	*0.0193*



* *p-value ≤ 0.05*

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A significant interaction was seen between baseline cough frequency and the primary efficacy outcome

- Previous studies with a P2X3 antagonist had reported a statistically significant interaction between the cough frequency at baseline and treatment effect[1-3]
- Preplanned analyses for RELIEF included:
  - Assessment of an interaction between baseline cough frequency and treatment effect **(p=0.026)**
  - Assessment of efficacy in two subgroups defined by higher baseline awake cough frequency:
    - ≥ or < baseline median (32.4 coughs/h)
    - ≥ or < 20 coughs/h

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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

Demographics in prespecified subgroups with higher baseline cough frequency

Subgroups		Safety analysis set	≥ 32.4 coughs/h	≥ 20 coughs/h
Number of participants		68	34 (50%)	54 (79%)
Sex	Male n (%)	10 (15%)	1 (3%)	6 (11%)
	Female n (%)	58 (85%)	33 (97%)	48 (89%)
Age, mean (years) ±SD		64.0 ±10.5	65.4 ±8.5	65.0 ±9.3
BMI (kg/m^2) mean ±SD		28.8 ±6.1	28.4 ±6.6	28.2 ±5.9
Country	UK n (%)	40 (59%)	19 (56%)	32 (59%)
	US n (%)	28 (41%)	15 (44%)	22 (41%)
Smoking status	Never n (%)	44 (65%)	24 (71%)	35 (65%)
	Former n (%)	24 (35%)	10 (29%)	19 (35%)
FEV_1/FVC ratio ±SD		73.7 ±7.4	71.5 ±6.6	72.5 ±6.7
Duration of cough, mean (years) ±SD		14.7 ±9.9	17.4 ±11.2	16.1 ±10.3
Baseline awake cough frequency, (geo mean) (coughs/h)		31.5	55.4	40.0

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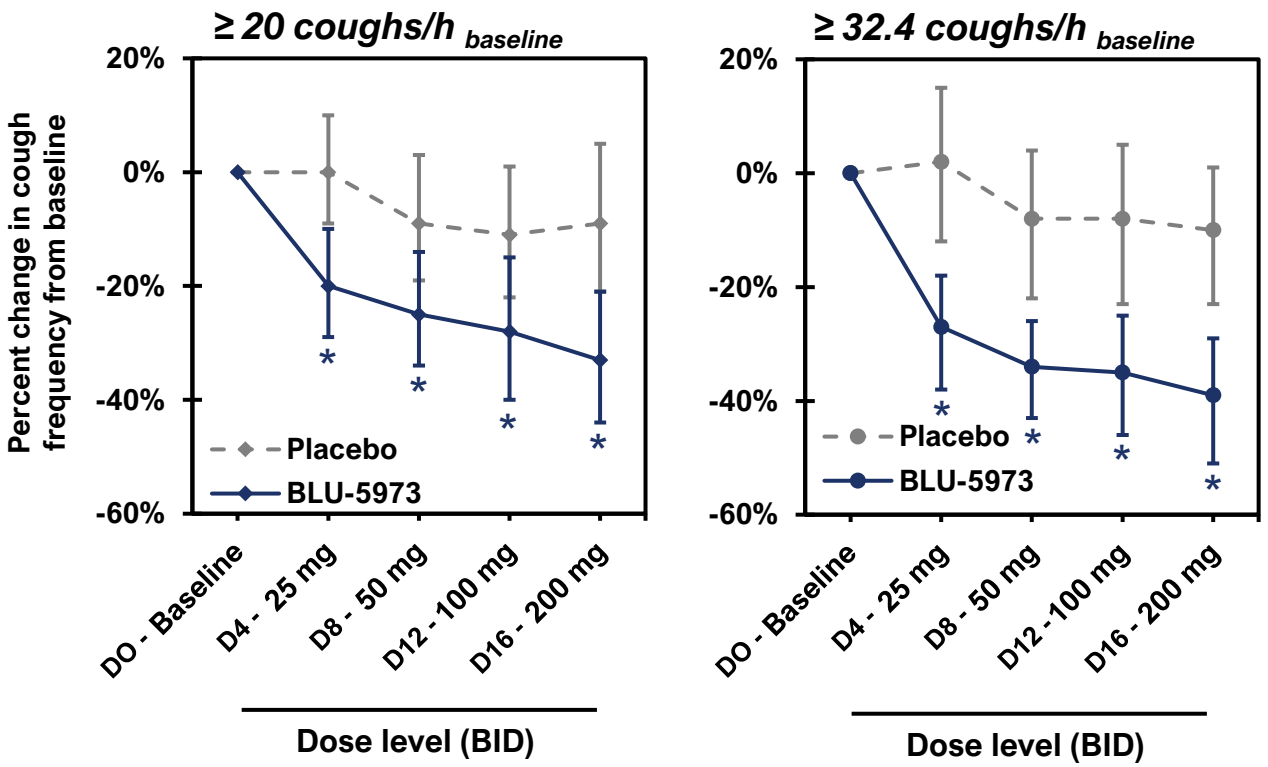
Change in awake cough frequency in patients with baseline awake cough frequency above 20 coughs/h and 32.4 coughs/h

Awake cough frequency change from baseline



Placebo-adjusted awake cough frequency change from baseline

≥ 20 coughs/h baseline

Dose	Δ	p-value	95% CI
25 mg	-20.3%	0.0010	*
50 mg	-17.7%	0.0186	*
100 mg	-19.4%	0.0320	*
200 mg	-27.0%	0.0026	*

≥ 32.4 coughs/h baseline

Dose	Δ	p-value	95% CI
25 mg	-28.1%	0.0005	*
50 mg	-28.4%	0.0003	*
100 mg	-29.5%	0.0014	*
200 mg	-32.4%	0.0006	*

-50 -30 -10 10 30 50 %

BLU-5937 better *Placebo better*

* *p-value ≤ 0.05*

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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%)

∗ *All causalities; events which started during one period/dose level and continued into another are counted in both*

- Similar incidence of treatment emergent adverse events (TEAEs) was reported for placebo and BLU-5937.
- Most common TEAEs included headache, back pain, dysgeusia and diarrhea.
- 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.

Safety and tolerability of BLU-5937 (known class-related adverse events)

Taste disturbances and paresthesia events*	Placebo	BLU-5937				
		25 mg BID	50 mg BID	100 mg BID	200 mg BID	Overall
	(N=61)	(N=61)	(N=61)	(N=60)	(N=58)	(N=61)
n of Subjects (%) with taste disturbance events						
Taste disturbances (total) †	**3 (4.9%)**	**4 (6.5%)**	**6 (9.8%)**	**6 (10.0%)**	**5 (8.6%)**	**6 (9.8%)**
Dysgeusia	2 (3.3%)	3 (4.9%)	5 (8.2%)	5 (8.3%)	4 (6.9%)	5 (8.2%)
Hypogeusia	1 (1.6%)	2 (3.3%)	2 (3.3%)	2 (3.4%)	2 (3.4%)	2 (3.3%)
Ageusia	0	0	0	0	0	0
n of Subjects (%) with other AEs of special interest						
Oral Paresthesia	1 (1.6%)	0	0	1 (1.7%)	1 (1.7%)	1 (1.6%)
Oral Hypoesthesia	0	0	1 (1.6%)	1 (1.7%)	1 (1.7%)	1 (1.6%)

* *Taste disturbances events which started during one period/dose level and continued into another are counted in both. Details of taste disturbances events during washout and follow-up periods not shown, but were added to the overall total*

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

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Conclusions

- Placebo-adjusted changes from baseline in awake cough frequency in the ITT in RELIEF favored BLU-5937 at all doses, but did not achieve statistical significance 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
- BLU-5937 was well tolerated with a < 10% incidence of mild to moderate taste disturbance
- The observed statistically significant interaction between baseline cough frequency and treatment effect demonstrates the importance of considering baseline cough frequency in the design of future clinical trials

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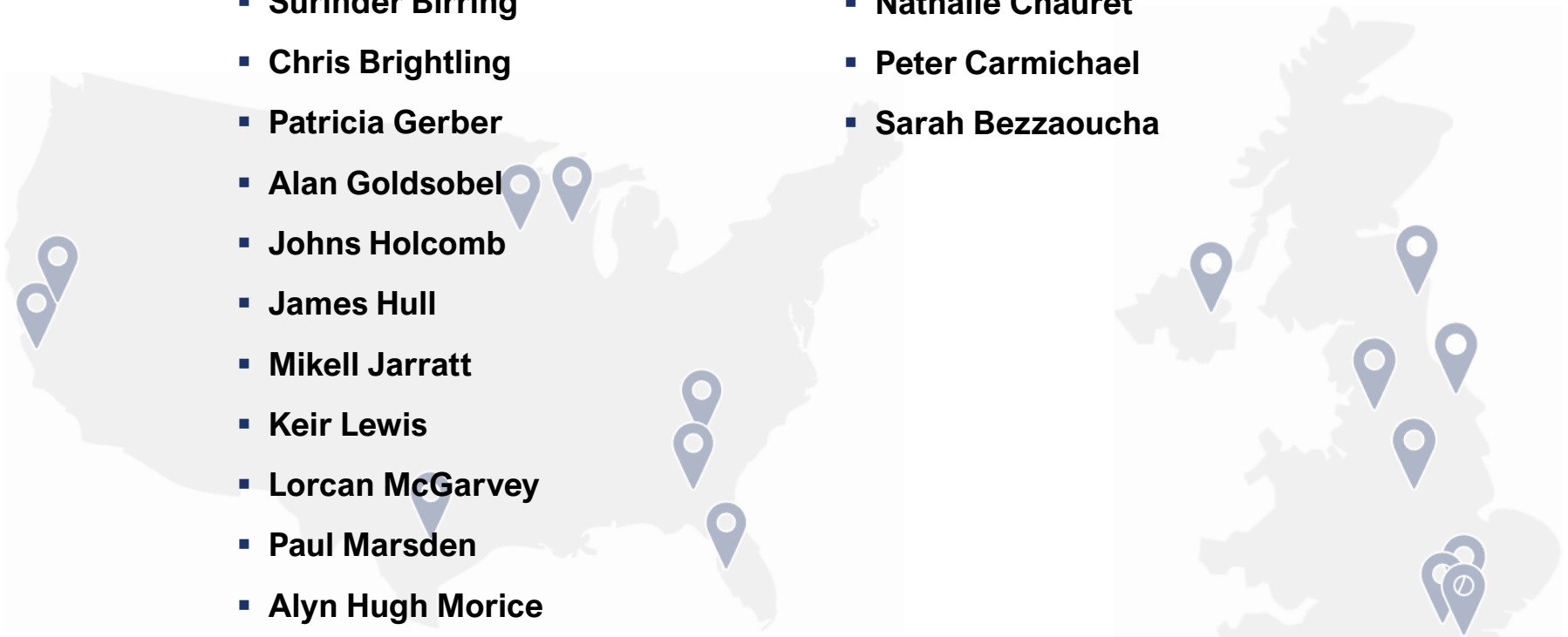

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