Improvements in cough frequency over 24 hours with BLU-5937, a selective P2X3 antagonist, in patient subgroups defined by baseline awake cough frequencies

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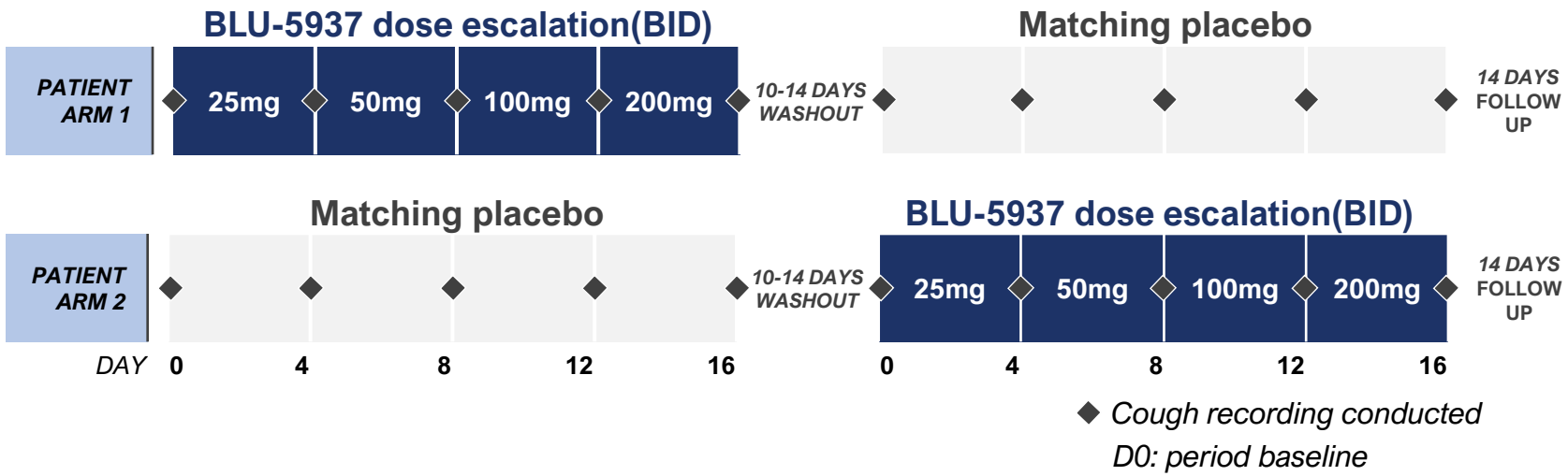
Disclosure to Learners

- **Financial relationships with relevant companies within the past 24 months:**
  - *Bellus Health, Advisory committee, Research - industry initiated ; Merck, Advisory committee, Research - industry initiated and grant funding, Speaker/faculty – non-promotional activity; Nocion, Research - industry initiated, Advisory committee; Bayer, Research - industry initiated, Advisory committee; Axalbion, Consultant, Research - industry initiated, Algernon, Consultant; Shionogi, Advisory committee; AstraZeneca, Consultant.*
  - *Vitalograph Ltd, Royalties paid to the hospital in which I work.*

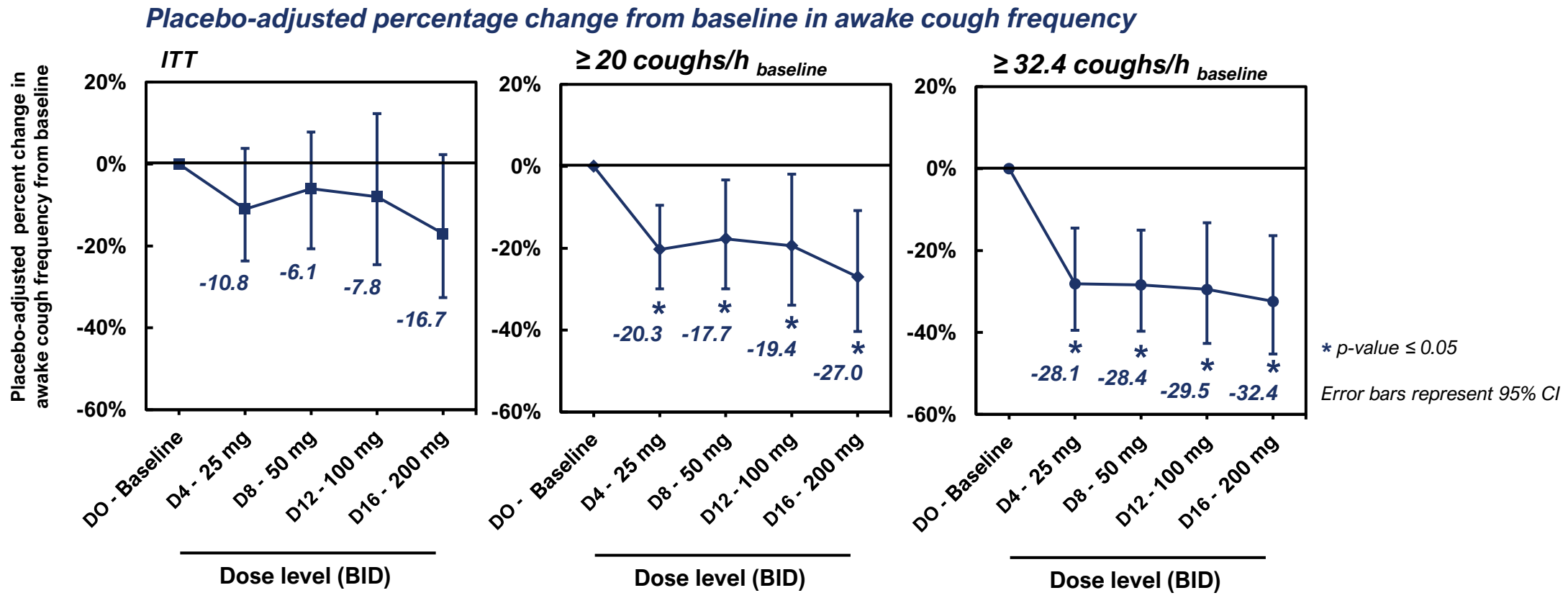
The RELIEF Study

- The RELIEF study (NCT03979638) was a phase 2 trial assessing the safety, tolerability and efficacy of BLU-5937 in subjects with refractory or unexplained chronic cough (RCC)
- Two-arm, 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 from baseline in awake cough frequency



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

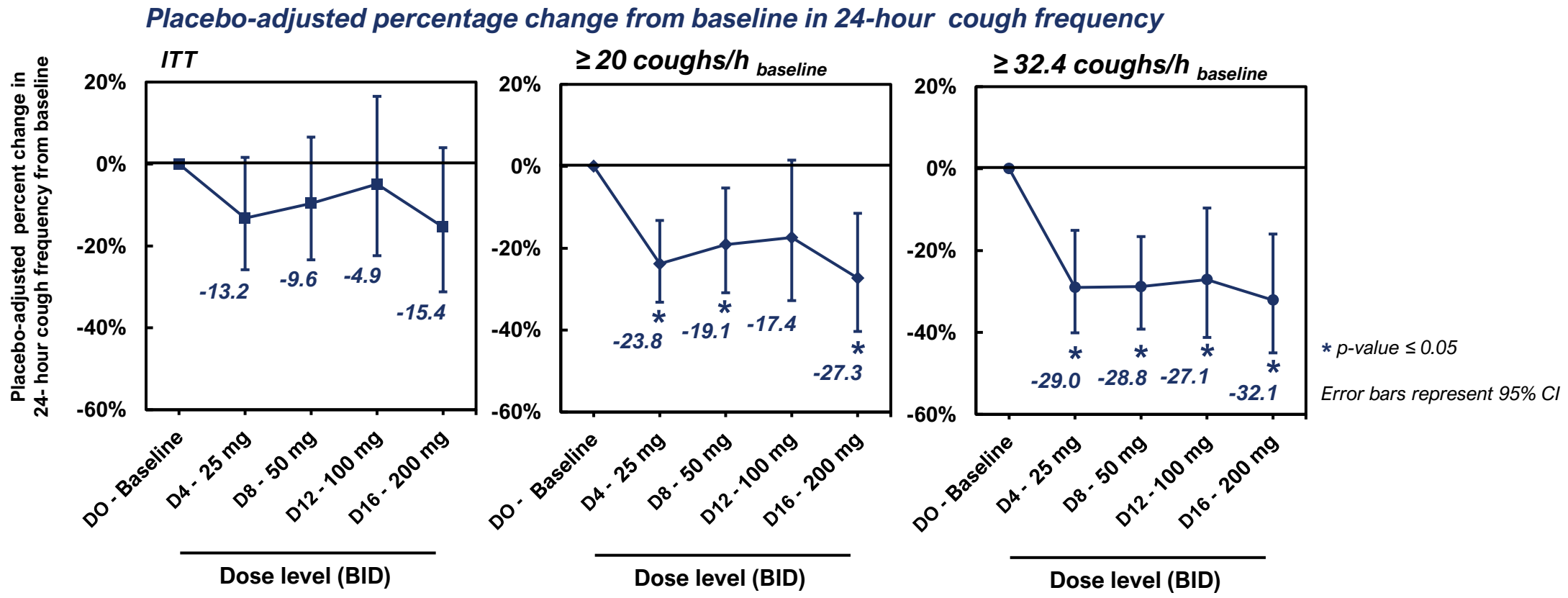
- Improvements on the primary endpoint in RELIEF were dependent on the subject's baseline cough frequency
- Improvements were not statistically significant in the intent-to-treat population (n=67)
- Nominally significant (pairwise p-values < 5%) improvements in awake cough frequency over placebo were reported in pre-specified subgroups with different awake cough frequencies at baseline†



† Subgroups were defined using average cough frequencies measured at screening and at baseline. One subgroup was defined using the population median (32.4 coughs/h). A second subgroup was defined by a clinically relevant threshold of 20 coughs/h. This subgroup included 80% of the ITT population.

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

- Analysis of cough frequency over a 24-hour period demonstrated nominally significant improvements over placebo at most dose levels in subgroups† defined by baseline awake cough frequency



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Change in nighttime cough frequency

- Placebo-adjusted reductions from baseline in nighttime cough frequency overall favored BLU-5937, but p-values were not nominally significant

Placebo-adjusted change from baseline (Δ) in nighttime cough frequency

Dose	Δ Awake	p-value	Δ Night	p-value
Intent-to-treat				
25 mg	**-10.8%***	*0.1424*	**-20.8%**	*0.2381*
50 mg	**-6.1%***	*0.4602*	**-30.2%**	*0.1283*
100 mg	**-7.8%***	*0.4181*	**5.3%**	*0.8263*
200 mg	**-16.7%***	*0.0855*	**-15.3%**	*0.4778*
≥ 20 coughs/h $_{baseline}$				
25 mg	**-20.3%***	*0.0010*	**-30.4%**	*0.1221*
50 mg	**-17.7%***	*0.0186*	**-30.0%**	*0.1965*
100 mg	**-19.4%***	*0.0320*	**-0.4%**	*0.9876*
200 mg	**-27.0%***	*0.0026*	**-25.0%**	*0.2750*
≥ 32.4 coughs/h $_{baseline}$				
25 mg	**-28.1%***	*0.0005*	**-24.4%**	*0.4057*
50 mg	**-28.4%***	*0.0003*	**-32.8%**	*0.2120*
100 mg	**-29.5%***	*0.0014*	**-22.5%**	*0.4102*
200 mg	**-32.4%***	*0.0006*	**-13.6%**	*0.6373*

** p-value ≤ 0.05*

Summary

- Clinically meaningful and nominally significant reductions in awake cough frequency were observed in subgroups defined by higher baseline awake cough frequency (≥ 20 or ≥ 32 coughs/h)

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

Conclusion

- Enriching refractory chronic cough populations based on awake cough frequency at baseline is a valid approach in clinical trials using 24-hour frequency as primary outcome