

Baseline characteristics and burden of disease in populations defined by cough frequency tiers in RELIEF, a phase 2 study on the efficacy and safety of BLU-5937 in refractory chronic cough

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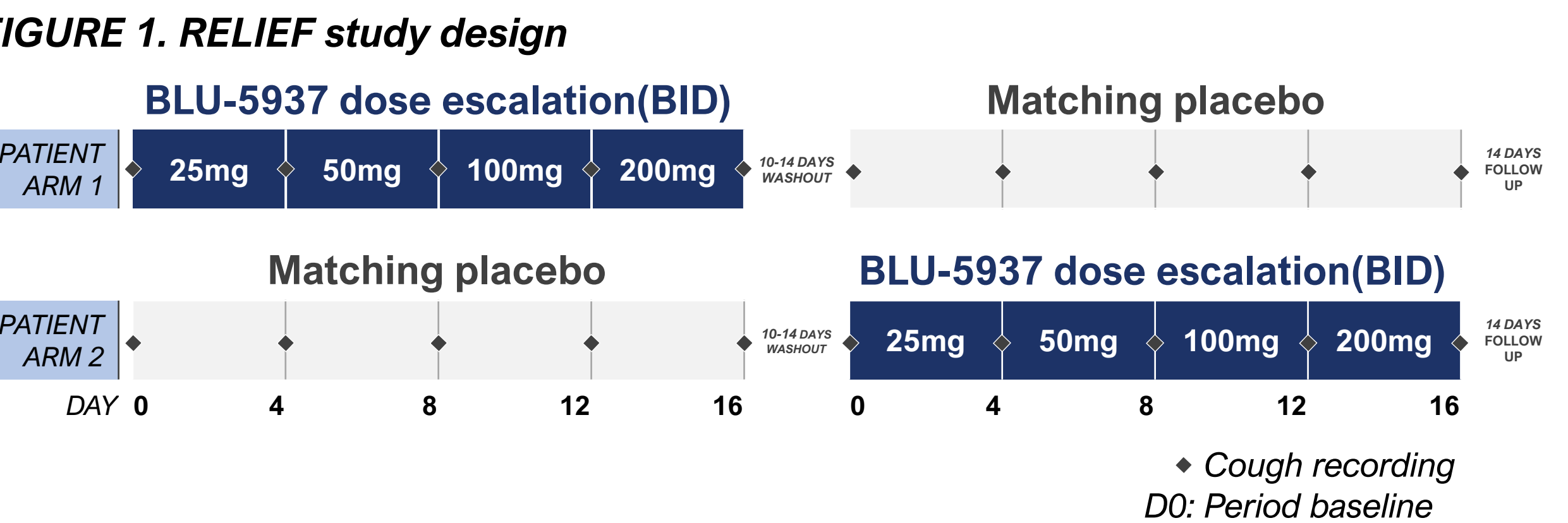
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Introduction

- Chronic Cough (CC) is a cough lasting for 8 weeks or more; it can be refractory to treatment or result from unexplained causes (RCC)¹.
- RCC can cause a significant physical, psychological, and social burdens, exacerbated by the lack of currently approved treatment¹.
- Inhibition of the ATP-gated ion channel P2X3 has shown promise in previous studies as a treatment avenue for RCC and antagonists are currently investigated².
- RCC patients show comparatively higher cough frequencies relative to other cough etiologies. This may be indicative of a hypersensitized cough reflex³.
- Previous trials of P2X3 antagonists have shown greater reductions in cough frequency with higher baseline cough frequency^{2,4,5}. The burden of cough in higher or lower cough frequency patients is not known.
- Here, we report the burden of cough in patients with higher vs lower cough frequency at baseline in the RELIEF trial.

Methodology

- The RELIEF study (NCT03979638) assessed the safety, tolerability, and efficacy of the P2X3 antagonist BLU-5937 in subjects with RCC.
- Participants (≥10.0 awake coughs/h at screening) were randomized to 16-day treatment (25, 50, 100, 200 mg BID) or placebo, with forced dose escalation every 4 days. After a 10-14-day washout, they were crossed over to the other regimen (fig. 1).



Pre-specified cough frequency subgroups

- Other trials of P2X3 antagonists in RCC reported a significant interaction between cough frequency at baseline and treatment effect^{2,4,5}.
- To further investigate this relationship, analyses of two subgroups defined by their awake cough frequency at baseline were planned
 - One analysis examined subgroups defined by a population-defined threshold, along the median of the average cough frequencies measured at screening (D-14) and at baseline (D0) (**32 coughs/h**).
 - A second analysis examined subgroups along an *a priori*, clinically relevant threshold of **20 coughs/h** (average of screening and baseline measurements).

Results

- Overall, 68 participants were dosed (safety set) and 67 were included in the Intent-To-Treat population (ITT). Patients ≥ 20 coughs/h represented 80% of the ITT (tab. 1).
 - Numerical reductions in awake cough frequency over placebo were observed at all doses in the intent-to-treat population but did not reach statistical significance at any dose (tab. 3). Analyses confirmed that the treatment effect depended on awake cough frequency at baseline (p=0.0258). Significant improvements (p<0.05) were observed in both higher cough frequency subgroups (tab. 3).
- ### Patients show similar demographics across cough frequency subgroups
- There were no significant differences in participants demographics (race, country and smoking history) between the overall population and between participants defined by their cough frequency at baseline (tab. 1). No clear clinically significant difference in BMI and FEV₁/FVC were reported for between subgroups (tab. 1).
 - A higher proportion of women were enrolled in RELIEF, representative of the reported prevalence of chronic cough. Women were overrepresented in participants ≥ 32 coughs/h at baseline (97%) relative to the overall trial population. However, patients ≥ 20 coughs/h showed a distribution closer to the overall population (tab. 1).
 - Patients in higher cough frequency subgroups present a longer duration of cough.

TABLE 1. Participants baseline demography and characteristics by cough frequency subgroups

	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)	
Race, n (%)	Caucasian	66 (97%)	34 (100%)	32 (94%)	53 (98%)	13 (93%)
	Black	1 (1.5%)	0	1 (3%)	0	1 (7%)
	Pacific Islander	1 (1.5%)	0	1 (3%)	1 (2%)	0
Country UK/US (%)	40/28 (59/41%)	19/15 (56/44%)	21/13 (62/38%)	32/22 (59/41%)	8/6 (57/43%)	
Smoking Status, never/former (%)	44/24 (65/35%)	24/10 (71/29%)	20/14 (59/41%)	35/19 (65/35%)	9/5 (64/36%)	
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)	

Similar most prevalent cough etiology between cough frequency subgroups

- Overall, the most common underlying medical conditions included GERD (53%), asthma (22%) and allergic rhinitis (19%) (tab. 2)
- Patients with a lower cough frequency reported a higher prevalence of seasonal allergies (tab. 2)

TABLE 2. Relevant conditions at baseline (>5%)

	Safety set	32 coughs/h	
		≥	<
Potential cough etiologies			
GERD	36 (53%)	15 (44%)	21 (62%)
Asthma	15 (22%)	8 (24%)	7 (21%)
Rhinitis allergic	13 (19%)	10 (29%)	3 (9%)
Seasonal allergy	10 (15%)	3 (9%)	7 (21%)
Rhinitis	4 (6%)	3 (9%)	1 (3%)
Sinusitis	3 (4%)	1 (3%)	2 (6%)
Rhinitis perennial	2 (3%)	0	2 (6%)
Eosinophilic bronchitis	2 (3%)	0	2 (6%)
Psycho co-morbidities			
Depression	11 (16%)	4 (12%)	7 (21%)
Anxiety	10 (15%)	8 (24%)	2 (6%)
Incontinence			
Stress urinary incontinence	4 (6%)	3 (9%)	1 (3%)
Urinary incontinence	4 (6%)	2 (6%)	2 (6%)

Higher burden of incontinence and anxiety with higher cough frequency

- Both higher and lower cough frequency subgroups reported significant psychological burden, with patients with a higher frequency at baseline reporting a higher prevalence of anxiety (tab. 2).
- Participants ≥ 32 coughs/h at baseline reported a higher incidence of stress urinary incontinence comparatively with participants < 32 coughs/h. However, the small populations size confound further analyses.
- Psychological comorbidities and incontinence remain challenging to characterize in depth, as patients are less likely to proactively report those conditions.

Burden of disease is similar across cough frequency subgroups

TABLE 3. Awake cough frequency (ACF) and relative placebo-adjusted change from baseline (Δ)

	ITT				≥ 32 coughs/h				≥ 20 coughs/h			
	25 mg	50 mg	100 mg	200 mg	25 mg	50 mg	100 mg	200 mg	25 mg	50 mg	100 mg	200 mg
Subjects (placebo/treatment)	59/60	58/59	58/56	58/58	30/28	31/28	31/27	31/28	46/46	46/45	47/44	46/45
Baseline ACF (coughs/h)	A _{mean} (SD)				61.1 (32.6)				47.3 (31.7)			
	G _{mean}				55.4				40.0			
Δ (% c/h)	-11%	-6%	-8%	-17%	-28%*	-28%*	-30%*	-32%*	-20%*	-18%*	-19%*	-27%*

- Cough frequency at baseline in the ITT and subgroups (tab. 3), were within range reported in other RCC studies^{2,4,5}
- Patient-reported impact of their cough on their quality of life was measured using the Leicester Cough Questionnaire (LCQ). Patient-reported severity of their cough was measured using a visual analog scale (CS-VAS).
- Participants in both higher cough frequency subgroups reported a burden on their quality of life similar to the ITT (10.1 ±3.5 vs 10.2 ±3.3) (fig. 2). Both the ITT and participants in higher cough frequency subgroups reported scores on the cough severity visual analog scale (CS-VAS) ≥ 70 mm (fig. 3).
- Comparison between cough frequency subgroups show that there were small to moderate worsening in cough impact on quality of life and cough severity between higher and lower frequency coughers (fig. 2 & 3).

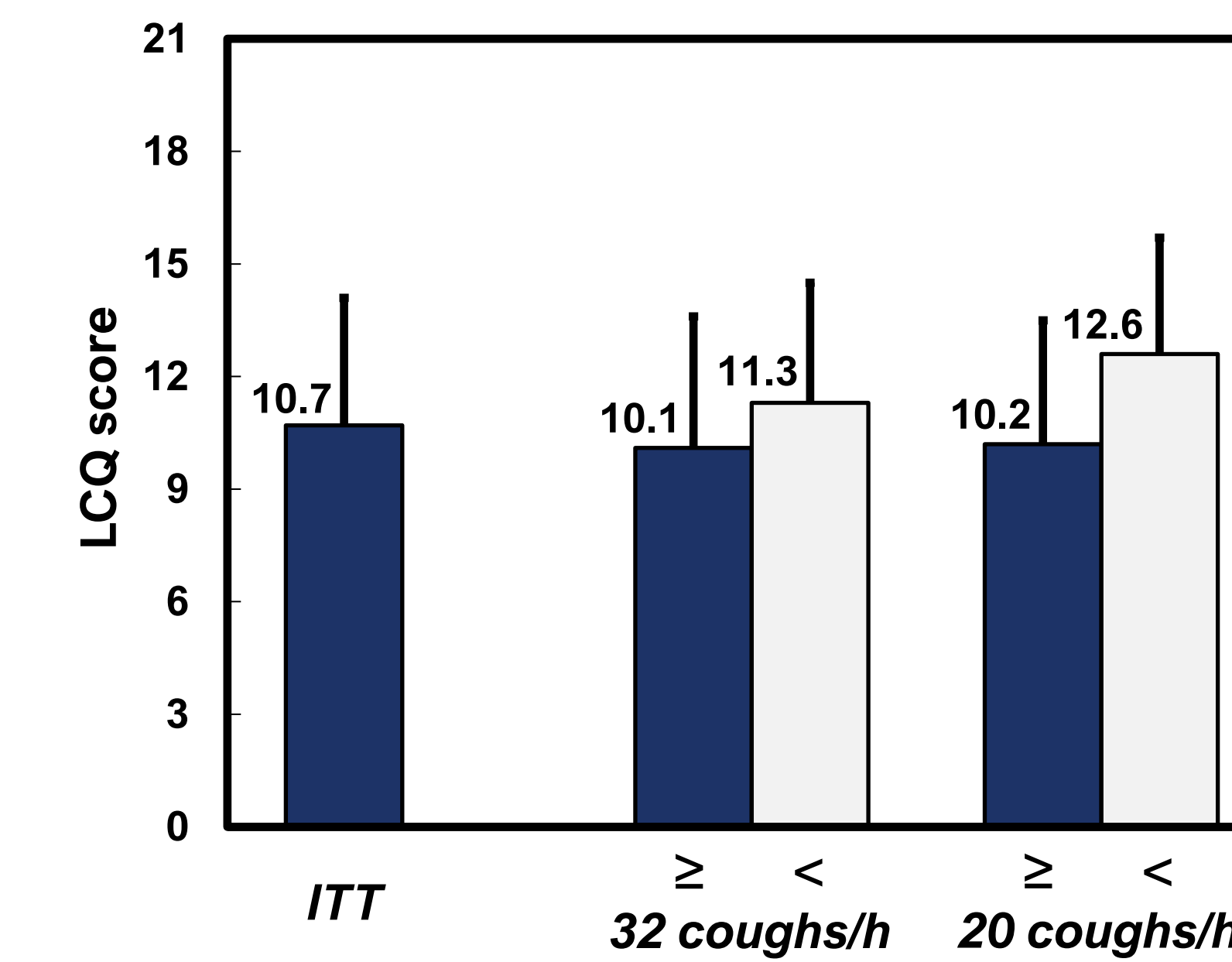


FIGURE 2. LCQ baseline score

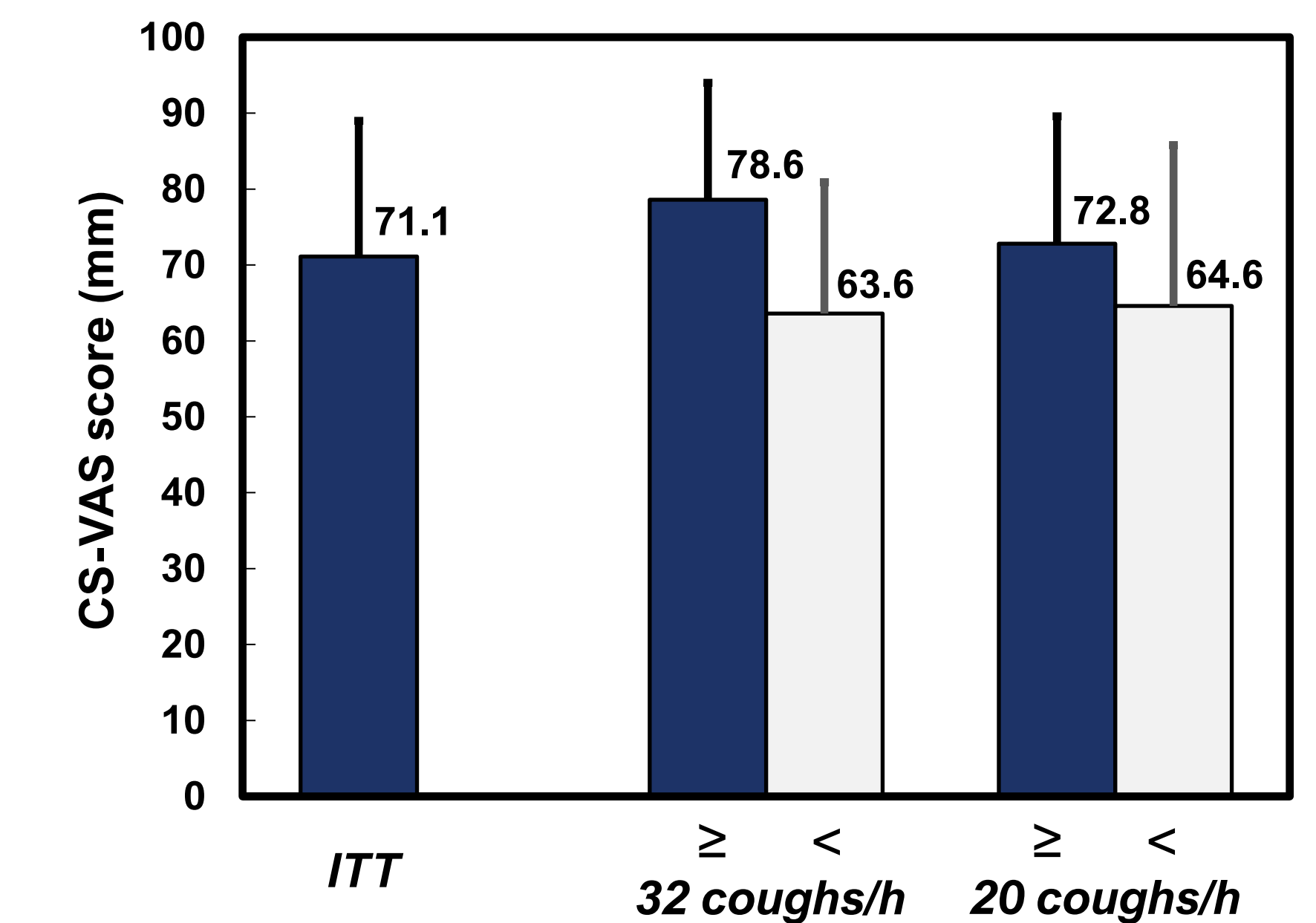


FIGURE 3. CS-VAS baseline score

Conclusions

- Populations in the RELIEF study defined by relatively higher and lower awake cough frequency all showed characteristics and demographics reflecting those reported for refractory chronic cough populations.
- Impairment in quality of life was only marginally different between subgroups with higher or lower cough frequency at baseline, suggesting a significant burden of disease in all populations.
- Moreover, the overall burden of disease in subgroups that demonstrated a significant response to BLU-5937 was similar to the overall trial population.

References

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