

Patient-Reported Outcomes From a Phase 2a Trial of Extended-Release Nalbuphine for Patients With Refractory Chronic Cough

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Background

- Refractory chronic cough (RCC) represents up to one-third of chronic cough cases¹ and is associated with a considerable disease burden²
 - Beyond persistent cough, RCC has a broad impact on patient well-being: 61% of affected individuals report anxiety or depression,² and many experience reductions in work (34%) and nonwork (30%) activities²
 - RCC also carries a significant economic burden¹ and remains an area of unmet need as no approved therapies are available in the United States
- Nalbuphine extended-release (NAL ER) tablets are being developed for the treatment of chronic cough in patients with RCC³ or idiopathic pulmonary fibrosis (IPF)^{4, 5}
- NAL ER acts on the cough reflex arc centrally and peripherally as a kappa agonist and a mu antagonist, targeting opioid receptors that play a key role in controlling chronic cough
- In the RIVER trial (NCT05962151), NAL ER treatment showed a significant reduction in 24-hour objective cough frequency compared with placebo after 21 days of treatment in patients with RCC³

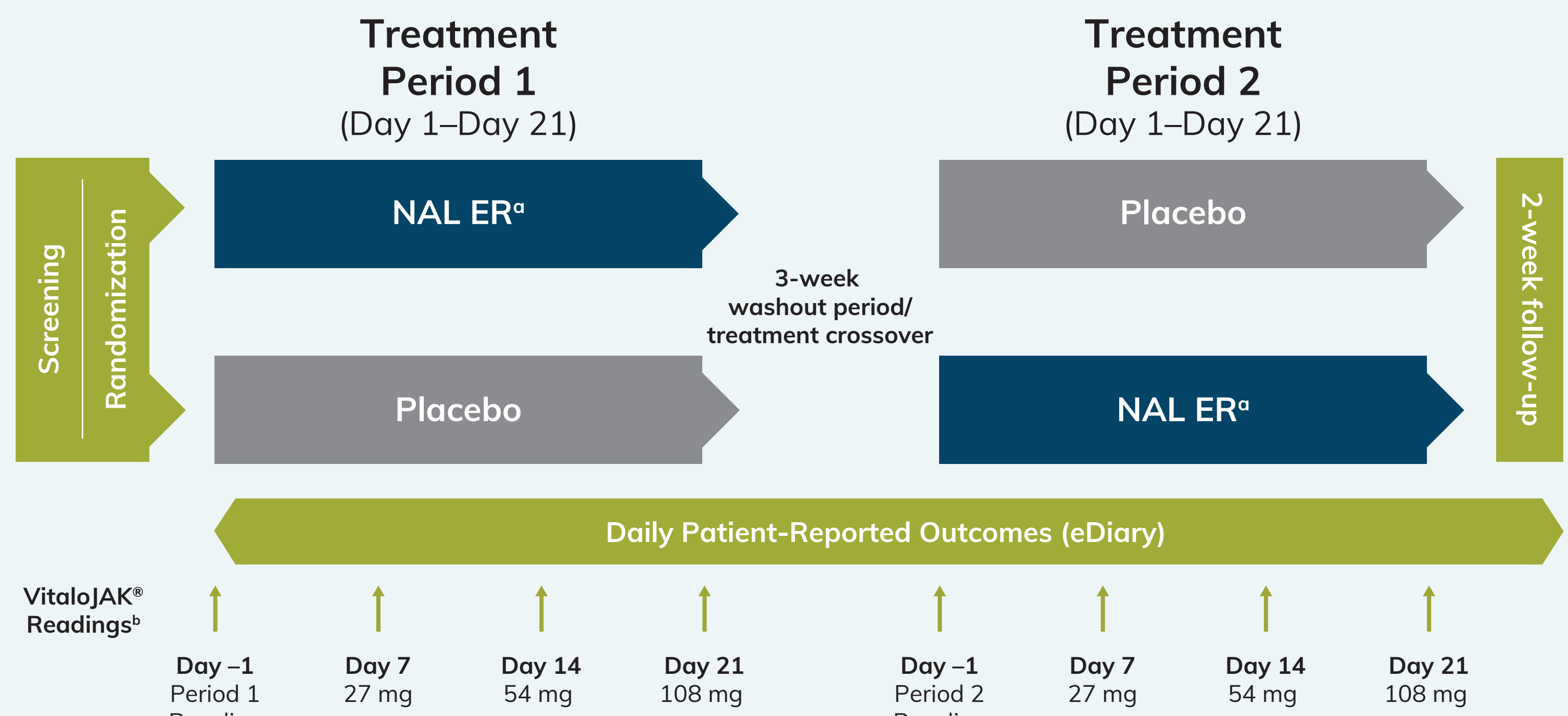
Objective

- To report the patient-reported outcomes of NAL ER for the treatment of RCC from the RIVER trial

Methods

- Study design
 - RIVER was a double-blind, randomized, placebo-controlled, 2-period crossover study in which the NAL ER dose was initiated at 27 mg twice daily (BID) and then titrated every 7 days to reach 54 mg BID at Day 14 and 108 mg BID at Day 21 (**Figure 1**)
 - Patients with RCC were stratified into 2 subgroups based on 24-hour objective cough frequency at screening, 10-19 coughs/hour or ≥20 coughs/hour
 - Patients were randomly assigned to 1 of the following 2 sequences:
 - NAL ER in treatment Period 1 followed by placebo in treatment period 2
 - Placebo in treatment Period 1 followed by NAL ER in treatment period 2
 - Treatment periods were separated by a 21-day washout period followed by a 14-day follow-up period
- Inclusion criteria
 - RCC diagnosis and persistent cough for ≥1 year
 - Chest radiography or computed tomography (CT) of the thorax performed within the previous 24 months that showed no abnormalities that could significantly contribute to RCC
 - A rating of ≥40 mm on the cough severity visual analog scale (CS-VAS)
 - Cough frequency of 10-19 coughs/hour or ≥20 coughs/hour over a 24-hour period
 - Forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) ratio ≥60%
- Exclusion criteria
 - Upper or lower respiratory tract infection <6 weeks before enrollment
 - History of smoking/vaping within the previous 12 months before screening
 - History of sleep apnea, bronchiectasis, chronic obstructive pulmonary disease, IPF, or uncontrolled asthma

Figure 1. Study Design



^aNAL ER was titrated starting at 27 mg BID on Day 1, with subsequent increases every 7 days, to achieve the dose shown for each respective visit day.
^bAt each scheduled visit (Days 7, 14, and 21), site staff fitted the participants with the electronic cough monitor (VitaloJAK; Vitalograph Ltd, Buckingham, United Kingdom). The device was worn for approximately 24 hours, removed, and returned to the clinical study center for data processing.

Patient-Reported Outcome Measures

- Relative change from baseline in cough severity on Days 7, 14, and 21 using the CS-VAS (no cough [0 millimeters, mm] to worst cough [100 mm])
- Relative change from baseline in cough frequency on Days 7, 14, and 21 using the Patient-Reported Cough Frequency measure (PR-CF; “Over the past 24 hours, how often did you cough”; not at all [0] to almost constantly [4])
- Patient Global Impression of Change for cough (PGI-C; much better [1] to much worse [7]) rating on Days 7, 14, and 21
- Patient Global Impression of Severity for cough (PGI-S; no cough [0] to severe cough [4]) rating on Days 7, 14, and 21
- Change from baseline score on the Leicester Cough Questionnaire (LCQ; 3-21 scale) on Day 21
- All patient-reported data are for the full analysis set defined as all patients who received ≥1 dose of study drug and have objective cough count data at baseline and for Day 21 in ≥1 treatment period

Results

- Of the 66 participants who were randomly assigned, 59 (89.4%) completed the treatment phase and were included in the full analysis set
- Baseline characteristics are summarized in **Table 1**

Table 1. Baseline Characteristics for Safety Population^a

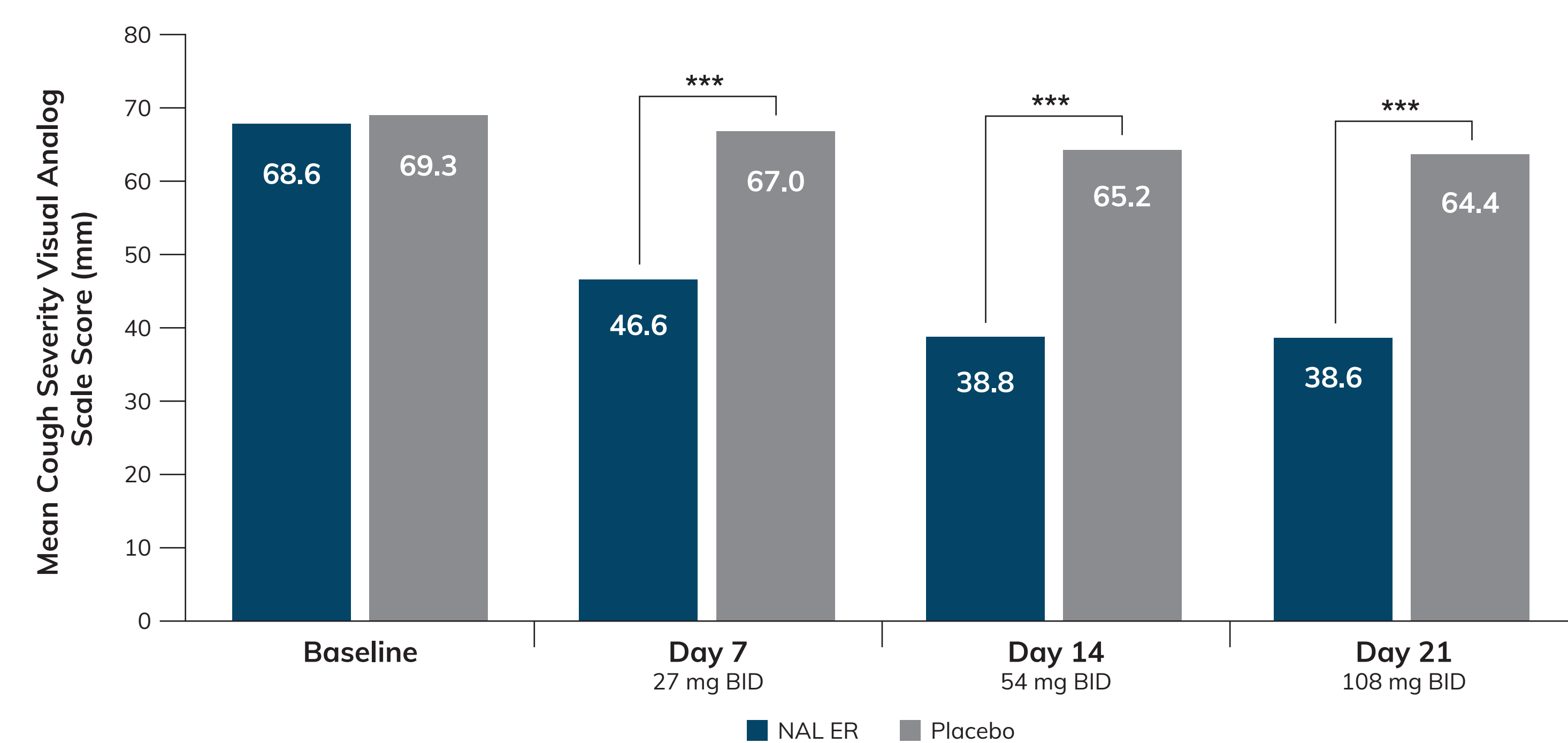
		Participants N = 66
Age, mean (SD), years		60.2 (10.5)
Sex, n (%)	Female	44 (66.7)
	Male	22 (33.3)
Race, n (%)	White	61 (92.4)
	Black or African American	4 (6.1)
	Asian	1 (1.5)
Duration of cough, mean (SD), years		12.6 (10.4)
Screening 24-hour cough frequency, coughs/hour	Mean (SD)	34.7 (29.2)
	Min, max	10.0, 165.9
Screening CS-VAS score, mean (SD)		72.2 (13.3)

^aSafety population: all patients who received ≥1 dose of study drug or placebo.

Patient-Reported Outcomes

- Patient perception of cough severity using the CS-VAS significantly improved from baseline by Days 7 (27 mg), 14 (54 mg), and 21 (108 mg) during NAL ER treatment compared with placebo ($P < .0001$) (**Figure 2**)
- Change from baseline in cough frequency measured using the PR-CF by the question, “Over the past 24 hours, how often did you cough?” was also statistically significant on Days 7 (27 mg), 14 (54 mg), and 21 (108 mg) during NAL ER treatment, compared with placebo ($P < .0001$) (**Figure 3**)

Figure 2. Patient-Reported Cough Severity Using Cough Severity Visual Analog Scale^a

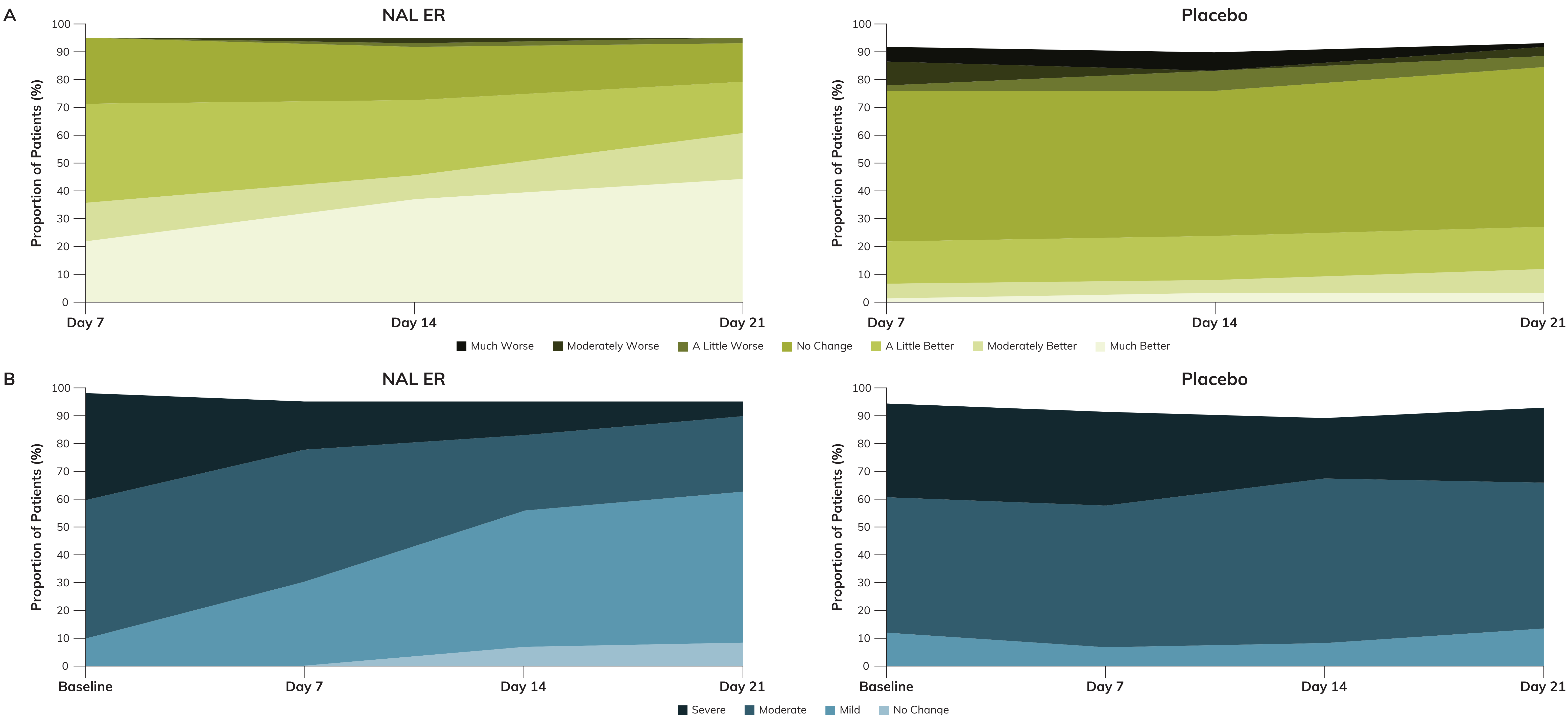


^aCS-VAS: no cough (0 mm) to worst cough (100 mm).

*** $P < .0001$ (difference in change in baseline between NAL ER and placebo).

- PGI-C (**Figure 4A**) and PGI-S (**Figure 4B**) ratings significantly improved during NAL ER treatment on Days 7 (27 mg), 14 (54 mg), and 21 (108 mg), compared with placebo

Figure 4. Patient Global Impression of (A) Change^a and (B) Severity^b Scores



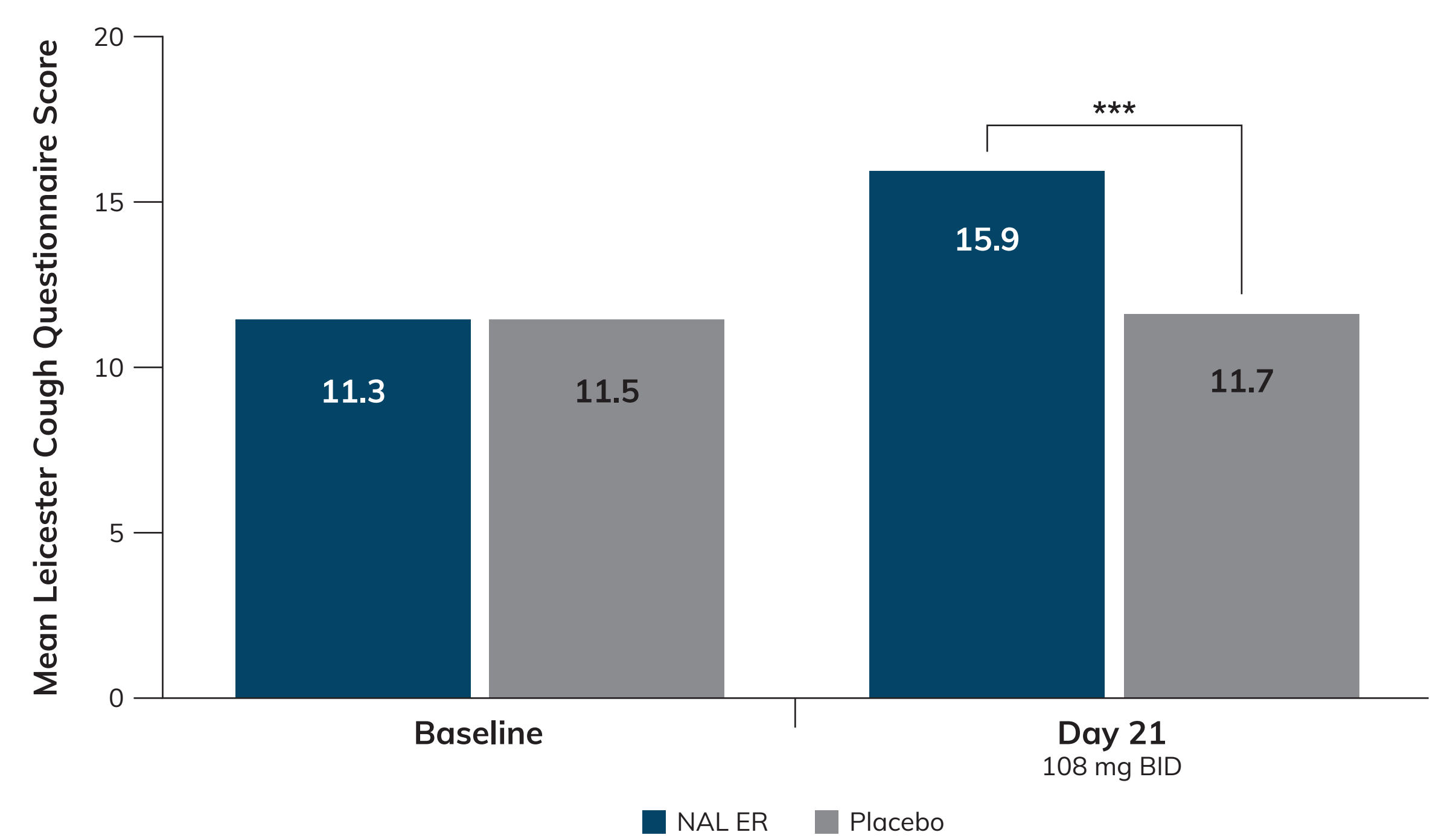
Values may not add to 100% due to rounding.

^aPGI-C: much better (1) to much worse (7).

^bPGI-S: no cough (0) to severe cough (4).

- By Day 21, LCQ scores significantly improved during NAL ER treatment, reflecting a 4.5-unit improvement compared with a 0.2-unit improvement with placebo (**Figure 5**)

Figure 5. Mean Leicester Cough Questionnaire Scores



*** $P < .0001$ (difference in change in baseline between NAL ER and placebo).

Conclusions

- Improvement in patient perception of cough severity and frequency during NAL ER treatment was observed at all time points during the study
- The patient-reported outcomes were consistent with objective cough monitoring data, highlighting the consistency between objective and subjective reduction in cough severity and frequency
- These findings warrant further development of NAL ER for patients with RCC

References

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Abbreviations

BID, twice daily; CS-VAS, cough severity visual analog scale; IPF, idiopathic pulmonary fibrosis; LCQ, Leicester Cough Questionnaire; NAL ER, nalbuphine extended-release; PGI-C, patient global impression of change for cough; PGI-S, patient global impression of severity for cough; PR-CF, patient-reported cough frequency; RCC, refractory chronic cough.

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