FREEDOM-EV: Combination Therapy with Oral Treprostinil for Pulmonary Arterial Hypertension (PAH)

Phase III, international, randomized, placebo-controlled, double-blind, event-driven study

Study Overview

To assess the ability of oral treprostinil to delay clinical worsening for people living with PAH

Participants with PAH on background monotherapy receiving oral treprostinil or placebo (1:1)

Oral treprostinil **346**

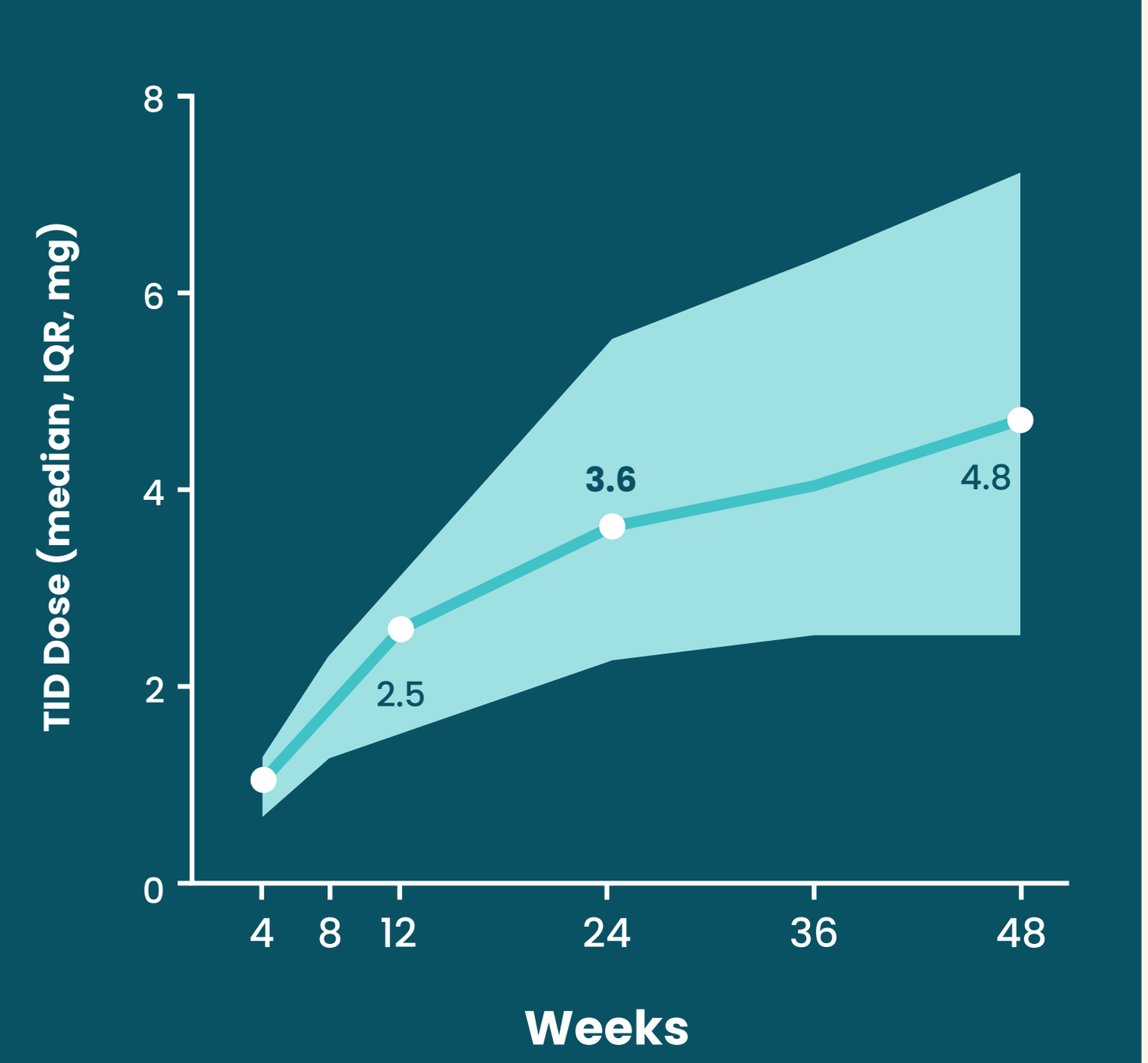
Placebo **344**

690 Participants

152 Centers

23 Countries

Oral treprostinil dosing



Starting dose: 0.125 mg TID   Max dose: 12 mg TID

Baseline Characteristics

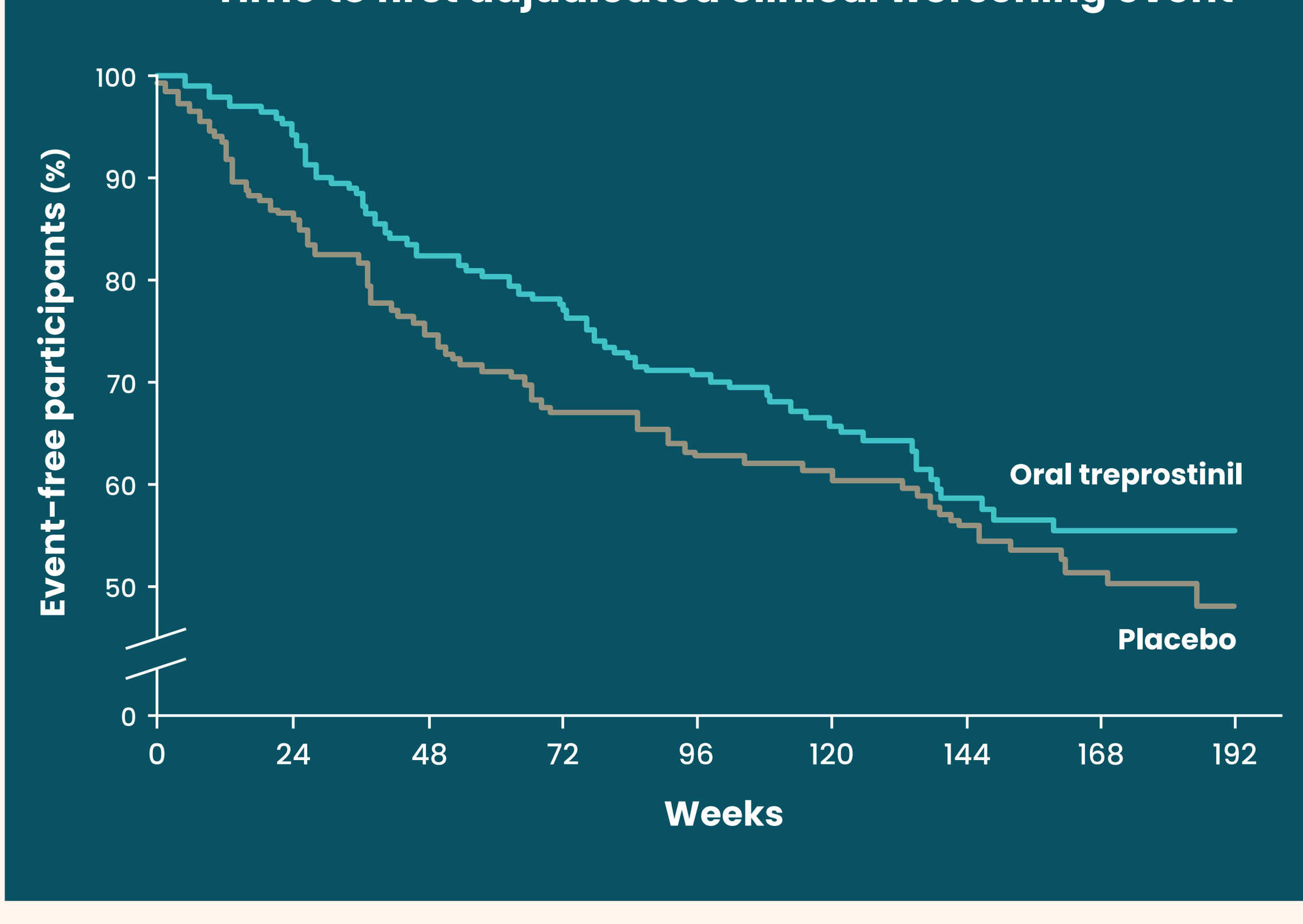
Time since diagnosis	Background therapy	Average age	WHO FC II	6MWD median
6.4 mo	5.4 mo	45.2 yrs	63%	405 m
(2.3, 13.3) median (IQR)	(2.4, 10.7) median (IQR)	±15.5 years		(342, 461) median (IQR)

Results

Primary Endpoint

Risk of clinical worsening is reduced with oral treprostinil compared to placebo

Time to first adjudicated clinical worsening event



COMPARED TO PLACEBO

26% reduction in risk of clinical worsening with oral treprostinil
HR 0.74 (95% CI, 0.56–0.97); p = 0.028

61% reduction in incidence of disease progression with oral treprostinil
HR 0.39 (95% CI, 0.23–0.66); p < 0.001

Risk-adjusted clinical worsening*

After adjusting for baseline risk profile, risk of clinical worsening for oral treprostinil vs. placebo

39% reduction
HR 0.61 (95% CI, 0.46–0.81); p < 0.001

* Data are from a post hoc analysis and should be interpreted with appropriate caution

Clinical worsening events

- **Death**
- **Hospitalization** due to worsening PAH
- **Progression** of disease
- **Prostacyclin** starting, infused or inhaled
- **Unsatisfactory** long-term response

Secondary Endpoints

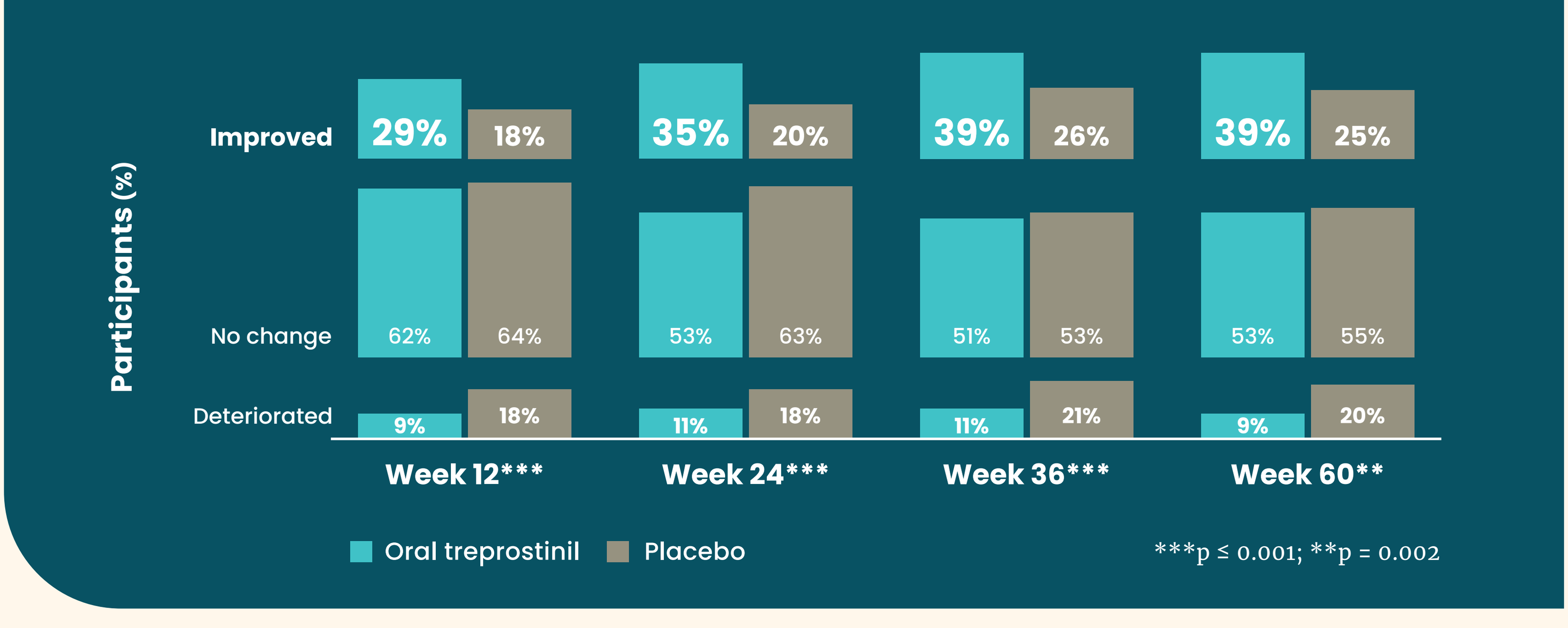
Risk Assessment

Noninvasive French low risk assessment criteria

WHO FC	NT-proBNP	6MWD
I–II	<300 pg/mL	>440 m

Improvement in risk category more likely for participants in the oral treprostinil group

Categorical change in noninvasive French risk assessment

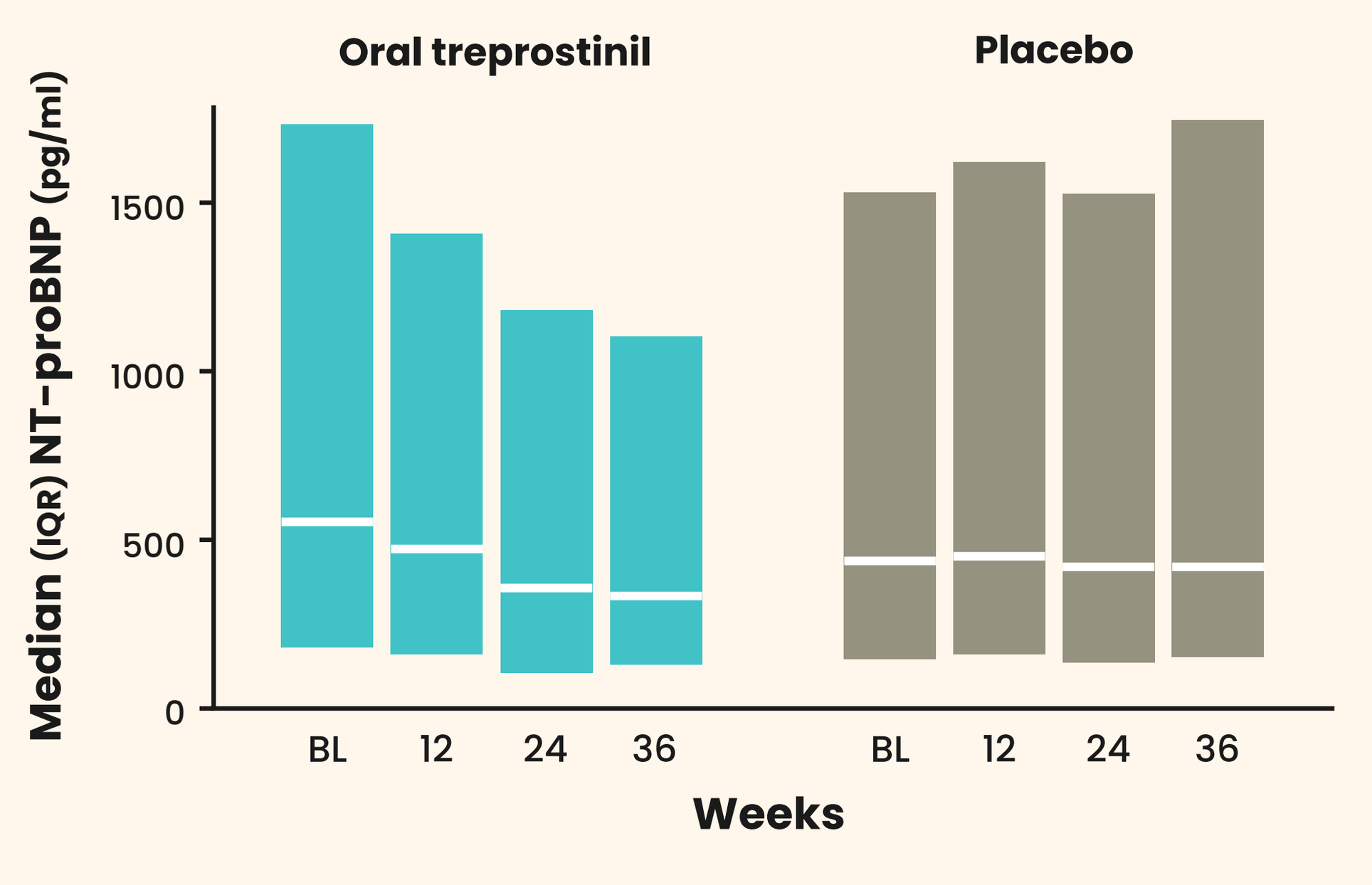


***p ≤ 0.001; **p = 0.002

NT-proBNP

NT-proBNP levels significantly decreased in the oral treprostinil group

NT-proBNP results by study visit



Percent change† relative to placebo

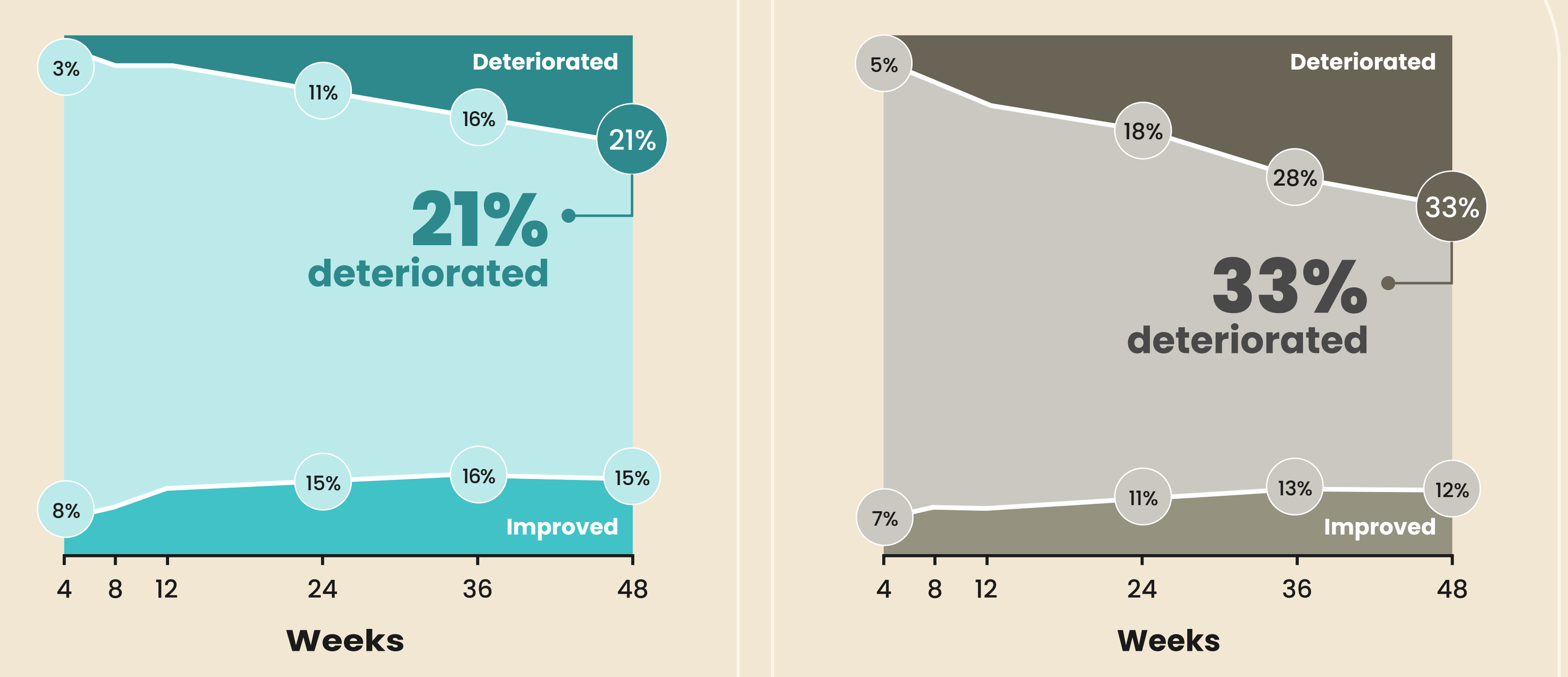
Week 12	Week 24	Week 36
−21%	−30%	−34%

all p < 0.001

†Difference (treatment vs. placebo) in geometric mean ratio to baseline

WHO FC

Oral treprostinil delayed deterioration in WHO FC



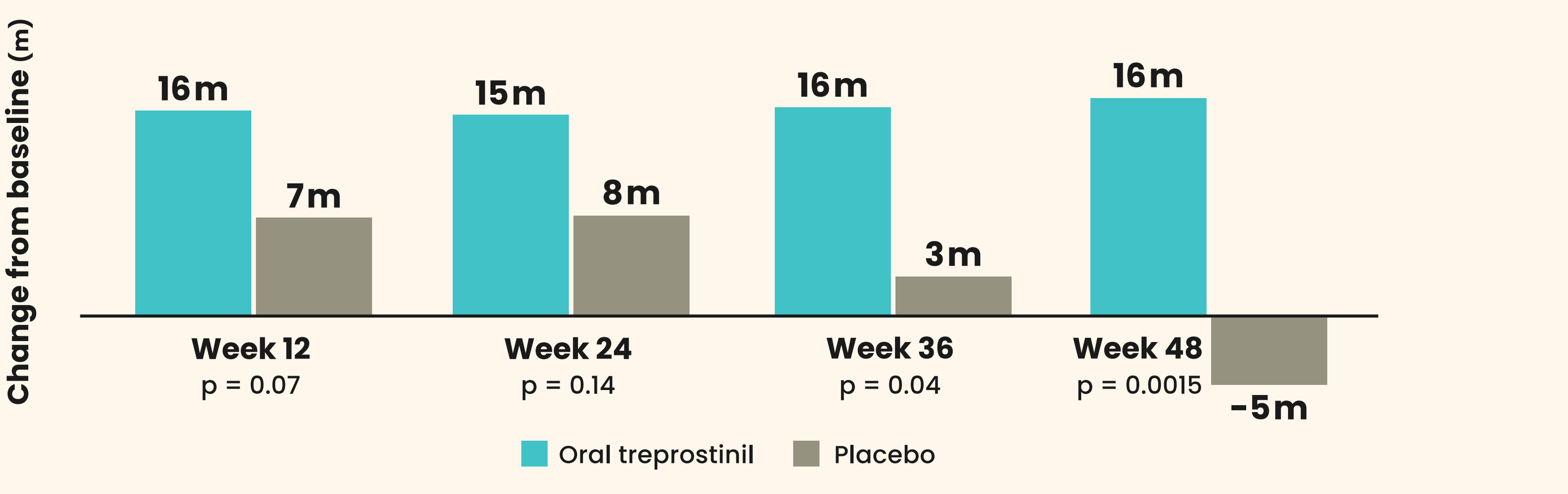
w12: p < 0.001   w24: p = 0.017   w36: p = 0.002   w48: p = 0.003
Data collected at discrete time points indicated on the x-axis

6WMD

6MWD significantly improved with oral treprostinil at weeks 36 and 48

(Change in 6MWD was not statistically significant at week 24)

Improved distance over time



Borg Dyspnea

Borg dyspnea scores after the 6MWT, improved in 36–38% of oral treprostinil participants

The safety profile in FREEDOM-EV was consistent with previous studies of oral treprostinil and known prostacyclin-related adverse events

Conclusion

In participants with PAH, the addition of oral treprostinil to background monotherapy can lower the risk of clinical worsening while improving key indicators of disease status

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; CI, confidence interval; LS, least squares; NT-proBNP, N-terminal pro–brain natriuretic peptide; OLE, open label extension; PAH, pulmonary arterial hypertension; PBO, placebo; TID, three times a day; WHO FC, World Health Organization functional class

FREEDOM-EV

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