

Title: Borg Dyspnea Score Adjusted Six Minute Walk Distance in Pulmonary Arterial Hypertension Clinical Trials

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RATIONALE: The six-minute walk test (6MWT) is commonly used in pulmonary arterial hypertension (PAH) clinical trials to measure exercise capacity when demonstrating the efficacy of a new therapy. 6MWT is an effort-based measure; its accuracy and variation are impacted by subject effort. The Borg Dyspnea Score (Borg) is usually recorded at the end of each 6MWT to measure this effort using shortness of breath as a surrogate. While measures of 6MWD and Borg are correlated, the statistical analyses are typically performed separately for each measure. A method is needed to analyze 6MWD and Borg as an integrated endpoint. We propose the Borg-adjusted 6MWD to analyze 6MWD data, incorporating change in Borg Dyspnea Score.

METHODS: A novel Borg-adjusted 6MWD is proposed whereby change in 6MWD is adjusted by a multiple of change in Borg score. The multiplier has been estimated by linear regression of change in 6MWD against the change in Borg score using data from the Placebo group in previous PAH clinical trials. Goodness-of-fit for the linear model was evaluated by R-squared statistics. Since change in 6MWD and Borg score are negatively correlated, the multiplier is negative. To apply the adjustment, the multiple of change in Borg score is subtracted from (added to) the change in walk distance when change in Borg score is increased (decreased). The Borg-adjusted 6MWD is calculated at each post-baseline visit. The treatment difference can be estimated using the Borg-adjusted 6MWD with parametric or non-parametric methods.

RESULTS: The Borg-adjusted 6MWD are evaluated using data from previous PAH clinical trials (see Table). The treatment differences, effect size, and p-values obtained from Borg-adjusted 6MWD method are compared with the results analyzing the 6MWD alone. Results suggest that an adjusted 6MWD, incorporating measurements of effort such as Borg score, is a more sensitive endpoint to detect the treatment effect in PAH clinical trials, which may be used to design smaller and more efficient PAH trials. Correcting 6MWD by other measures of effort or fatigue such as heart rate recovery may be expected to show similar sensitivity. Further sensitivity analyses to include effects of variable impacting 6MWD, such as age and weight, may be considered.

Table

	Multiplier	Placebo-Correct Median Difference (95% Confidence Limit)	P-value (Cochran-Mantel-Haenszel)	Placebo-Correct Mean Difference	Standard Deviation	Effect Size
FREEDOM-C: Original and Borg-Adjusted Analysis						
Original Change in 6MWD		11.0 (0.0, 22.0)	0.072	15.9	83.2	0.19
Borg adjusted change in 6MWD	-9.00	14.0 (2.0, 25.0)	0.034	18.1	96.1	0.19
Borg adjusted change in 6MWD (multiplier estimated using pooled data)	-7.52	13.0 (1.8, 24.5)	0.035	18.1	93.9	0.19
FREEDOM-C2: Original and Borg-Adjusted Analysis						
Original Change in 6MWD		10.0 (-2.0, 22.0)	0.089	10.4	80.2	0.13
Borg adjusted change in 6MWD	-5.51	12.3 (0.0, 25.0)	0.049	13.4	80.3	0.17
Borg adjusted change in 6MWD (multiplier estimated using pooled data)	-7.52	13.0 (0.5, 26.5)	0.041	14.4	80.6	0.18
FREEDOM-M: Original and Borg-Adjusted Analysis						
Original Change in 6MWD		23.0 (4.0, 41.0)	0.013	20.6	77.3	0.27
Borg adjusted change in 6MWD	-8.23	24.8 (3.8, 46.1)	0.013	21.8	83.2	0.26
Borg adjusted change in 6MWD (multiplier estimated using pooled data)	-7.52	24.5 (3.5, 45.5)	0.014	21.6	82.7	0.26