Win Ratio Analysis of the FREEDOM-EV Trial – A Hierarchical Approach to Multiple Clinical Endpoints

R. James White, MD, PhD[1]; Franck Rahaghi, MD[2]; Vijay Balasubramanian, MD[3]; Jean Elwing, MD[4]; Taekwon Hong, MA[5]; Youlan Rao, PhD[6]; Louis Holdstock, PhD[6]; Meredith Broderick, PharmD, JD[6]; C.Q. Deng, MD, PhD[6], Stephan Rosenkranz, MD[7]

[1]University of Rochester Medical Center; [2]Cleveland Clinic Florida; [3]University of California San Francisco, Fresno; [4]University of Cincinnati Medical Center; [5]North Carolina State University; [6]United Therapeutics Corporation; [7]University of Cologne

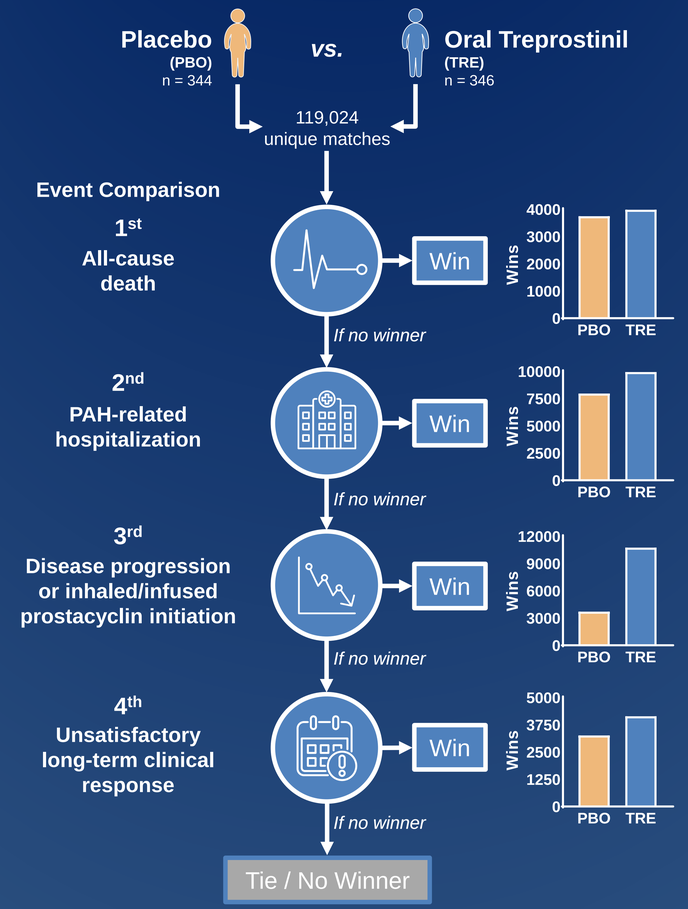
BACKGROUND

- FREEDOM-EV (NCT01560624): global, event-driven, placebo-controlled trial.
- Three times daily oral treprostinil (TRE) **delayed disease progression** in PAH participants when **added early to oral monotherapy.**[1]
- Oral TRE reduced the risk for composite clinical worsening (39% reduction after adjustment for baseline mortality risk).[1]
- "**Win ratio analysis**": a statistical approach that **ranks clinical outcomes** in composite endpoint trials (as compared to **standard analysis** which is the **time to any first event**).[2,3]
- Win ratio analysis **compares each oral TRE participant to each placebo (PBO) participant** as a different approach to mitigating the observed baseline imbalance in mortality risk.

METHODS

- All 690 participants in FREEDOM-EV included in analysis.
- Every oral TRE (n = 346) participant compared pairwise to every PBO participant (n = 344).
- Hierarchical ranking from **most** to **least** important was:
  1. **Death:** death from any cause
  2. **PAH-related hospitalization:** **adjudicated, non-elective hospitalization** related to PAH and/or right heart failure; lung or heart/lung transplantation; atrial septostomy
  3. **Disease progression or initiation of inhaled/infused prostacyclin:** **adjudicated 15% decrease in 6-minute walk distance (6MWD) and worsening PAH symptoms** (increase in WHO FC from baseline; worsening of symptoms of right heart failure)
  4. **Unsatisfactory long-term clinical response:** **adjudicated** decrease from baseline in 6MWD, sustained WHO FC III or IV symptoms
- In each matched pair of hierarchical events, the "**loser**" is the participant who had the **most important event first.** "Loser" is whomever had an all-cause death first; if neither participant died, "loser" is whomever had an adjudicated hospitalization due to worsening PAH…and so on through the event hierarchy (Figure 1). **Tie indicates that no event occurred in the matched pair.**
- The win ratio is calculated by dividing the total number of wins in the oral TRE arm by the total number of wins in PBO arm.

Figure 1. Schematic of Win Ratio Analysis.



$$\text{Win Ratio} = \frac{\text{Number of Wins in Oral Treprostinil Arm}}{\text{Number of Wins in Placebo Arm}}$$

$$\text{Win Ratio} = \frac{28802 \text{ wins}}{18663 \text{ wins}} = 1.54$$

(95% CI 1.16-2.05, p = 0.003)

RESULTS

- **Baseline demographics:** mean 45 years old; median time since PAH diagnosis of 6 months; on background monotherapy for median 5 months; mean 6MWD of 396 m; 63% WHO FC II.[1]
- **Overall event frequency was low.** Figure 2 shows **all events** (whether or not first; a participant could have had more than one event) during the **median 58 weeks of follow-up**. **Oral TRE assigned participants had fewer of each kind of event** considering all events during the blinded phase.

***Figure 2*. Frequency of each clinical event in FREEDOM-EV.**

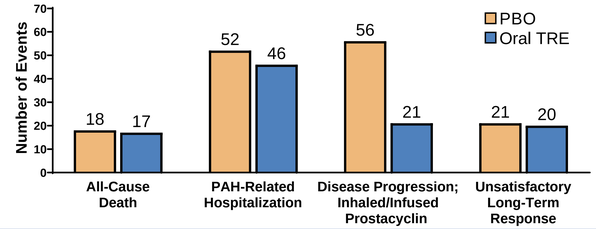


***Table 1*. Matches with winners and win percentages for oral TRE and PBO by event (same data, Fig. 1).**

	All-Cause Death	PAH-Related Hospitalization	Disease Progression; Inhaled/Infused Prostacyclin	Unsatisfactory Long-term Response	Total
Oral TRE Wins	3980 (8%)	9934 (21%)	10750 (23%)	4138 (9%)	28802 (61%)
PBO Wins	3744 (8%)	7959 (17%)	3702 (8%)	3258 (7%)	18663 (39%)
Total	7724 (16%)	17893 (38%)	14452 (30%)	7396 (16%)	47465 (100%)

Win ratio: 1.54 (95% CI 1.16-2.05, p = 0.003)

- Total 119,024 pairwise "matches" were analyzed (346 oral TRE x 344 PBO).
- 47,465 (40%) matches with winners and 71,559 (60%) matches tied (no event in the match).

DISCUSSION

- **Win ratio analysis demonstrated oral TRE was superior** in hierarchical analysis of meaningful clinical outcomes: **more wins for PAH-related hospitalizations and disease progression.**
- Win ratio results corroborate and expand the primary composite endpoint finding – a reduction in risk of clinical worsening – **oral TRE reduced rate for each type of clinical worsening event**.
- Win ratio approach **prioritizes most clinically relevant endpoints** and **mitigates baseline risk differences** (by comparing all possible pairs); adds important information to 'time to first composite event' in PAH studies, especially when frequency of events is low (in a relatively low risk population).

REFERENCES

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