Case Study: Digital Outcome Measures of Physical Activity Approved as Primary Endpoint in Pivotal Cardiopulmonary Study

Bellerophon Therapeutics, a clinical stage biotherapeutics company focused on developing treatments for cardiopulmonary diseases, was able to save their clinical development program through the use of objective, continuous digital outcome measures.

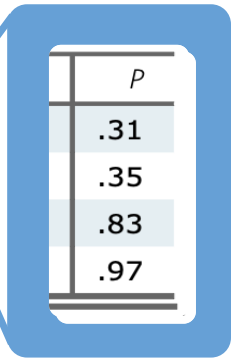
The Situation

Bellerophon deployed traditional Clinical Outcome Assessments (COAs), oxygen saturation (SpO2) and 6 Minute Walk Distance (6MWD), as primary endpoints in their Phase 2b clinical trial. Although these measures were clinically positive, they were not statistically significant.[1,2] The evidence generated was not strong enough to proceed to a Phase 3 clinical trial.

TABLE 4] Oxygen Saturation and 6MWD

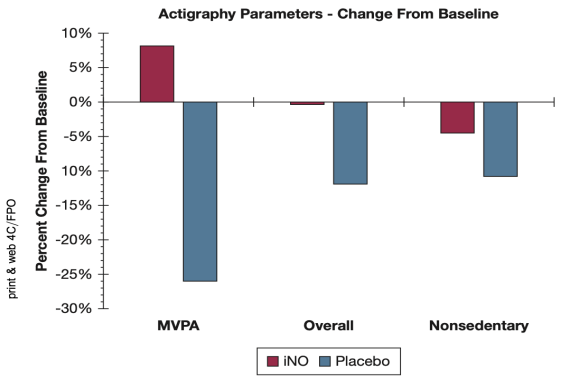
Actigraphy Parameter	Placebo	iNO	Difference	*P*
Relative oxygen desaturation	10.5% (12.6%)	-9.3% (8.0%)	19.8% (14.2%)	.31
SpO_2 nadir	-1.4% (1.6%)	0.3% (0.7%)	1.7% (1.5%)	.35
6MWD (m)	0.5 (6.7)	7.2 (11.7)	6.7 (18.8)	.83
Distance saturation product (meter %)[a]	-2.0 (16.4)	8.5 (11.2)	10.5 (19.1)	.97

Relative oxygen desaturation is calculated as: (desaturation at end of study − desaturation at baseline) ÷ desaturation at baseline; a negative number indicates a reduction in desaturation as compared with baseline. SEs for each parameter are provided in the parentheses. Statistical analysis was conducted for active vs placebo via Mann-Whitney test at week 8 on available data. See Table 1 legend for expansion of abbreviations.
[a]Distance saturation product is calculated as: 6MWD × SpO_2 Nadir.



The Approach

Fortunately, as part of the clinical study design, the sponsor included ActiGraph's wearable data collection solution to evaluate possible changes in study participants' Physical Activity (PA) including, but not limited to, the change in Moderate to Vigorous Physical Activity (MVPA) from baseline, as an exploratory endpoint. Upon statistical analysis, MVPA showed both clinical and statistically significant changes with treatment, and ActiGraph assisted Bellerophon to present the analysis to the FDA.



Nathan, Steven D., Kevin R. Flaherty, Marilyn K. Glassberg, Ganesh Raghu, Jeffrey Swigris, Roger Alvarez, Neil Ettinger, et al. 2020. "A Randomized, Double-Blind, Placebo-Controlled Study of Pulsed, Inhaled Nitric Oxide in Subjects at Risk of Pulmonary Hypertension Associated With Pulmonary Fibrosis." *Chest* 158 (2): 637–45.

The Outcome

The FDA endorsed the ActiGraph MVPA endpoint as the primary endpoint in the follow up Phase 3 pivotal trial (currently ongoing), making this the first FDA-endorsed primary endpoint in a pivotal trial using wearable data.[3] ActiGraph's PA digital endpoints, specifically MVPA, not only saved this clinical development program, but also allowed the sponsor to show the efficacy of their treatment in a less-biased, more patient-centered and meaningful way.

In addition, a recent development report on the Phase 3 REBUILD pivotal trial announced that FDA has approved a request to reduce the sample size by more than half, from 300 participants to 140, based on an effect size generated from the Phase 2 study data.
The benefit of this reduced sample size is that the Sponsor is accelerating completion of the study, with top-line data now expected several months earlier than originally planned.

"The revised study size is based on an effect size generated from Phase 2 study data in 44 patients with the same primary endpoint being evaluated in the Phase 3 study, MVPA. The analysis presented to the FDA indicated that the trial remains adequately powered to demonstrate a statistically significant result on MVPA," said Dr. Steven D. Nathan, M.D., F.C.C.P., Medical Director of the Advanced Lung Disease and Lung Transplant Program at Inova Fairfax Hospital and Chair of Bellerophon's REBUILD Steering Committee.[4]

Recommendation

De-risk your clinical program by incorporating objective, continuous digital endpoint measures of PA as adjunct assessments to traditional COAs and other periodically collected endpoints (e.g. 6MWD, ETT, PFT etc.) in your clinical trial.

References

1. **Paper from Bellerophon**
   A Randomized, Double-Blind, Placebo-Controlled Study of Pulsed, Inhaled Nitric Oxide in Subjects at Risk of Pulmonary Hypertension Associated With Pulmonary Fibrosis

2. **Poster from Bellerophon**
   Actigraphy as a clinically meaningful endpoint to detect change after treatment with iNO (30 mcg/kg-IBW/hr) in patients at risk

3. **ClinicalTrials.gov Study Record**
   A Study to Assess Pulsed Inhaled Nitric Oxide in Subjects With Pulmonary Fibrosis at Risk for Pulmonary Hypertension - Full Text View - ClinicalTrials.gov

4. **Company Press Release**
   Bellerophon Announces FDA Acceptance of Change to Ongoing Phase 3 REBUILD Study of INOpulse® for Treatment of Fibrotic Interstitial Lung Disease