Biological Quality Control and Core Laboratory Considerations for Cardiopulmonary Exercise Testing in a Clinical Trial of Effects of Ralinepag on Exercise Capacity in Patients with Pulmonary Arterial Hypertension: ADVANCE CAPACITY

J. Porszasz[1], R. Benza[6], J. Blonshine[3], S. Blonshine[3], R. Casaburi[1], M. Cunningham[2], M. Guazzi[4], L. Holdstock[2], R. Oudiz[1], F. Torres[5], D. Yehle[2], J.L. Vachiery[7]

[1]The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center- Torrance (USA), [2]United Therapeutics - Research Triangle Park (USA), [3]TechEd Consultants - Mason (USA), [4]University of Milano - Milan (Italy), [5]UT Southwestern - Dallas (USA), [6]Ohio State University - Columbus (USA), [7]Erasme Academic Hospital (Belgium)

Introduction

Patients with pulmonary arterial hypertension (PAH) have impaired cardiopulmonary function, resulting in severely reduced exercise capacity and ventilatory inefficiency. Cardiopulmonary exercise testing (CPET) offers insight into PAH pathophysiology and is a useful tool to assess PAH severity and therapeutic efficacy. However, use of CPET in clinical trials of PAH treatments has been limited by technical difficulties.[1, 2, 3, 4] This study will assess the effects of once-daily ralinepag on. exercise capacity using CPET with intensive rigor and quality control (QC) procedures and a central laboratory.

Design

28-week multicenter, randomized, double-blind, placebo-controlled study evaluating ralinepag (a selective, oral non-prostanoid, IP receptor agonist) in PAH, 2:1 randomization to ralinepag or placebo (Figure 1). Primary endpoint is change from Baseline to Week 28 in peak VO_2, with V_E/VCO_2 slope as a key secondary endpoint. N ≈ 193 subjects (135 evaluable Baseline and Week 28 CPETs).

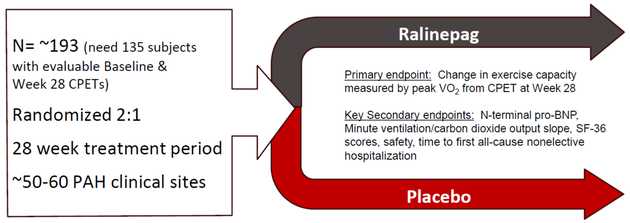
A central laboratory will read all CPET data and oversee quality control across all sites. The laboratory includes recognized CPET experts with extensive experience in randomized controlled trials utilizing CPET. They can analyze data from 6 different manufacturer's CPET systems. The flow of data from each subject to the central lab via a central repository (Intrinsic) for analysis, or to TechEd Consultants, Inc. (for Biological QC [BioQC]) is depicted in Figure 5.

Standardized analysis methods ensure repeatability and consistency.

Rigorous quality control is enforced across the study (Figures 2 and 3).

Site selection and site BioQC training is ongoing and enrollment has started.

Figure 1. Study Design Scheme for ADVANCE CAPACITY



CPET Methods and Quality Control

Figure 2. Levels of Quality Control for ADVANCE CAPACITY

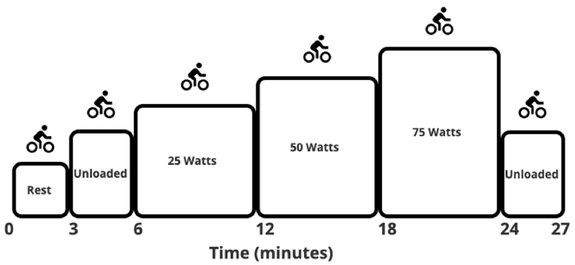
Before the Study
- Rigorous site selection process (Figure 4)
  - Input from steering committee
  - CPET laboratory evaluation by independent vendor
- Rigorous quality control training

During the Study
- Regular biological quality control (BioQC) with standardized protocol
  - 16 hours of CPET procedure training prior to site activation
  - BioQC performed every 6 weeks and syringe linearity every 2 weeks
- Secure transmission of breath-by-breath raw data to central lab
- Central repository stores all data securely

Data Analysis

Highly qualified central laboratory
- Creates standardized output from raw CPET data
- Analyzes and interprets all studies with dual reads and quality checks

Figure 3. Standard BioQC Test Protocol



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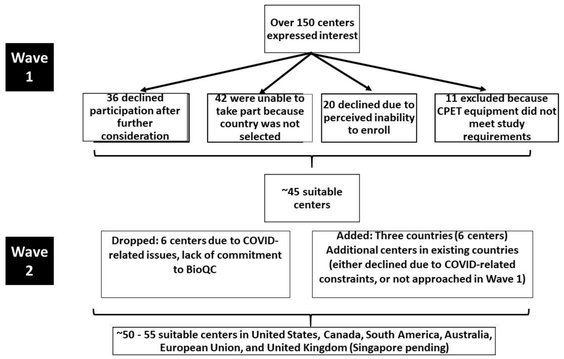
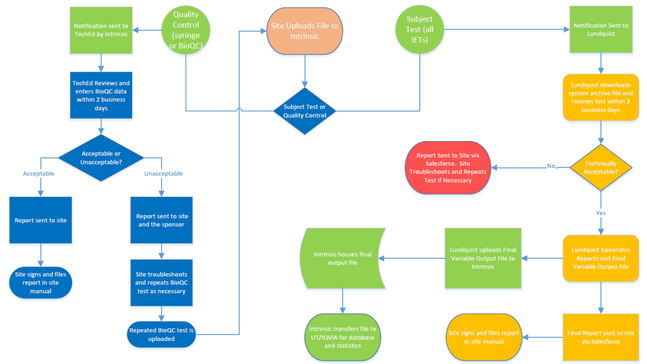
Site selection process

Figure 4. Site Selection Process



Data Flow and Central Laboratory Procedures

Figure 5. Flow of data from subject to central laboratory



Conclusion

This trial has the potential to offer a method for CPET use in future global clinical trials.

References

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