Chronic Heart Failure Working Group

14th Annual PRO Consortium Workshop – Silver Spring, MD – April 19-20, 2023

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

Background

Rationale for Chronic Heart Failure (CHF) Working Group

- PRO Consortium member representatives and FDA advisors identified CHF as a priority area with an unmet need for a 'fit-for-purpose' clinical outcome assessment (COA) approach to evaluate clinical benefit in CHF clinical trials.
- Based on emerging technologies that enable the collection of data via mobile sensor devices (e.g., activity trackers/monitors), there is an increased interest in leveraging these for the collection of clinical trial endpoint data in patients with CHF.
- During working group formation, Amgen offered to share its developmental PRO measures and results of ongoing work exploring the use of activity monitor data in persons with CHF.

Goal of the CHF Working Group

- Develop a measurement strategy to assess symptom severity, symptom impact on physical function, and physical activity for adults with CHF by incorporating both patient-reported outcome (PRO) and activity monitor data
- Obtain FDA qualification of measures to assess efficacy endpoints in CHF clinical trials

Concepts of Interest

- Concepts of interest for the PRO measures, developed by Amgen, are self-reported severity of CHF symptoms (*Chronic Heart Failure-Symptom Scale* [*CHF-SS*]) and self-reported impact of CHF symptoms on physical functioning (*Chronic Heart Failure-Impact Scale* [*CHF-IS*]).
- Concept of interest for the activity monitor-based endpoint measure is physical activity with specific variable(s) to be determined.

Context of Use

- Target population includes adults with a clinician-confirmed history of CHF for ≥3 months with New York Heart Association class II to IV symptoms for ≥4 weeks as confirmed by medical records, documented diagnosis of CHF with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF), in stable condition for at least 4 weeks, treated with stable, optimal pharmacological therapy for a minimum of 4 weeks prior to screening.

Targeted Labeling Language

- Patients treated with [*Drug X*] reported reductions in severity of CHF symptoms, if experiencing at least mild/moderate symptoms at baseline, compared with treatment [YY]. (*Based on group comparisons of means*)
- Compared with [YY], significantly more patients treated with [*Drug X*] reported reductions in severity of CHF symptoms if experiencing at least mild/moderate symptoms at baseline. (*Based on group comparison using responder analysis*)
- Patients treated with [*Drug X*] reported an improvement in physical function if experiencing limitations in physical function at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed worsening in physical function if experiencing limitations in physical function at the start of the trial.
- Patients treated with [*Drug X*] reported an improvement in physical activity if experiencing limitations in physical activity at the start of the trial.
- Patients treated with [*Drug X*] reported a delayed worsening in physical activity if experiencing limitations in physical activity at the start of the trial.

Milestones

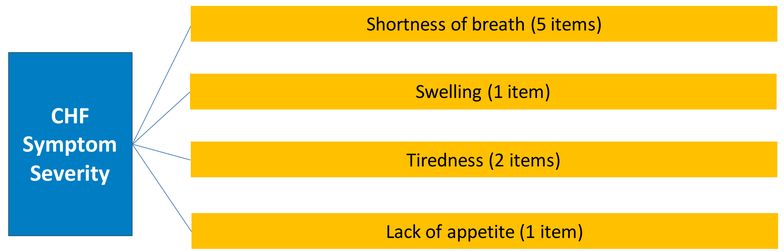
Milestone	Expected Date	Completed Date
Letter of Intent submission for 3 measures to FDA		DEC 2018
Acceptance of 3 measures into the COA Qualification Program		APR 2019
Qualification Plan submission for *CHF-SS* to FDA		MAR 2023
Qualification Plan submission for *CHF-IS* to FDA	Q3 2023	
Qualification Plan submission for activity monitor-based endpoint measure to FDA	Q4 2023	
Full Qualification Package submissions to FDA	TBD	

Highlights

Example Endpoint Model for Treatment of CHF

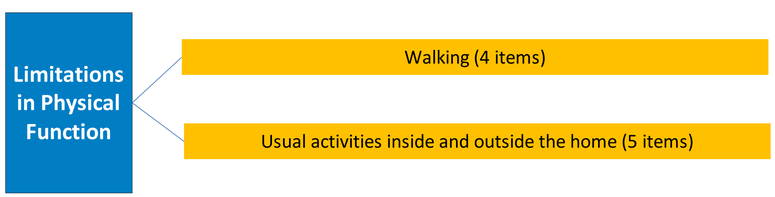
Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Time to cardiovascular (CV) death or time to heart failure (HF) event	Event rate
Secondary	Evaluate effects of [*Drug X*] on time to: • CV death • HF hospitalization • All-cause death	Event rate
Potential New Primary or Secondary	Reduction in (or delayed worsening of) severity of CHF symptoms Reduction in (or delayed worsening of) limitations in physical function Improvement in (or delayed worsening of) activity monitor-based variable reflecting a meaningful aspect of physical activity	PRO (*CHF-SS*) PRO (*CHF-IS*) Activity monitor-based COA

Chronic Heart Failure-Symptom Scale (*CHF-SS*) Conceptual Framework



Number of Items: 9 items addressing 4 symptom domains
Recall Period: Past 7 days
Response Options: 5 to 6-level verbal rating scale
Symptom Attribute: Intensity or frequency as a measure of severity
Data Collection Mode: Paper or tablet used for data collection (up to this point)

Chronic Heart Failure-Impact Scale (*CHF-IS*) Conceptual Framework



Number of Items: 9 items addressing 2 domains
Recall Period: Past 7 days
Response Options: 6-level verbal rating scale
Impact Attribute: Level of difficulty with performance of physical function-dependent tasks
Data Collection Mode: Paper or tablet used for data collection (up to this point)

Working Group Activities

Completed Activities

- Amgen agreed to share the PRO measures with the CHF Working Group for qualification.
- Cognitive interviews to obtain further qualitative evidence requested by FDA were completed by Amgen in December 2019, finalizing the content of the *CHF-SS* and *CHF-IS*.
- Data collection for a separate concept elicitation study (N=31) to identify the meaningful aspects of physical activity to support development of the concept of interest for the activity monitor-based endpoint measure was completed by Evidera in December 2020.
- Amgen completed a stand-alone study (N=100) to evaluate the psychometric properties of the PRO measures and the use and usefulness of an activity monitor, including evaluation of data to identify variables that could support endpoints, in January 2021; data were shared with C-Path for future analysis.
- The concept elicitation report was submitted to FDA in July 2021.
- An advisory panel was convened (December 2021; March 2022) with the goal of alignment on existing (or proposed novel) activity monitor metric(s) that best reflect/capture the meaningful aspects of physical activity identified by persons with CHF.
- Informal meeting with FDA took place in October 2022 to discuss the proposed metrics for the activity monitor-based endpoint measure and obtain FDA feedback.
- The WG determined that a step count-related metric was most appropriate to pursue.
- The *CHF-SS* Qualification Plan was submitted to FDA in March 2023.

Unique Issues for the Working Group

- This is the PRO Consortium's first working group proposing qualification of an activity monitor-based endpoint measure.
- One of the main challenges is determining what variable(s) from the activity monitor will be used to derive an endpoint.
- It remains an empirical question regarding how to incorporate the PRO data and the activity monitor-based data to derive appropriate endpoints in clinical trials.

Next Steps

- Statistical analysis plan(s) and other supplemental documents associated with the step count-related metric will be developed.
- Qualification Plans will be submitted to FDA for the *CHF-IS* and the activity monitor-based endpoint measure when completed.

Working Group Participants

Company/Organization	Representative
AstraZeneca	Folke Folkvaljon, MSc
Bayer	Luke Bamber, MSc
Bristol Myers Squibb	Kathleen Wyrwich, PhD; Wendy (Yue) Zhoug, PhD
Eli Lilly & Company	Jiat Ling Poon, PhD; Jay Trudeau, PhD; Gilwan Kim, PharmD, MS
GSK	Robyn von Maltzahn, MSc; Wen-Hung Chen, PhD
Janssen Global Services, LLC	Stacy N. Davis, PhD, MPH; Robert Janiczek, PhD
Merck Sharp & Dohme, LLC	Josephine Norquist, MS
Affiliation	**Other Participants**
Cerevel Therapeutics	Gary Globe, PhD, MBA
eCOA Consortium	Bill Byrom, PhD (Signant Health); Paul O'Donohoe, MSc (Medidata Solutions)
Gwaltney Consulting	Chad Gwaltney, PhD
U.S. Food and Drug Administration	Charu Gandotra, MD, MSCTR, FACC
Research Partner	**Research Team**
Evidera	Milena Anatchkova

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