Chronic Heart Failure Working Group

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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 for evaluating 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 increased interest in leveraging these for the collection of clinical trial endpoint data in patients with CHF.
- During formation of the Working Group, Amgen offered to share its developmental patient-reported outcome (PRO) measures and results of ongoing efforts supporting use of activity monitor data in patients with CHF.

Goal of the CHF Working Group

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

Concepts of Interest

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

Context of Use

- The target population includes adults with a clinician-confirmed history of chronic heart failure for ≥3 months with New York Heart Association class II–IV symptoms for ≥4 weeks as confirmed by medical records, confirmed and documented diagnosis of chronic heart failure with preserved ejection fraction (HFpEF) or chronic heart failure with reduced ejection fraction (HFrEF), in stable condition for at least 4 weeks, and 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 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. (*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 deterioration/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 deterioration/worsening in physical activity if experiencing limitations in physical activity at the start of the trial.

Milestones

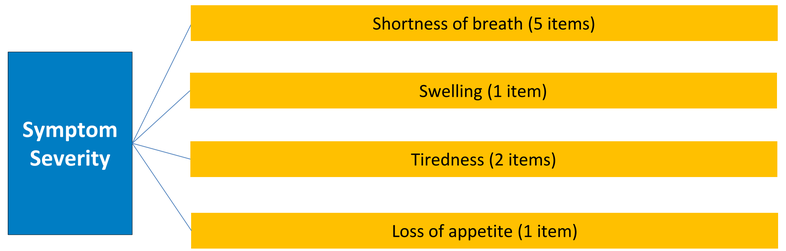
Milestone	Expected Date	Completed Date
Submit Letter of Intent (LOI) to FDA		DEC 2018
Submit Qualification Plan to FDA	TBD	
Submit Full Qualification Package to FDA	TBD	

Highlights

Example Endpoint Model for Treatment of CHF

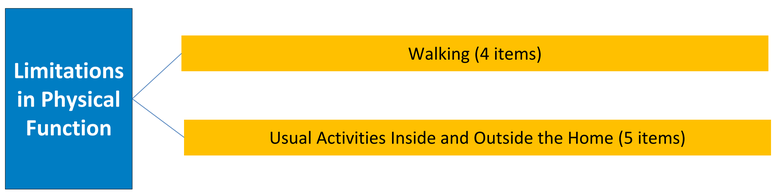
Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Time to cardiovascular (CV) death or time to heart failure (HF) event	Event rate
Secondary	Evaluate effects of [*Drug X*] on time to: • CV death • HF hospitalization • All-cause death	Event rate
Potential New Primary or Secondary	Reduction 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/mobility	PRO (*CHF-SS*) PRO (*CHF-IS*) Activity monitor-based COA

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



Core 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



Core 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

- Prior research completed by Amgen on the *CHF-SS* and the *CHF-IS* in both HFpEF and HFrEF patients confirmed item relevance, concept coverage, and appropriateness of response options and recall period.
- FDA feedback was requested early and provided to Amgen on several occasions during the development process. In the latest communication, FDA requested additional qualitative evidence from HFpEF and HFrEF patients.
- Amgen has agreed to share these measures with the CHF Working Group for qualification.
- Letter of Intent was submitted to FDA in December 2018.

Unique Issues for the Working Group

- This is the PRO Consortium's first working group that is 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 the endpoint.
- It remains an empirical question as to whether it makes clinical and clinimetric sense to combine the PRO data with activity monitor-based data to derive a composite endpoint.

Next Steps

- Additional cognitive interviews with the *CHF-SS* and *CHF-IS* are being conducted by Amgen to obtain the additional qualitative evidence requested by FDA.
- Further psychometric evaluation of the measures is planned as part of Amgen's CHF development program.
- Additionally, a stand-alone study is planned by Amgen to evaluate the use and usefulness of an activity monitor in CHF treatment trials, including evaluation of the data to identify the variables that would support an endpoint.
- All results will be shared with the CHF Working Group.

Working Group Participants

Company/Organization	Representative
Amgen	Gary Globe, PhD, MBA
AstraZeneca	Anna Niklasson, PhD
Bayer	Luke Bamber, MSc; Corinna Weidt, PhD
Ironwood	Funke Ojo, MPH; David Reasner, PhD
Janssen	Renee Pierson, MBA; Jeremiah Trudeau, PhD
Lilly	Jiat-Ling Poon, PhD
Merck	Josephine Norquist, MS; Mei Yang, PhD
Novartis	Maximiliano Di Domenico, MD; Janet Munro, MPhil, MBBS; Abhishek Kavati, PhD, MBA, MS
Sanofi	Catherine Brun-Strang, MD, PhD; Matthew Reaney, MSc, CPsychol
Other Participant	**Affiliation**
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