Cognition Working Group

Presented at the Ninth Annual PRO Consortium Workshop – Silver Spring, MD – April 25-26, 2018

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Cognition Working Group (WG)

- PRO Consortium member representatives and FDA advisors identified mild cognitive impairment due to Alzheimer's disease (MCI due to AD) as a priority area for measuring AD treatment benefit
- After extensive qualitative research, a draft PRO measure (i.e., *Interpersonal Function and Daily Activities Questionnaire v0.1* [*IFDAQ*]) was developed to assess instrumental activities of daily living (IADLs) and interpersonal functioning in patients with MCI due to AD.
- FDA stated concerns regarding the ability of patients with MCI due to AD to maintain sufficient cognitive insight to accurately self-report over the duration of clinical trials. Therefore, FDA indicated that qualification of a PRO instrument had a low probability of success in the target context of use.
- With FDA agreement, the Cognition WG revised its scope of work to focus on the evaluation of a performance-based outcome (PerfO) measure for use in patients with MCI due to AD to measure day-to-day functioning.

Goal of the Cognition WG

- The Cognition WG's goal is to qualify a PerfO measure to improve upon the current state of assessment of treatment benefit in clinical trials for patients with MCI due to AD. The measure will capture the patient's performance of tasks that reflect essential aspects of day-to-day functioning.

Draft Labeling Language

- Patients treated with X demonstrated [XX]% improvement in day-to-day functioning as compared to [XX]% improvement for patients treated with placebo.
- Patients show less decline in performance of day-to-day functioning over time when treated with X [XX]% as compared to placebo [XX]%.

Milestones

Milestone	Expected Date	Completed Date
Based on FDA interaction with the WG, the decision was made to work on qualification of a PerfO measure rather than a PRO measure		JAN 2015
Consult with expert panel members and identify PerfO measures that would be the best candidates for WG consideration		Q4 2015
Convene consensus development meeting to evaluate the measures identified to assess day-to-day functioning in patients with MCI due to AD		MAR 2016
Develop Letter of Intent (LOI) for proposed COA qualification of *University of California San Diego Performance-based Skills Assessment* (*UPSA*) to assess day-to-day functioning in treatment trials for patients with MCI due to AD		MAY 2016
FDA responded to LOI and provided approval to enter the *UPSA* into the CDER COA DDT qualification program		OCT 2016
Submit Initial Briefing Package (IBP) to FDA	TBD	
Submit Qualification Plan (QP) to FDA	TBD	
Submit Qualification Briefing Package to FDA for exploratory use of the *UPSA* in patients with MCI due to AD	TBD	

Highlights

Endpoint Model for Treatment of MCI Due to AD

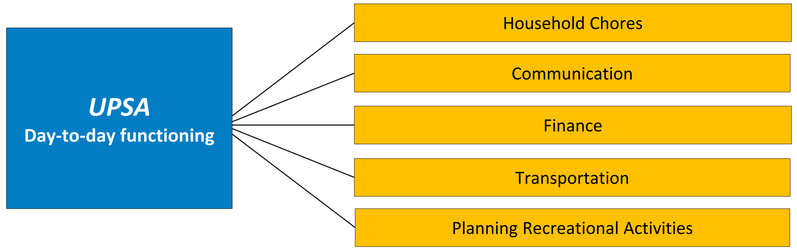
Endpoint Hierarchy	Endpoint Concept(s)	Type of Endpoint
Current		
Co-Primary	**Cognition** Cognitive (neuropsychological) test battery	PerfO*
	Function Performance of instrumental activities of daily living	PerfO
Proposed		
Primary	**Function** Performance of instrumental activities of daily living	PerfO (*UPSA*)

*To be determined by each sponsor when designing its clinical trials

Target Population

- Patients 45 years of age and older
- Patients diagnosed with MCI due to AD

Hypothesized Conceptual Framework



Working Group Updates

The PerfO assessment project formally launched in February 2015, and the following activities have been completed in partnership with NeuroCog Trials (NCT):

- Compiled and reviewed documentation related to the *UPSA* across previous clinical research studies and sponsor-provided *UPSA* data in the context of schizophrenia treatment
- Summary of key findings from initial review:
  - The *UPSA* demonstrates generally strong psychometric properties across different versions, primarily from evidence in patients with schizophrenia.
  - The *UPSA* and each component subdomain shows promise for sensitivity to decline or improvement in older patients with MCI due to AD.
- The expert panel meeting was held on March 14, 2018 to address the following four questions:
  1. What are the thoughts regarding the use of the *UPSA* as an endpoint for MCI?
  2. What gaps exist in current versions of the *UPSA* that could be filled by other items and/or domains?
  3. Are there any gaps in the report that could be addressed in existing literature?
  4. From among the existing *UPSA* items/domains, is there a subset that sufficiently captures the core cognition-dependent activities that would be necessary to effectively assess treatment benefit in MCI due to AD?

Unique Issues for the Working Group

- Several versions of the *UPSA* have emerged and been used in schizophrenia treatment trials, but there is limited empirical evidence to guide version selection for qualification of the *UPSA* in patients with MCI due to AD

Lessons Learned

- The FDA is willing to consider use of a PerfO measure in assessing day-to-day functioning as an efficacy endpoint in MCI due to AD clinical trials, potentially as a single primary endpoint
- The consensus development meeting provided an excellent framework for shaping and aligning future strategy

Next Steps

- Key areas for further evaluation of *UPSA* include cultural adaptation in multinational trials, content validity, psychometric evaluation in MCI due to AD and comparison to existing informant-reported measures
- The following to be performed in conjunction with NeuroCog Trials, Inc.:
  - Identify any gaps in prior adaptations and draw recommendations for adapting the *UPSA* for use in global clinical trials for MCI due to AD
  - Work with developers of *UPSA* and relevant experts to determine if additional changes are necessary to enable use in the MCI due to AD population
  - Determine the most appropriate version of the *UPSA* for use in future clinical trials of MCI due to AD
  - Identify and describe ways in which the *UPSA* can be revised to reflect contemporary activities while retaining ability to assess concepts of interest
  - Conduct translatability assessment of the revised *UPSA* and identify activities in other cultures that may be conceptually equivalent

Working Group Participants

Company/Organization	Name
AbbVie	Katy Benjamin, PhD (Co-Chair); Yash Jalundhwala, MS; Xiaolan Ye, PhD, MS
AstraZeneca AB	Daniel Eek, PhD
Boehringer Ingelheim	David Brill, PhD; Matt Sidovar, MSc
Eli Lilly and Company	Scott Andrews, PharmD (Co-Chair); Julie Chandler, PhD
Merck Sharp & Dohme Corp	Cathy Anne Pinto, PhD, MS
Novartis	Valery Risson, PhD, MBA
Pfizer, Inc.	Joel Bobula, MA
Roche/Genentech	Fiona McDougall, PhD, ClinPsyD
Sanofi	Matthew Reaney, MSc, PGDip

Expert Panel Members	Affiliation
Paul Aisen, MD	University of Southern California
Terry E. Goldberg, PhD	Columbia University Medical Center
Phil Harvey, PhD	University of Miami
Tom Patterson, PhD	University of California, San Diego
Pierre Tariot, MD	Banner Alzheimer's Institute

Consulting Organization	Research Team
NeuroCog Trials, Inc.	Richard S.E. Keefe, PhD; Trina Walker, RN; William Horan, PhD; Anzalee Khan, PhD