Cognition Working Group

Presented at the Eighth Annual PRO Consortium Workshop – Bethesda, MD – April 26-27, 2017

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.
- After extensive qualitative research, a draft PRO measure (i.e., *Interpersonal Function and Daily Activities Questionnaire v0.1* [*IFDAQ*]) was developed to assess complex activities of daily living 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.
- This was confirmed during a teleconference with representatives from FDA's Clinical Outcome Assessments (COA) Staff and the Division of Neurology Products (DNP) held on October 7, 2014, when the FDA indicated that qualification of a PRO instrument had a low probability of success in the target context of use.
- FDA supported exploration of a performance-based outcome (PerfO) measure to assess functional ability in the target population; hence, the Cognition WG has revised its scope of work to focus on the evaluation of PerfO measures that could be used in patients with MCI due to AD to measure day-to-day functioning. No qualified assessment tool is currently available to meet this need.

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 Qualification Briefing Package to FDA for exploratory use of the *UPSA*	TBD	

Highlights

Endpoint Model for Treatment of MCI Due to AD

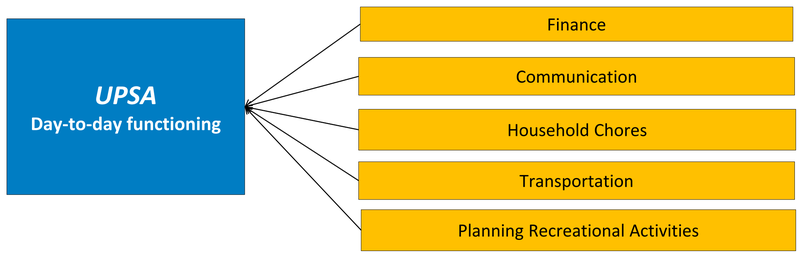
Endpoint Hierarchy	Endpoint Concept(s)	Type of Endpoint
Current		
Co-Primary	**Cognition** • Cognitive (neuropsychological) test battery **Function** • Performance of instrumental activities of daily living	**PerfO*** **PerfO**
Proposed		
Primary	**Function** • Performance of instrumental activities 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 project formally launched in February 2015, and the following activities have been completed:

- WG decision to submit LOI to COA DDT Qualification Program for *UPSA* as a trial endpoint measure in patients with MCI due to AD
- Received feedback on LOI from FDA and gained acceptance into COA DDT Qualification Program
- Developed strategy to address feedback contained in FDA response letter and support creation of Initial Briefing Package (IBP) -- see **Next Steps**

Unique issues for the working group

- *IFDAQ v0.1* will continue to be refined for potential use in very early disease (being used in one ongoing study [A4])
- Key areas for potential further evaluation of *UPSA* include cultural adaptation in multinational trials, content validity, psychometric validation in MCI due to AD and comparison to existing informant-reported measures

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

In conjunction with NeuroCog Trials, Inc.

- Conduct review of clinical research studies where the *UPSA* was implemented
- 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 an MCI due to AD population
- 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	Xiaolan Ye, PhD, MS; Thomas Marshall, PharmD; Yash Jalundhwala, 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	Mark Marsico, MPH
Novartis	Frederic de Reydet de Vulpillieres, MS
Pfizer, Inc.	Joel Bobula, MA
Genentech	Chris Edgar, PhD, MSc (Co-Chair)
Sanofi	Florence Joly, PharmD, MSc; Matthew Reaney, MSc, PGDip
Expert Panel Members	**Affiliation**
Jeffrey S. Wefel, PhD, ABPP	MD Anderson Cancer Center
Robert A. Stern, PhD	Boston University
Consultant	**Affiliation**
Terry E. Goldberg, PhD	Litwin Zucker Alzheimer's Center, Feinstein Institute for Medical Research; Hofstra Northwell School of Medicine
Consulting Organization	**Research Team**
NeuroCog Trials, Inc.	Richard S.E. Keefe, PhD; Trina Walker, RN