Cognition Working Group

Presented at the Fifth Annual PRO Consortium Workshop – Silver Spring, MD – April 29-30, 2014

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Cognition Working Group (WG)

- PRO Consortium member representatives and FDA advisors identified mild levels of cognitive impairment due to Alzheimer's disease (MCI due to AD) as a priority area.
- This area lacks a PRO instrument that is fit for the purpose of measuring important patient-experienced aspects in the evaluation of treatment benefit in clinical trials.

Goal of the Cognition WG

- The Cognition Working Group is developing a patient-reported outcome measure to improve upon the current state of measurement of mild cognitive impairment due to Alzheimer's disease (MCI due to AD). The measure will capture the patient's perspective on aspects of daily functioning that are expected to be impacted at pre-dementia stages: complex activities of daily living (ADL) performance and interpersonal functioning . The measure will contribute to the description of disease progression, and the measurement of treatment effects.

Draft Labeling Language

- Patients treated with X demonstrated [XX]% improvement on performance of Complex ADLs as compared to [XX]% improvement for patients treated with placebo.
- Patients treated with X demonstrated [XX]% improvement on Interpersonal Functioning as compared to [XX]% improvement for patients treated with placebo.
- After [X] months of treatment, the mean difference in the [XX] change scores for X treated patients compared to patients on placebo was [X]. X treatment was statistically significantly superior to placebo.
- Patients show less decline (or improvement) on Complex ADLs and Interpersonal Functioning over time when treated with X [XX]% as compared to placebo [XX%].

Milestones

Milestone	Expected Date	Completed Date
Scoping Stage		12/06/2010
Content Validity Stage		
Vendor selection and contracting		7/29/2010
Complete background research (literature review and 1st expert panel)		9/30/2010
Complete initial qualitative research and generate items (concept elicitation, selection and item generation – patients interviews & expert panels)		06/03/2011
Refine initial instrument (cognitive interviewing, final expert panel)		9/10/2012
Content Validity Summary document submitted to FDA for interim review		9/20/2013
FDA feedback received		12/04/2013
Gap analysis by Adelphi Values	3Q 2014	
Quantitative component of the Content Validity Stage	TBD	
Submit briefing document to FDA for qualification of the PRO instrument for use in exploratory studies	TBD	

Content of Interest

Endpoint Model for Treatment of MCI Due to AD

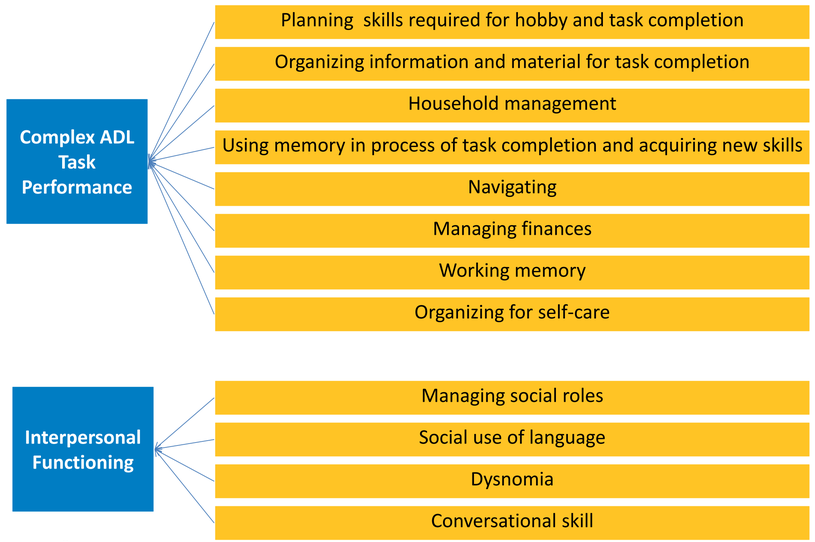
Endpoint Hierarchy	Endpoint Concept(s)	Type of Endpoint
Primary	**Cognition** • Cognitive test battery	**PerfO and/or ObsRO***
	Function • Performance of complex activities of daily living • Interpersonal functioning	**PRO**

*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 (Revised based on qualitative research results and expert panel feedback)



Updates

- Completed an additional round of cognitive debriefing with patients on revised 26-item instrument
- Finalized instrument based on cognitive debriefing
- FDA Briefing Document for qualitative research finalized and submitted in September 2013
- Received feedback from FDA on Briefing Document in December 2013
- Adelphi Values has been selected as the vendor for the quantitative step in the Content Validity Stage and Psychometric Analysis Stage of instrument development
- Project Agreements for next phase of work being negotiated with sponsors
- Takeda and Sanofi will be joining the Cognition WG

Working Group Plans

Presentations/publications

- Manuscript being prepared for final approval and submission to *Alzheimer's & Dementia: Journal of the Alzheimer's Association*
  - Title: "Development of a patient-reported outcome (PRO) instrument to assess complex activities of daily living and interpersonal functioning in patients with mild cognitive impairment due to suspected Alzheimer's disease: the qualitative research phase"
  - Authors: MF Gordon, WR Lenderking, A Duhig, J Chandler, JJ Lundy, D Miller, E Piault, RS Doody, D Galasko, S Gauthier, L Frank on behalf of the Cognition WG

Topics for Discussion

Unique issues for the working group and resolution:

- Issues identified by FDA during review of Briefing Document to be addressed in next phase:
  - Recall period needs to be specific and appropriate for broad use across clinical trials
  - Method for handling functions or tasks that are not relevant to all clinical trial subjects
  - Potential impact of loss of insight in longitudinal clinical trial subjects
- WG members working to identify upcoming clinical trials in which to use instrument
- Draft instrument is being used in the 3-year A4 prevention trial in pre-dementia (NIA sponsored public private partnership)

Lessons learned

- Improve coordination of deliverables between WG members and vendor
- Pay attention to deliverables as received to insure deliverables are complete and accurate
- Define milestones in contracts based on expected deliverables

Working Group Participants

Company/Organization	Name
AbbVie	Stephanie Cline
AstraZeneca AB	Daniel Eek
Boehringer Ingelheim Pharmaceuticals, Inc.	David Brill, Mark Gordon, Jeramiah Trudeau
Eisai Inc.	Wan Tsong
Merck Sharp & Dohme Corp	Julie Chandler(Co-Chair), Yi Mo
Pfizer, Inc.	Katja Rudell
Genentech	Elisabeth Piault-Louis (Co-Chair), Diana Rofail, Glenn Morrison
PCORI	Lori Frank - Nonmember Participant

Expert Panel Members	Affiliation
Paul Aisen, MD	University of California, San Diego, School of Medicine
Jeffrey Cummings, MD	Lou Ruvo Brain Institute, Las Vegas
Rachelle S. Doody, MD, PhD	Baylor College of Medicine
Steven H. Ferris, PhD	New York University School of Medicine
Douglas Galasko, MD	University of California, San Diego, School of Medicine
Serge Gauthier, MD, FRCPC	McGill Centre for Studies in Aging
Mary Sano, PhD	Mount Sinai School of Medicine
Bruno Vellas, MD	University of Toulouse
Gordon Wilcock, FRCP	University of Oxford, Nuffield Department of Medicine
Bengt Winblad, MD, PhD	Karolinska Institutet, Stockholm

Contract Research Organization	Research Team
Adelphi Values	Alan Shields, PhD, remaining team TBD once project starts