Cognition Working Group

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PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Cognition Working Group (WG)

- PRO Consortium member representatives and FDA advisors identified Stage 2/3 Alzheimer's disease (mild cognitive impairment [MCI] due to Alzheimer's disease [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 Stage 2/3 AD.
- FDA stated concerns regarding the ability of patients with Stage 2/3 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 Stage 2/3 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 Stage 2/3 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 Stage 2/3 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 Stage 2/3 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	Q2 2019	
Submit Qualification Plan (QP) to FDA	TBD	
Submit Full Qualification Package to FDA for the *UPSA-MCI* in patients with Stage 2/3 AD	TBD	

Highlights

Example Endpoint Model for Treatment of Stage 2/3 AD

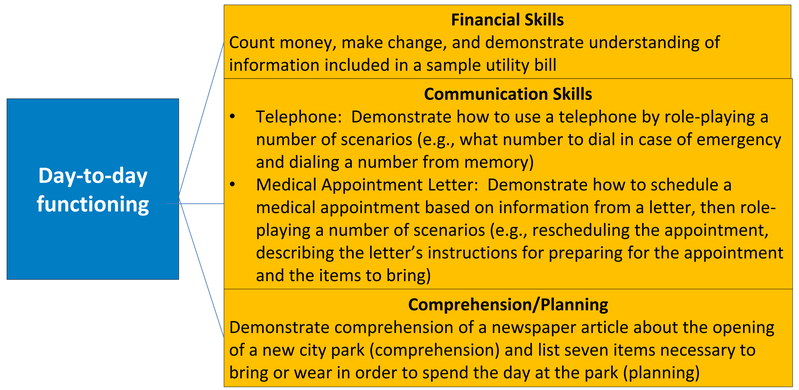
Endpoint Hierarchy	Endpoint Concept(s)	Type of Endpoint
Current		
Co-Primary	**Cognition** Cognitive (neuropsychological) test battery	PerfO*
	Function Performance of instrumental activities of daily living	PerfO*
Proposed		
Primary	**Function** Performance of instrumental activities of daily living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

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

Target Population

- Patients 50 years of age and older
- Patients diagnosed with Stage 2/3 AD

Hypothesized Conceptual Framework



Working Group Activities

The WG held two expert panel meetings in March and May of 2018. Key questions that were addressed included:

1. What are the thoughts regarding the use of the *UPSA* as an endpoint measure for use in MCI due to AD treatment trials?
2. What gaps exist in current versions of the *UPSA* that could be filled by other items and/or domains?
3. Are there gaps in the background report that could be addressed in existing literature?
4. From among the existing *UPSA* subscales, is there a subset that sufficiently captures the core cognition-dependent activities that would be necessary to effectively assess treatment benefit in patients with MCI due to AD?
5. What versions were used in Dr. Goldberg's research in MCI?
   - What subscales were included in each and which subscales provided more valuable information than others?

Working Group Activities - Continued

Completed Activities for the Working Group

- Background report (included literature review and secondary statistical analysis), translatability report, and a summary report that described the process that led to the three subscale UPSA-MCI

Unique Issues for the Working Group

- Several versions of the *UPSA* have been used in schizophrenia treatment trials, but there is limited empirical evidence to guide version selection for qualification of the *UPSA* in patients with Stage 2/3 AD
- A new biological definition of AD and clinical staging have emerged making the use of previous research in MCI challenging (Jack et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia* 2018;14:535-562)

Lessons Learned

- The FDA is willing to consider use of a PerfO measure in assessing day-to-day functioning as an efficacy endpoint in Stage 2/3 AD clinical trials, potentially as a single primary endpoint
- The consensus development meeting involving the WG, key opinion leaders, FDA, and C-Path provided an excellent framework for shaping and aligning future strategy

Next Steps

- Initial Briefing Package submission
- Qualitative research with the *UPSA-MCI* (e.g., pilot testing)
- Quantitative pilot study protocol and quantitative analysis plan that would be the basis for the Qualification Plan
- Key areas for further evaluation of *UPSA-MCI* include cultural adaptation in multinational trials, content validity, psychometric evaluation in patients with Stage 2/3 AD, and potential comparison to existing informant-reported measures

Working Group Participants

Company/Organization	Name
AbbVie Inc.	Katy Benjamin, PhD (Co-Chair); Yash J. Jalundhwala, PhD, MS; Xiaolan Ye, PhD, MS
AstraZeneca	Daniel Eek, PhD
Boehringer Ingelheim	Matthew Sidovar, MSc, MA
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Merck Sharp & Dohme Corp	Cathy Anne Pinto, PhD, MS
Novartis	Valery Risson, PhD, MBA
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Sanofi	Matthew Reaney, MSc, Cpsychol; Florence Joly, PharmD

Advisory Panel Members	Affiliation
Terry E. Goldberg, PhD	Columbia University Medical Center
Philip D. Harvey, PhD	University of Miami Miller School of Medicine
Thomas Patterson, PhD	University of California, San Diego
Pierre Tariot, MD	Banner Alzheimer's Institute
Kathleen Welsh-Bohmer, PhD	Duke University Medical Center; VeraSci

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