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 [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.

Goal of the Cognition WG

- The Cognition WG’s goal is to qualify a PRO measure to improve upon the current state of assessment of clinical benefit in clinical trials for patients in clinical Stage 2 and Stage 3 of biologically-defined AD. The measure will capture the patient’s performance of tasks that reflect essential aspects of day-to-day functioning.

Concept of Interest

- Day-to-day functioning based on performance of instrumental activities of daily living.

Target Population

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

Targeted Labeling Language

- Patients treated with X demonstrated [XX]% improvement in day-to-day functioning as compared to placebo [XX]%.
- Patients diagnosed with Stage 2/3 AD

Milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Target Date</th>
<th>Completed Date</th>
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<tbody>
<tr>
<td>Letter of Intent submission to FDA</td>
<td>MAY 2016</td>
<td></td>
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<tr>
<td>FDA feedback received to Letter Of Intent and approval provided to enter the University of California San Diego Performance-based Skills Assessment (UPSA) into the CDER COA DDT qualification program</td>
<td>OCT 2016</td>
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<tr>
<td>Initial Briefing Package submission to FDA</td>
<td>OCT 2019</td>
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<tr>
<td>Received IBP feedback from FDA</td>
<td>FEB 2020</td>
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<tr>
<td>Qualification Plan submission to FDA</td>
<td>TBD</td>
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<tr>
<td>Full Qualification Package submission to FDA</td>
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Highlights

Example Endpoint Model for Treatment of Stage 2/3 AD

<table>
<thead>
<tr>
<th>Endpoint Hierarchy</th>
<th>Endpoint Concept(s)</th>
<th>Endpoint Type</th>
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<tbody>
<tr>
<td>Co-Primary</td>
<td>Cognitive/neuropsychological test battery</td>
<td>PerFO*</td>
</tr>
<tr>
<td>Function</td>
<td>Performance of instrumental activities of daily living</td>
<td>PerFO</td>
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Proposed

Primary Function

- Performance of instrumental activities of daily living

PerFO (UPSA-3D)  

Hypothesized Conceptual Framework

Day-to-day functioning

- Financial Skills
- Communication Skills
- Comprehension/Planning

Existing Measure Proposed for Qualification

Measure – University of California San Diego Performance-based Skills Assessment-Three Domain (UPSA-3D)

Financial Skills (11 items)

- Description: Count money, make change, and demonstrate understanding of information included in a sample utility bill

Communication Skills (12 items)

- Description:
  - Telephone: Demonstrate how to use a telephone by role-playing a number of scenarios (e.g., what number to dial in case of emergency and dialing a number from memory)
  - Medical Appointment Letter: Demonstrate how to schedule a medical appointment based on information from a letter, then role-playing a number of scenarios (e.g., rescheduling the appointment, describing the letter’s instructions for preparing for the appointment and the items to bring)

Comprehension/Planning (14 items)

- Description: Demonstrate comprehension of a newspaper article about the opening of a new city park (comprehension) and list seven items necessary to bring or wear in order to spend the day at the park (planning)

Working Group Activities

Completed Activities

- Background report (including literature review and secondary statistical analysis), translatability report, and a summary report that described the process that led to the third subscale version of the UPSA-3D
- Expert panel meetings were held in March and May 2018, to address key questions regarding endpoint measures, existing gaps, and existing UPSA subscales
- Submitted Initial Briefing Package for the University of California San Diego Performance-based Skills Assessment-Alzheimer’s Disease (UPSA-3D) to FDA
- A decision was made to change UPSA-AD to UPSA-3D to reflect its three-domain structure and to avoid the implication that the measure is not applicable beyond AD

Challenges

- 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
- Technology has changed significantly in the past 10 years and the skills tested may not be completely relevant today, however, adaptations can be made

Next Steps

- Conduct qualitative research (e.g., pilot testing and participant interviews) with the UPSA-3D
- Develop quantitative pilot study protocol and quantitative analysis plan that would be the basis for the Qualification Plan
- Key areas for further evaluation of UPSA-3D include cultural adaptation for multinational trials, content validity confirmation, and psychometric evaluation in participants with Stage 2/3 AD

Working Group Participants

<table>
<thead>
<tr>
<th>Company/Organization</th>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>AbbVie Inc</td>
<td>Katy Benjamin, PhD (Co-Chair); Yash J. Jalundhwala, MD, PhD, MS, Xiaoan He, PhD, MS</td>
<td>NYU, NYU Langone Medicine</td>
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<tr>
<td>AstraZeneca</td>
<td>Daniel Eek, PhD</td>
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<td>Boehringer Ingelheim</td>
<td>Matthew Sidovar, MSc, MD</td>
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<tr>
<td>Eli Lilly and Company</td>
<td>Julie Chandler, PhD (Co-Chair); Nicki Bush, MHS</td>
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<tr>
<td>Merck Sharp &amp; Dohme Corp</td>
<td>Cathy Anne Pinto, PhD, MS; Josephine Nonquint, MS; Yanfen Guan, MD, PhD</td>
<td>Duke University Medicine; University of California San Diego; Banner Alzheimer’s Institute; Duke University Medicine; University of California San Diego; Banner Alzheimer’s Institute; Duke University Medical Center; VeraSci; VeriSor; University of California San Diego; Banner Alzheimer’s Institute; Duke University Medical Center; VeraSci; Merck Sharp &amp; Dohme Corp; Boehringer Ingelheim; Eli Lilly and Company; AstraZeneca; AbbVie Inc; AstraZeneca; Boehringer Ingelheim; Eli Lilly and Company; Merck Sharp &amp; Dohme Corp; Novartis; Roche/GenevaTech; Sanofi; VeraSci; VeriSor; University of California San Diego Performance-Based Skills Assessment (UPSA)</td>
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Administration of Cognition Working Group

- Administered by trained study personnel

Prepared for the 11th Annual PRO Consortium Workshop (April 22-23, 2020), which was cancelled due to COVID-19