A Comprehensive Review of Disease Progression Models (DPM) Across the Entire Spectrum of Alzheimer Dementia (AD)

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Objectives: Summarize DPMs across the entire AD spectrum

Methods: DPMs for the following 4 disease stages are summarized (a) mild to moderate [M2M] AD (b) prodromal AD [pAD] (c) Asymptomatic at Risk for AD [ARAD] (d) Pre-symptomatic AD [PSAD] in Autosomal Dominant AD [ADAD]

Results: The endpoints for DPM include (a) co-primary cognitive and functional endpoints ADAS-cog and ADL for M2M-AD (b) CDRSB for pAD (c) Composite endpoint ADCS-PACC for pre-clinical AD. AD is being studied at earlier stages for secondary prevention and duration of follow-up in the DPMs for disease-modifying-agents is increasing from 1.5 to 4.5 years across M2M-AD to ARAD. Modeling cognitive and functional endpoints in M2M to pAD requires special considerations for bounded outcomes such as (a) structural models with asymptotes e.g. Richard’s function (b) data distribution e.g. beta regression (c) drop-out due to long follow-up. DPMs require these structural and distributional considerations to ensure that predictions stay within the boundaries of the scale to allow for floor and ceiling effects. DPM for pre-clinical stages of the disease (ARAD/PSAD) generally employ linear mixed effects modeling with normally distributed data since endpoints are z-scaled composite measures. Key covariates in DPM include amyloid status where amyloid negative subjects exhibit flat disease trajectories and other key factors for progression rate include APOE and age. Finally, one of the underlying processes driving progression rate is disease severity within each stage of AD. DPMs follow an underlying S-shaped disease trajectory; progression rates are slow at earlier and later stages within a disease state and progression rates are fastest around the mid-portion, which represents the dynamic portion of the scale.

Conclusions: Modeling consideration and choice of endpoints for the different disease stages are guided by recent draft guidelines and policies from international bodies and regulatory agencies which are also summarized.

Table 1: Disease Progression Model Characteristics

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>End-point</th>
<th>Duration of Disease-Modifying Trials</th>
<th>Example of currently ongoing trials</th>
<th>Distributional Assumption</th>
<th>Structural Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>ADAS-cog and ADL</td>
<td>1.5 year</td>
<td>EXPEDITION3, AMARANTH, A4</td>
<td>Beta distribution</td>
<td>Richard’s Function</td>
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<tr>
<td>pAD</td>
<td>CDRSB</td>
<td>2 years</td>
<td>AMARANTH, A4</td>
<td>Normal distribution</td>
<td>Linear mixed effects with quadratic terms or cubic splines with knots for accommodating non-linearity</td>
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<tr>
<td>ARAD</td>
<td>ADCS-PACC</td>
<td>3.5 to 4.5 years</td>
<td>DIAN-TU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSAD</td>
<td>Cognitive composite</td>
<td>4 years</td>
<td></td>
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</tbody>
</table>

1 AD: Alzheimer’s disease
2 pAD: prodromal AD
3 ARAD: Asymptomatic at risk for AD (pre-clinical stage of AD)
4 PSAD: Pre-symptomatic AD (pre-clinical stage of AD) due to an autosomal-dominant mutation, also called familial or early onset AD, due to mutations in presenilin 1 (PSEN1), presenilin 2 (PSEN2) or amyloid precursor protein (APP)
5 ADAS-cog: Alzheimer’s disease assessment cognitive scale
6 ADL: Activities of daily living endpoints such as disability assessment for dementia
7 CDRSB: Clinical dementia rating sum of boxes
8 ADCS-PACC: Alzheimer’s disease cooperative study-preclinical Alzheimer’s cognitive composite
9 EXPEDITION3: Effect of Paspive Immunization on the Progression of Mild AD: Solanezumab (LY2062430) Versus Placebo [NCT01906665]
10 AMARANTH: A 24-month, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy, Safety, Tolerability, Biomarker, and Pharmacokinetic Study of AZD3293 in Early Alzheimer’s Disease (The AMARANTH Study) [NCT02245732]
11 A4: Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease (A4 Study) [NCT02008357]
12 Recent studies for treatment or secondary prevention of late onset AD require biomarker enrichment to exclude amyloid negative subjects that exhibit flat trajectories in the DPM
13 DIAN-TU: Dominantly Inherited Alzheimer Network-Trial Unit [NCT01760008]