
AD Prevention Trials: An Industry Perspective

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- **Regulatory**

- Precedent – A4, TOMMorow, API Novartis (2E4)
 - Attempts versus Success
 - No approvals
 - No gold standard/validation
- Scientific consensus as alternative
- Global perspective (agreement across HA, validation across cultures, etc) must be maintained
- Demonstrating value still requires multiple studies establishing a clear cognitive-functional link for minimally important change in pre-dementia

Regulatory position: EMA draft guideline

Limited confidence in existing regulatory path?

- **Feasibility**

- “**feasibility issues** including length of the trial and number of drop-outs are recognized”. “Until a biomarker will be qualified as a reliable surrogate... patients should be followed up for a sufficient time to capture relevant cognitive changes”.

- **Eligibility criteria**

- “... the diagnostic construct of preclinical AD as well as the disease model in such an early stage **still need to be validated**”. “Population for prevention trials can be enriched”. “... the relative contribution of each risk factor to the onset of the disease is **not yet established** and it is difficult to translate population risk at an individual level”.

- **Trial duration**

- “Prevention trials require **large samples and long follow up**, typically of **at least 5 years**. However, since scientific information to provide a firm regulatory framework for prevention trials is still lacking, no firm recommendation can be made and therefore scientific advice is recommended in case this is pursued.”

- **Endpoint(s)**

- “prevention of cognitive impairment” “no “gold standard“... Novel outcome tools... **not yet validated** and cannot be endorsed solely as primary endpoints”. “... time to event analysis could be a complementary measure”.

- End of consultation (deadline for comments) 31 July 2016

Unknowns of trial design in preclinical AD

An unattractive prospect for industry?

- **Feasibility**
 - Patient access and willingness to participate (for many years)
 - Anticipated attrition rates
 - Sample size
- **Eligibility criteria**
 - Reliability of biomarkers
 - Enrichment for progression
- **Trial duration**
 - Even longer than current pAD stage trials (5+ years)
- **Endpoint(s)**
 - Continuous Versus Time to Event
 - Regulatory perspective on defining 'Clinically Evident Decline', 'Disability' or other event
 - Culturally bound
- **Product Label**
 - What (differentiated) label might be achieved
- **Eventual Market**
 - Infrastructure issues on screening and treatment
 - Who to treat and when (relative cost and invasive nature of existing biomarkers prohibitive of large scale adoption)
 - Willingness to treat otherwise healthy individuals (for life) and bear cost
 - Current ability to demonstrate cost savings to health care systems (already a challenge for MCI due to AD/pAD stage)

The path forward

- **Cross-industry consortia**
 - DIAN
 - Alzheimer's Prevention Initiative Treatment Trials
 - Opportunity to explore and validate trial design and feasibility questions without bearing full risk
 - Provides an impetus to shift regulatory science

DIAN-TU Cognitive Battery

Considerations in the selection of cognitive tests:

1. Some overlap with the DIAN observational study to allow for comparison and provide continuity
2. Sufficient published validation literature, widely used in pharmaceutical research, and covering main domains of cognition affected by AD
3. Some overlap with measures used in other secondary prevention trials (A4, API and TOMMorrow), so that results can be compared
4. Ease of administration and participant acceptability

API composite cognitive test score

- **Creation of composite**
 - Used longitudinal data from cognitively unimpaired presenilin 1 (PSEN1) E280A mutation carriers
 - Mean-to-standard-deviation ratios of change over time calculated in search for optimal combination of 1 to 7 cognitive tests/subtests
 - Combinations that performed well evaluated for:
 - Robustness across follow-up
 - Occurrence of items within top-performing combinations
 - Representation of relevant cognitive domains
 - Optimal test combination included:
 - CERAD Word List Recall
 - CERAD Boston Naming Test (high frequency items)
 - Mini-Mental State Examination (MMSE) Orientation to Time
 - CERAD Constructional Praxis
 - Raven's Progressive Matrices (Set A)

Summary of cognitive tests used in the four main secondary prevention clinical trials of



	DIAN-TU		A4		API		TOMMorrow	
	Paper & Pencil	Computerized	Paper & Pencil	Computerized	Paper & Pencil	Computerized	Paper & Pencil	Computerized
Memory	WMS-R Logical Memory	International Shopping List Test	WMS-R Logical Memory	Face-Name Associative Memory Task	10 Word Delayed Recall		CVLT-II	
		Cogstate One Card Learning	16-item Free & Cued SRT	Cogstate One Card Learning			Brief Visuospatial Memory Test-R	
		Cogstate One Back		Cogstate One Back				
		Object Pattern Separation Task		Object Pattern Separation Task				
		Groton Maze Learning Test						
Executive Function	Raven's Progressive Matrices (12)	Groton Maze Learning Test			Raven's Progressive Matrices (9)		Trail Making B	
	Digit Span Backward						Digit Span Backward	
	Trail Making B							
Language	Semantic fluency (Vegetables)				Multilingual Naming Test		Multilingual Naming Test	
	Semantic fluency (Animals)						Semantic Fluency (Animals)	
	Lexical/Phonemic Fluency (FAS)						Lexical/Phonemic Fluency (FAS)	
Attention	WAIS-R Digit Symbol	Cogstate Detection	WAIS-R Digit Symbol	Cogstate Detection				
	Digit Span Forward	Cogstate Identification		Cogstate Identification			Trail Making A	
		Timed Chase Test					Digit Span Forward	
Visuospatial					CERAD Constructional Praxis		BVMT-R Figures (copy)	
							Clock Drawing	
Global	MMSE		MMSE		MMSE (Orientation)			
Other	CDR		CDR					
	MAC-Q		MAC-Q					

Considerations for cognitive test batteries

- **What is the correct way to select amongst feasible component tests**
 - Clinical presentation of MCI due to AD/prodromal AD?
 - Statistical modelling for optimal signal to noise ratio in measuring disease progression?
 - Patient/caregiver insights into disease burden/impact?
 - Modern psychometrics (IRT)?
 - Association to functional impairment?
 - Ultimately, what is the underlying concept(s) we are attempting to measure?

Doing now what patients need next