Development of $^{18}$F-AV-45 for Imaging of Alzheimer’s Disease Pathology in Humans

SPEAKERS

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CEO, Avid  
Adjunct Faculty  
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*Neurologist*  
Medical Director, Avid  
Director of the Center of Excellence for Research on Neurodegenerative Disease  
Dept of Neurology, U Penn
Development of $^{18}$F-AV-45 for Imaging of Alzheimer’s Disease Pathology in Humans

AGENDA

10:00 - 10:10 am  Introduction & $^{18}$F-AV-45 Data  
D Skovronsky, MD PhD

10:10 - 10:20 am  Clinical Utility & Reference Standard  
C Clark, MD

10:20 - 10:30 am  Avid development proposal  
D Skovronsky, MD PhD
Introduction: AD

Alzheimer’s Disease is a CLINICOPATHOLOGIC Disease Entity

Definitive diagnosis requires both:

- Clinical Findings (Dementia)
- Neuropathology Findings

Amyloid plaques are a required component for diagnosing definite AD

Highest level of diagnostic certainty ante-mortem is “Probable AD”
Definitive diagnosis only possible post-mortem
Introduction:

18F-AV-45 PET Imaging

“Probable AD” Patient  Cognitively Normal Elderly

A 10 minute 18F-AV-45 PET scan shows abundant cortical amyloid deposition in the AD patient (red = SUVr >2.5) but not in the elderly control (blue = SUVr ~ 1.0).

18F-AV-45 PET imaging provides information about the presence or absence of amyloid pathology.
Target = Amyloid plaque pathology

Indication = Imaging amyloid pathology

Clinical Utility = No significant amyloid excludes AD

Reference Standard = Amyloid plaque histopathology
Proposed Indication:

\(^{18}\)F-AV-45 is indicated for imaging brain amyloid plaque pathology to aid in the evaluation of patients with signs or symptoms of cognitive impairment.

Clinical Utility:

**NDA:** Patients with no significant brain amyloid do not have AD. Biomarker for anti-amyloid therapy trials.

**To be demonstrated:** Patients positive for brain amyloid have increased likelihood of having AD or developing AD.
**18F-AV-45 Data: Selection under Exploratory INDs**

- **AV-45**
  - Probable AD
  - Cognitively Normal Control
  - Best tracer selected for full development

- **AV-138**

- **AV-144**

- **AV-19**

12 potential amyloid imaging ligands were tested in exploratory FDA IND trials

SUVR 50-70 min post dose


**Avid Radiopharmaceuticals**

**18F-AV-45 Data: Development Summary to Date**

<table>
<thead>
<tr>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
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**Exploratory trials on 12 amyloid ligands**

**18F-AV-45 Selected**

**Ph I**
- **n=9**
- Brain Imaging
  - Metabolism, Safety

**Ph I / II**
- **n=20**
- Radiation dosimetry
  - Safety

**Ph I / II**
- **n=20**
- Dose ranging
  - Safety

**Ph II**
- **n=180**
- Test – retest reproducibility
  - Safety

**Preselected Populations**
- (AD, MCI, Cog. Intact)

---

**Cumulative Safety & Imaging Database**

**284 subjects**

All under IND using standardized methods for drug production, imaging, data analysis
18F-AV-45 Reproducibility (n=20)

Test – retest variability 3 - 5%
Test – retest correlation 0.98 - 0.99
**18F-AV-45 Data: Quantitation**

- **Quantitation**

  - 60 subjects (22 AD, 38 HCs)
  - 15 sites

**Neocortex (Precuneus)**

- Average

**Neocortex (Average)**

- 180 subject Phase IIb Trial Imaging vs clinical diagnosis in preselected populations (analysis ongoing)

**Current clinical database contains:**

- 125 Cognitively Normal Elderly Controls
- 99 AD Patients
- 60 MCI Patients

60 subjects (22 AD, 38 HCs)

15 sites
• All \(^{18}\text{F-AV-45}\) drug product conforms to uniform set of IND specs (strength, specific activity, pH, identity, purity)

• \(^{18}\text{F-AV-45}\) produced in compliance with USP <823>, which FDA recommends for IND studies (similar to \(^{18}\text{F-FDG}\))

• Avid implementing additional controls as per FDA draft 21 CFR Part 212 guidance.

Distribution area

PET center
Development of $^{18}$F-AV-45 for Imaging of Alzheimer’s Disease Pathology

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Generally Accepted Clinical Truths

- Patient care best when the diagnosis is correct
- Better to identify disease early
- Diagnosis most reliable when based on pathology
- Correct diagnosis improves:
  - Clinical management
  - Treatment decisions
  - Prognostic information to patient & family

Accurate AD diagnosis is important:
The evidence is that the medical community spends significant time and money diagnosing Alzheimer’s today.
Prevalence of non-AD pathologic diagnosis: 25%

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>AD</th>
<th>Non-AD diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jellinger et al., 1990</td>
<td>675</td>
<td>77%</td>
<td>23%</td>
</tr>
<tr>
<td>Victoroff et al., 1995</td>
<td>196</td>
<td>76%</td>
<td>24%</td>
</tr>
<tr>
<td>Brunnstrom et al, 2008</td>
<td>524</td>
<td>64%</td>
<td>36%</td>
</tr>
<tr>
<td>Univ Penn ADC, 2008</td>
<td>226</td>
<td>76%</td>
<td>24%</td>
</tr>
</tbody>
</table>

1 includes patients with a diagnosis of mixed dementia, e.g. AD + Vascular dementia or AD + dementia with Lewy bodies.

Expert Clinician Diagnostic Accuracy

- 78% overall **accuracy** for a clinical diagnosis of AD
- 17% **false positive rate** for a clinical diagnosis of AD (range 10 – 35%)

2 University of Penn Alzheimer’s Disease Center clinical-pathological data pathology
Clinical Utility: Current Diagnostic Algorithm

Individuals at risk for late-life dementia

<table>
<thead>
<tr>
<th>Cognitive change</th>
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<td>Brief cognitive assessment</td>
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</table>

Clinical evaluation for dementia differential dx

AD-clinical

Not AD

Autopsy

83% AD 17% Not AD
Amyloid imaging leads to better patient management

**Negative $^{18}$F-AV-45 PET**
- No significant amyloid pathology (not AD)

**Positive $^{18}$F-AV-45 PET**
- Amyloid pathology likely

Amyloid imaging can help rule-out AD in those patients who have cognitive impairment and diagnostic uncertainty.
Clinical Utility: Therapeutics

Utility for clinical trials developing new therapies

• Improve patient selection for disease modifying therapies in trials (~30 such trials ongoing)
  – Exclude amyloid negative individuals
  – Identify amyloid positive individuals
    • First horizon AD
    • Second horizon MCI
    • Third horizon primary prevention

• Potential outcome measure?
Reference Standards should:

• Provide **DIRECT** information about the target of interest

• Be well **STANDARDIZED** - based on well controlled trials

• Be **VALIDATED** vs. truth standard

• Be **INDEPENDENT** of the test agent

• Be **GENERALLY AVAILABLE** to the drug development community

• Be **FDA APPROVED** or **FDA VALIDATED** as a measure of truth
## Candidate Reference Standards

<table>
<thead>
<tr>
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- Good definition of regional atrophy
- Spatial information on hypometabolism
- Research data available
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25
CSF $\text{A}_{\beta}^{42}$ baseline values

ADNI Data

CSF biomarker performance characteristics
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Pathology correlation studies have been used to validate imaging for other targets.

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Imaging Modality</th>
<th>Mean Interval to Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverman et al., 2001</td>
<td>138</td>
<td>$^{18}$F-FDG PET</td>
<td>2.9 yrs</td>
</tr>
<tr>
<td>Walker et al., 2007</td>
<td>20</td>
<td>$^{123}$I-FP-CIT SPECT</td>
<td>2.8 yrs</td>
</tr>
<tr>
<td>Jagust et al., 2008</td>
<td>93</td>
<td>MRI for vascular pathology</td>
<td>2.7 yrs</td>
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Previous limitation = delay between scan and autopsy.
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Phase III Study

Image elderly individuals (with varying degrees of cognitive impairment) who have consented to brain donation studies and follow to autopsy.

- **18**F-AV-45 PET
- Evaluation by 3 blinded readers
- Autopsy, Neuropathology analysis
- Amyloid plaque evaluation by expert neuropathologist

Reference Standard: Proposed Autopsy Study

Study population will include subjects who are clinically cognitively normal, mildly impaired and have probable AD.

Goal is to have an autopsy population that includes a wide range of levels of amyloid deposition (from negative to abundant plaques).
**Image Evaluation**
Qualitative read:
- Amyloid negative / amyloid positive
- Blinded readers
Quantitative evaluation:
- SUV ratio to cerebellum (SUVR)
- Pre-established thresholds for + / -

**Neuropathology**
Qualitative read (CERAD rating)
- None or sparse / moderate or frequent
- Blinded reader
Quantitative evaluation:
- Plaque count per high power field

**Key Outcome Variables**
Negative Predictive Value (primary)
- Percentage of negative PET scans that are none/sparse for amyloid pathology at autopsy
Correlation of SUVR to plaque counts (secondary)
18F-AV-45 Scans
Spectrum of Pathology
Anticipated prospective quantitative analysis in 30 - 50 subjects to validate $^{18}\text{F-AV-45}$
• FDA guidance suggests pathology detection as one potential indication for imaging agents
  – Guidance for Industry: Developing Medical Imaging Drug and Biological Products Part 2: Clinical Indications, June 2004

• Imaging results may be compared to histopathology as a truth standard
  – Guidance for Industry: Developing Medical Imaging Drug and Biological Products Part 3: Design, Analysis, and Interpretation of Clinical Studies, June 2004

→ Avid proposal follows FDA guidance
Well-controlled trials in cognitively impaired populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>n</th>
<th>Long Term Follow-Up</th>
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<tbody>
<tr>
<td>A05</td>
<td>AD MCI Normal Elderly</td>
<td>180</td>
<td>All Subjects</td>
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<tr>
<td></td>
<td>Presenting for evaluation of cognitive impairment</td>
<td>~ 100</td>
<td>Selected Cases</td>
</tr>
<tr>
<td>A10</td>
<td>AD FTD Normal Elderly</td>
<td>~ 50</td>
<td>Selected Cases</td>
</tr>
<tr>
<td>Treatment Trials</td>
<td>AD (prior to initiation of novel therapy)</td>
<td>300 - 500</td>
<td>All Subjects (Placebo vs. Rx)</td>
</tr>
</tbody>
</table>
INITIAL APPROVAL
Clinical Trials:
Phase III autopsy study
Immediate Benefits:
1. Clinically useful to exclude AD in differential diagnosis
2. Standardized biomarker to facilitate development of disease modifying therapeutics

POST-APPROVAL
Clinical Trials:
Long term outcome trials
Future Benefits:
1. Clinically useful to indicate positive likelihood of AD in differential diagnosis
2. Establish prognostic utility of scans in patients with mild impairments or preclinical subjects to enable prevention trials
18F-AV-45 is indicated for imaging brain amyloid plaque pathology

Threshold for NDA approval

Adequate Scientific Certainty
Pathology to Image Correlation

Autopsy studies validating imaging using histopathology reference standard

Well-controlled multi-center trials in cognitively impaired individuals vs. clinical reference standard

Preclinical data & academic single center clinical research

Time

5 - 10 years ago 2 years ago 0 (Today) 2 years 5 - 10 years

Evidence of Effectiveness and Clinical Value

Therapeutic biomarker trials

Longitudinal prognostic & outcome studies