Peripheral and Central Nervous System Drugs Advisory Committee Meeting

October 23, 2008

GE-067: GE Healthcare’s β-Amyloid Imaging Agent

[Images of PET scans: Alzheimer's Disease and Age matched control]
# GE-067 Presentation to Advisory Committee

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<td>Professor David Brooks</td>
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<td>Dr. Keith Johnson</td>
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<td>Harvard and Mass General Hospital, Boston</td>
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</table>
Development of GE-067

- Thioflavin-T
  - Post-mortem histology stain

- Pittsburgh compound B (PIB)
  - Thioflavin-T, chemically modified to facilitate uptake into the brain = PIB
  - $[^{11}\text{C}]$PIB - ‘standard’ for imaging β-amyloid in clinical research (>40 sites, >2000 subjects)
  - Inclusion in ADNI (NIH-sponsored study)

- GE-067
  - GE-067 differs only by the addition of fluorine-18
Labeling Intent for GE-067

Single tracer dose PET radiopharmaceutical for detection of β-amyloid pathology in the brain

*In-vivo tool* to replace post-mortem histopathology

Intended to designate a patient as β-amyloid-positive or β-amyloid-negative, independent of clinical diagnosis

*Not* intended to replace clinical diagnosis of a particular disease or to perform differential diagnosis

Useful across the spectrum of clinical syndromes with cognitive impairment (allows for the likely possibility of mixed pathologies)
Proposed Registration Plan for GE-067

Step 1. Detection

The detection of brain β-amyloid deposition

Step 2. Life-Cycle

Diagnosis

Disease Progression

Therapy Monitoring
1) ALZ101: (n=20, 10 ADs and 10 HVs) - [11C]GE-067

Significant uptake of tracer in AD brains as measured by volume of Interest (VOI) Analysis compared to controls after injection of [11C]GE-067

2) ALZ102: One Year Follow-Up Study

There were no significant changes over this period and the data showed less than 10% (typically 5-7%) variability
3) ALZ103 Program

22 subjects scanned with GE-067 in 3 steps: 1) Dosimetry, 2) Brain Kinetic Modelling and 3) Image Optimization
ALZ103: GE-067 Uptake Ratios

- AD HV
- αβ negative
- αβ positive

Graph showing uptake ratios for different regions (pre-frontal, ant-cing, post-cing) with markers for AD and HV, and categories for αβ positive and negative.
### β-Amyloid Detection Claim: Registration Study Design

<table>
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<tr>
<th>Study Goal</th>
<th>• Multi-center open label study to demonstrate that GE-067 can be used as <em>in vivo</em> tool for β-amyloid detection</th>
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<tr>
<td>Primary Objective</td>
<td>• Establish the range of GE-067 β-amyloid uptake in normals, probable ADs and amnestic MCI patients</td>
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</table>
| Secondary Objectives | • Determine **performance characteristics** which allow this test to be confidently used as an *in vivo* tool (e.g. test-retest variability, image interpretation, reader robustness)  
  • Establish whether positive and negative cases can be accurately determined by **visual inspection**  
  • Show **concordance** between GE-067 and \([^{11}C]PIB\) (SoT) uptake  
  • Safety |
## β-Amyloid Detection Claim: Registration Study Design

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<tr>
<th>Study Groups</th>
<th>GE-067 Scan</th>
<th>$[^{11}\text{C}]\text{PIB}$ Scan</th>
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<tr>
<td>1a Probable AD subjects: (NINCDS-ADRDA), MMSE 18-26, CDR&gt;0.5 (aged &gt;55+)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>1b Probable AD subjects: TEST RE-TEST</td>
<td>✔️</td>
<td>-</td>
</tr>
<tr>
<td>2 Amnestic MCIs: (Petersen criteria) (aged&gt;55+)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>3a Younger Normals: MMSE&gt;28 (aged &lt;55 years)</td>
<td>✔️</td>
<td>-</td>
</tr>
<tr>
<td>3b Older Normals: MMSE&gt;28 (aged &gt;55 years)</td>
<td>✔️</td>
<td>-</td>
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[11C]PIB as a Standard of Truth for β-Amyloid Detection

1. A Standard of Truth should be as accurate as possible

2. For Amyloid Detection:
   - Gold Standard is post-mortem pathology

3. Use of [11C]PIB as SoT
   - Correlation with pathology
   - Established methods to measure uptake units
   - Distinct difference between normal and abnormal ranges
   - Reproducibility/Robustness

[Chemical Structure Image]
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First Post-PiB Autopsy: 76 y/o Dx of DLB Died 3 months after \([^{11}\text{C}]\text{PiB Scan}\) (SDH); MMSE=25

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Table. Comparison of Biochemical Analysis of A\(\beta\) With Quantitative PET in Affected Brain Regions

<table>
<thead>
<tr>
<th>Region</th>
<th>DVR From PET Scan*</th>
<th>Soluble A(\beta)40, fmol/g</th>
<th>Soluble A(\beta)42, fmol/g</th>
<th>Insoluble A(\beta)40, pmol/g</th>
<th>Insoluble A(\beta)42, pmol/g</th>
<th>PiB Binding, pmol/g†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>1.311</td>
<td>6938</td>
<td>14618</td>
<td>906</td>
<td>4685</td>
<td>444</td>
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<tr>
<td>Parietal</td>
<td>1.299</td>
<td>6788</td>
<td>9554</td>
<td>882</td>
<td>3703</td>
<td>325</td>
</tr>
<tr>
<td>Cingulate</td>
<td>1.504</td>
<td>4342</td>
<td>9884</td>
<td>881</td>
<td>3884</td>
<td>556</td>
</tr>
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Bacsikai et al., Arch Neurol. 2007;64:431-434
[\textsuperscript{11}C]PiB Retention \textit{In Vivo} Correlates Well with A\textsubscript{\textbeta} Levels Determined Post-Mortem

Ikonomovic et al. Brain 2008;131:1630-1645
In Vivo \[^{11}\text{C}]\text{PiB}\) Retention Correlates Well with Post-Mortem PiB and A\(\beta\) Measures...but not NFT Measures

\[ r=0.81, p<0.0001 \]

\[ r=0.86, p<0.0001 \]

\[ r=0.17, p=0.49 \]
In Vivo $[^{11}\text{C}]$PiB Retention Correlates Well with Aβ Levels Determined Post-Mortem

Ikonomovic et al. Brain 2008;131:1630-1645

(r=0.73; p<0.003)
5/5 with no or trace amyloid were PiB-neg

1/2 with diffuse plaques was PiB-pos

3/3 with clear neuritic plaques were PiB-pos
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Quantitative Determination of “PiB+” Metrics

In Cognitively Normal Healthy Volunteers:
Continuous Distribution
Skewed High
Quantitative Determination of “PiB+” Metrics

Standard Box & Whisker Plots

PiB CER90 DVR

“Mild” Outliers

Upper “Inner Fence”

3rd Quartile

1st Quartile
Quantitative Determination of “PiB+” Metrics

Define PiB+ Cases (positive in any brain area)
Quantitative Determination of “PiB+” Metrics

All AD Cases
PiB+ in Several Brain Areas
Distinct Difference Between Normal and Abnormal Ranges

All AD Cases
PiB+ in Several Brain Areas (expanded scale)

All Controls <55 Years Old
PiB- in All Areas

Cohen’s Effect Size ($d$):
small effect: 0.2 to 0.3
medium effect: 0.5 to 0.7
large effect: 0.8 to 1.0

4.5 3.2 5.3 4.3 2.4 2.1 3.2 (PiB- and PiB+) vs. AD
6.9 5.3 6.8 5.1 2.9 3.1 5.4 (PiB- Only) vs. AD
Correlation of Visual Reads with Quantitative Definition of “PiB+” in Healthy Volunteers and AD

Agreement in 57/62 (92%) of Controls...

...and 22/22 (100%) of AD Patients
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Use of [11C]PIB as SoT
- Correlation with pathology
- Established methods to measure uptake units
- Distinct difference between normal and abnormal ranges
- Reproducibility/Robustness
Reproducibility/Robustness: Single Site Test/Re-Test Robustness

<table>
<thead>
<tr>
<th>Method</th>
<th>ANC</th>
<th>CAU</th>
<th>FRC</th>
<th>LTC</th>
<th>MTC</th>
<th>OCC</th>
<th>PAR</th>
<th>PCG</th>
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<td>7.7</td>
<td>4.6</td>
<td>5.2</td>
<td>7.8</td>
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<td>ART60</td>
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<td>5.0</td>
<td>7.9</td>
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<td>23.8</td>
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<td>CER90</td>
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<td>3.0</td>
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<td>SRTM</td>
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Reproducibility/Robustness:
Reproducibility Across 14 Sites

University of Pittsburgh – Amyloid Imaging Group
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Utility of Amyloid Imaging

• To detect or exclude the presence of $\beta$-amyloid pathology in order to aid clinical management

• To rationalize the use of current and future treatments when underlying pathology cannot be confidently predicted on the basis of clinical evaluation
Case History: Mild Cognitive Impairment

A 70 year-old man presented with anxiety, benzodiazepine dependence, and forgetfulness. Neuropsychologic testing revealed amnestic Mild Cognitive Impairment.

He underwent PIB PET and was found to have evidence of $\beta$-amyloid deposition. FDG PET revealed equivocal hypometabolism.

At follow-up evaluation 18 months later, he had worsening of symptoms and satisfied clinical criteria for Alzheimer’s disease. He was started on acetylcholinesterase therapy.

$\beta$-amyloid imaging identified the underlying pathology early, permitting accurate diagnosis.
11C-PIB uptake in MCI

7 out of 21 converted to AD over 8 months (33%)
Case History: FTLD

68 year-old man presented with difficulty maintaining his operative skills as an orthopedic surgeon. His referring physician found memory impairments and thought he likely had early Alzheimer’s disease.

The patient underwent PIB PET and was found to have no evidence of β-amyloid deposition.

FDG PET revealed bilateral frontal greater than parietal hypometabolism.

Over 3 years, his illness evolved to include severe impairments in language and comportment in addition to prominent memory impairment.

PIB imaging was valuable in excluding β-amyloid pathology, permitting accurate diagnosis.
Case History: Primary Progressive Aphasia

65 year-old woman presented with worsening word-finding and comprehension difficulty. FDG PET revealed severe left hemisphere hypometabolism consistent with a progressive aphasia.

This disorder is associated with multiple pathologic substrates. The patient underwent PIB PET and was found to have abundant \( \beta \)-amyloid deposition.

Subsequently, her illness evolved to include prominent memory impairment, more typical of Alzheimer’s disease.

\( \beta \)-amyloid imaging was valuable in for early identification of the underlying pathology, permitting accurate diagnosis.
Case History: Semantic Dementia

55 year-old woman presented with a 3-year history of word-finding difficulty, compulsive behavior, and non-comprehension of the roles of objects. She was fluently dysphasic and dysgraphic, with profound dysnomia (BNT 3/15). FDG PET was non-diagnostic.

SD can be a variant of both Alzheimer’s and frontotemporal dementias. The patient underwent PIB PET and was found to have abundant $\beta$-amyloid deposition.

Subsequent course was consistent with Alzheimer’s disease.

$\beta$-amyloid imaging was valuable in identifying the underlying pathology, permitting accurate diagnosis. 

Rabinovici et al Neurology 2007
Summary: Use of an Amyloid Imaging Agent

• To perform a similar role in life to that of post-mortem analysis

• To demonstrate the presence or absence of $\beta$-amyloid pathology in individual patients

• To guide management along with other tools in particular clinical circumstances
GE-067 Binding/Retention to Amyloid-Positive Brain Is Equivalent to that of [C-11]PiB

![Graph showing the correlation between GE-067 SUVR\textsubscript{90-120} and [C-11]PiB SUVR\textsubscript{35-90} with a correlation coefficient of r = 0.95 and a 95% confidence limit (CL)].