

# **FDA SHOULD EXPEDITE APPROVAL OF AMYLOID PET LIGANDS**

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# CONFLICTS

- **Consulted for: GE, AVID, Bayer Schering concerning amyloid PET**
- **Site PI for AVID study of AV 157 and AV 45. Co PI of SBIR with AVID. Possible Site PI of a Bayer/Schering BAY 94-9172 study**
- **Consulted for: Pfizer, Elan, Lilly, Neurochem, Forest, Eisai, Merck, Bristol Meyers, J&J, Nestle, Synarc, Medivation, Commentis, Genentech, Mitsubishi, Amgen**
- **ADNI receives funds from 15 companies**

# FDA SHOULD APPROVE AGENTS WHICH DETECT AMYLOID IN THE BRAIN

- FDA should approve amyloid/PET imaging agents
  - “for detection of amyloid in the brain”
  - “to aid in the diagnosis of dementia and Alzheimer’s disease”
  - The primary clinical use of these agents *initially* will be to assist in “**ruling out**” the diagnosis of AD.

# **FDA SHOULD APPROVE AGENTS WHICH DETECT AMYLOID IN THE BRAIN CRITERIA FOR APPROVAL:**

- Safety**
- Specific binding to amyloid in vitro**
- Binding to plaques in humans/animals**
- Lack of signal in animals without amyloid**
- Lack of signal in young human controls**
- High signal in humans with AD**

# ADDITIONAL CRITERIA FOR APPROVAL

- Sensitivity/Specificity studies in humans comparing AD, FTD to controls are *not that useful* because 20-40% of normal controls have high amyloid levels in brain
- Autopsy, while useful, should **NOT** be required in these studies. This will unnecessarily prolong approval of important agents

# **WHY THE FDA SHOULD EXPEDITE APPROVAL OF AMYLOID/PET LIGANDS**

- **There are several reasons: Background**
- **Currently, AD is perceived by most MDs and the public as a disorder associated with dementia, without effective Rx**
- **In fact, AD pathology exists for many years prior to cognitive decline/dementia**
- **More than 20 disease modifying treatments are in clinical trials**

# **WHY THE FDA SHOULD EXPEDITE APPROVAL OF AMYLOID/PET LIGANDS**

- In general, early treatment of any disease is good**
- Increasingly, experimental data will support the view that biomarker measurements, including amyloid imaging, are useful in detecting AD pathology, and predicting risk**
- Development of effective therapy will accelerate awareness of need for early detection/treatment**
- During the next several years, it will be important to shift the perceptions within the public and medical community concerning AD.**

# **WHY THE FDA SHOULD EXPEDITE APPROVAL OF AMYLOID/PET LIGANDS**

- **Therefore, it is generally agreed, that there is an increasing need to**
  - **Develop methods and criteria for diagnosis of AD prior to development of dementia**
  - **Shift public/medical awareness: AD pathology takes years before symptoms/impairments**
  - **Identify methods which predict risk**
- **F18 amyloid imaging is an important component of this process**

# HOW WILL THESE COMPOUNDS BE USED

- **Primary initial use will be to “rule out AD pathology” in subjects**
  - **Whose condition could be to AD or to other causes (FTD, LBC, VC)**
  - **Who have major concerns about the possibility of having AD (strong family history)**
  - **Who wish to make future plans requiring high cognitive function (starting a business)**

# **OTHER WAYS HOW THESE COMPOUNDS WILL BE USED**

- **Clinical treatment trials (at least 2 currently)**
  - **As predictors of future decline**
  - **As outcomes to detect reduction of brain amyloid load**
  - **FDA approval of these agents will hugely facilitate their use in treatment trials, because it increases their use and availability**

# **OTHER WAYS HOW THESE COMPOUNDS WILL BE USED**

- **Ultimately, in the long term, F 18 amyloid agents may be shown to**
  - **Diagnosing AD earlier (Dubois criteria)**
  - **Predict risk for cognitive decline/dementia due to AD**
  - **In mildly impaired or in normal subjects**
- **Although this is not an immediate use, FDA approval of such agents will hugely facilitate their use in research and facilitate the above**

# DO NOT REQUIRE EXTENSIVE AUTOPSY FOLLOWUP FOR VALIDATION

- Requiring extensive autopsy studies for validation will unnecessarily prolong approval of these agents
- In my opinion, extensive autopsy validation should *not be required*
- This would deprive the community of rapid access to these important agents

# “AMYLOID HYPOTHESIS”

- The “amyloid hypothesis” proposes that amyloid accumulation is a causal factor in Alzheimer’s disease
- This hypothesis has not been proven
- However, AD does not occur in the absence of amyloid accumulation
- Therefore, the diagnostic importance of amyloid imaging is *not* linked to the amyloid hypothesis

# **POSSIBLE MISUSE OF F18 AMYLOID IMAGING AGENTS**

- **F 18 amyloid agents, once approved and available will be misused**
  - **They will be use ‘for diagnosis of AD’**
  - **Some will make false claims and promote their misuse for commercial gain**
- **This is an unfortunate consequence of our medical system. Should not prevent approval**

# CONCLUSIONS

- **FDA should quickly approve F 18 amyloid agents**
- **Criteria: binding in vitro and animals, high signal in AD, and lack of signal in subjects without brain amyloid. Autopsy should not be required**
- **Reasons: Will R/O AD pathology. May help clinical trials and facilitate early detection**

# **FINAL CONCLUSIONS**

- F 18 amyloid agents will have immediate use to detect amyloid and to R/O AD**
- This alone justifies rapid approval**
- In the future these agents will have huge use in treatment trials, for prediction of risk/early detection, and prevention trials**
- Our field needs rapid approval of these agents**