CAMD Annual Regulatory Science Workshop

CSF Biomarker Team – Refocusing on Low Hanging Fruit

October 19, 2016

Mary Savage, Co-Chair **(seeking additional co-chair)**

Director, Companion Diagnostics

Merck & Co., Inc., West Point, PA

CAMD
CRITICAL PATH INSTITUTE

CEREBROSPINAL FLUID (CSF) BIOMARKER TEAM

- **AbbVie** – Holly Soares
- **Alzheimer's Association** – Maria Carrillo and James Hendrix
- **Biogen** – Alvydas Mikulskis
- **Biomarkable** – Hugo Vanderstichele
- **Boehringer Ingelheim** – Mark Gordon
- **Critical Path Institute** – Steve Arneric, Volker Kern, Klaus Romero, and Jenn Ferstl
- **Eisai** – Johan Luthman and June Kaplow
- **Eli Lilly** – Jeffrey Dage
- **Icon** – David Raunig
- **Meso Scale Diagnostics** – Robert Umek
- **Merck & Co., Inc.**– Mary Savage
- **Novartis** – Richard Meibach
- **Pfizer** – Danny Chen
- **Roche Genentech** – Tobias Bittner and Richard Batrla-Utermann
- **UC Davis** – Laurel Beckett
- **University of Antwerp** – Sebastiaan Engelborghs
- **University of Goteborg** – Kaj Blennow
- **University of Pennsylvania** – Les Shaw

Note: Team Co-Chairs are underlined

OUTLINE

1. Team Objectives
2. Context-of-Use (COU) for CSF Biomarkers
   - Pre-2014
   - 2014-2016
   - 2016 new
3. Feedback Requested: Datasets, analysis parameters and success criteria that could support Biomarker Qualification
4. Relevant Datasets to Support COU
   - Studies with 'sufficient' analytical validation
   - Supportive studies with partial validation

TEAM OBJECTIVES

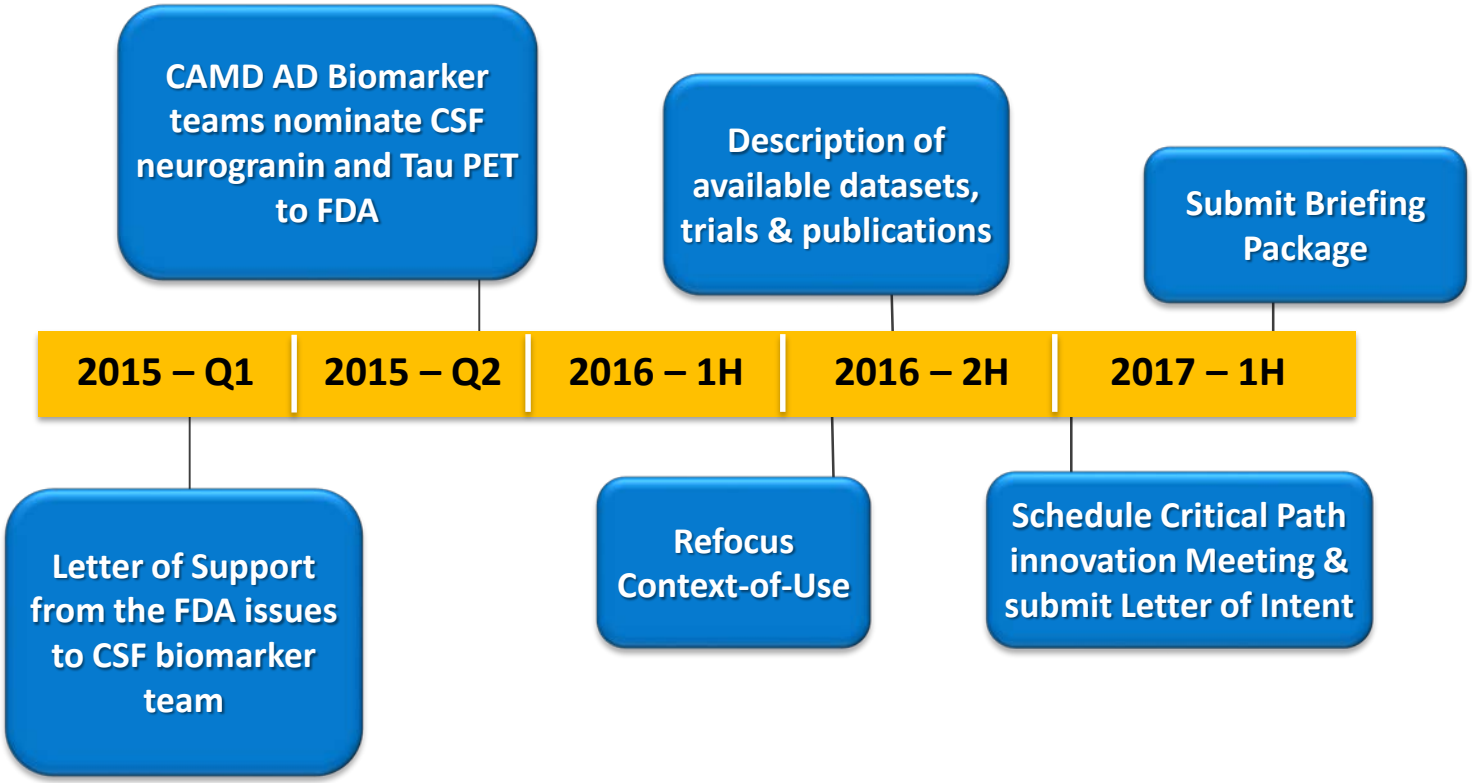
Advance through the formal FDA regulatory biomarker qualification path

2016 Focus NEW COU for in drug development: CSF assay as surrogate for brain amyloid PET

- CSF $A\beta_{42}$ +/- 'second' analyte concordance with amyloid PET
- Gather existing info
  - Raw data sets with validated assays
  - Regulatory guidance
- Restart informal regulatory interaction/submit new proposal to BQRT for feedback
- Prepare for formal regulatory review

TEAM OBJECTIVES (continued)

Advance through the formal FDA regulatory biomarker qualification path

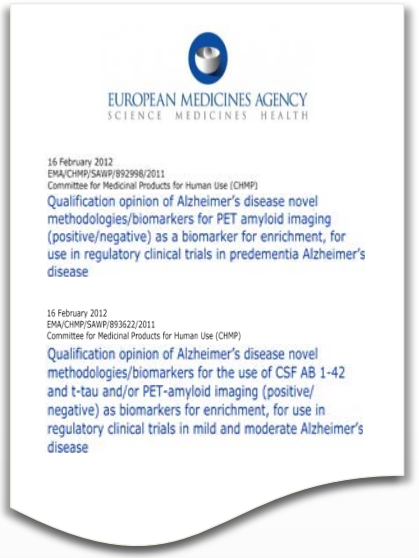


REGULATORY GUIDANCE REGARDING CSF BIOMARKERS FOR AD

2012 Guidance From EMA

- Supports CSF $A\beta_{1-42}$/tau BMx to enrich for AD patients in clinical trials
- Precise threshold values to define the AD population not defined

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125019.pdf



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 February 2012
EMA/CHMP/SAWP/892998/2011
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for PET amyloid imaging (positive/negative) as a biomarker for enrichment, for use in regulatory clinical trials in predementia Alzheimer's disease

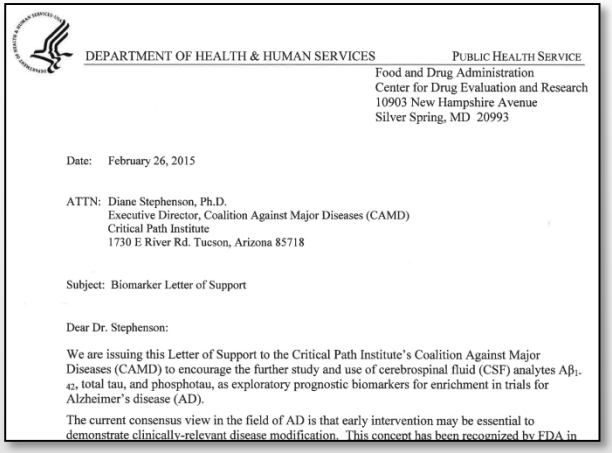
16 February 2012
EMA/CHMP/SAWP/893622/2011
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for the use of CSF AB 1-42 and t-tau and/or PET-amyloid imaging (positive/negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate Alzheimer's disease

2015 FDA letter of support for CSF prognostic biomarkers

- $A\beta_{1-42}$/tau/ptau to identify progressing MCI
- Determine clinical utility of biomarkers in clinical trials
- Good scientific and QC lab practices of assay and test system.
- Reference methods, standard sample collection / handling / storage.
- Sharing/integrating data across trials; accelerated path for AD drug development

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM439713.pdf



DEPARTMENT OF HEALTH & HUMAN SERVICES — PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: February 26, 2015

ATTN: Diane Stephenson, Ph.D.
Executive Director, Coalition Against Major Diseases (CAMD)
Critical Path Institute
1730 E River Rd. Tucson, Arizona 85718

Subject: Biomarker Letter of Support

Dear Dr. Stephenson:

We are issuing this Letter of Support to the Critical Path Institute's Coalition Against Major Diseases (CAMD) to encourage the further study and use of cerebrospinal fluid (CSF) analytes $A\beta_{1-42}$, total tau, and phosphotau, as exploratory prognostic biomarkers for enrichment in trials for Alzheimer's disease (AD).

The current consensus view in the field of AD is that early intervention may be essential to demonstrate clinically-relevant disease modification. This concept has been recognized by FDA in

CONTEXT-OF-USE FOR CSF BIOMARKERS: 2014-2016

Context-of-Use: The proposed use for CSF analytes is for enric
based on inclusion in a clinical trial. The rationale is to target p
AD (aMCI specifically) more likely to show cognitive and functi
the course of a clinical trial

Longitudinal Populations Required

Biomarker Analyte(s): CSF $A\beta_{1-42}$, tau and/or phospho-tau

Biomarker Application: Prognostic enrichment

Target Population: Patients with amnestic mild cognitive impairment (aMCI)

- MMSE scores between 24-30 (inclusive)
- Subjective memory complaint
- Objective memory loss by education adjusted Wechsler Memory Scale Logical Memory II
- CDR of 0.5
- Absence of significant levels of impairment in other cognitive domains
- Essentially preserved activities of daily living
- Absence of dementia (ADNI criteria)

REVISIT CONTEXT-OF-USE FOR AD CSF BIOMARKERS

COU from 2014 meeting with FDA was maintained at 2016 AAIC CAMD splinter meeting, however…

…until longitudinal/prognostic datasets are available, will be difficult to support further dialogue with FDA

Team Decision: Setting COU aside unless/until datasets available to CAMD

REVISED : CSF MEASURES AS AN ALTERNATIVE PLATFORM TO AMYLOID PET TO DETECT AMYLOID DEPOSITION IN THE BRAIN

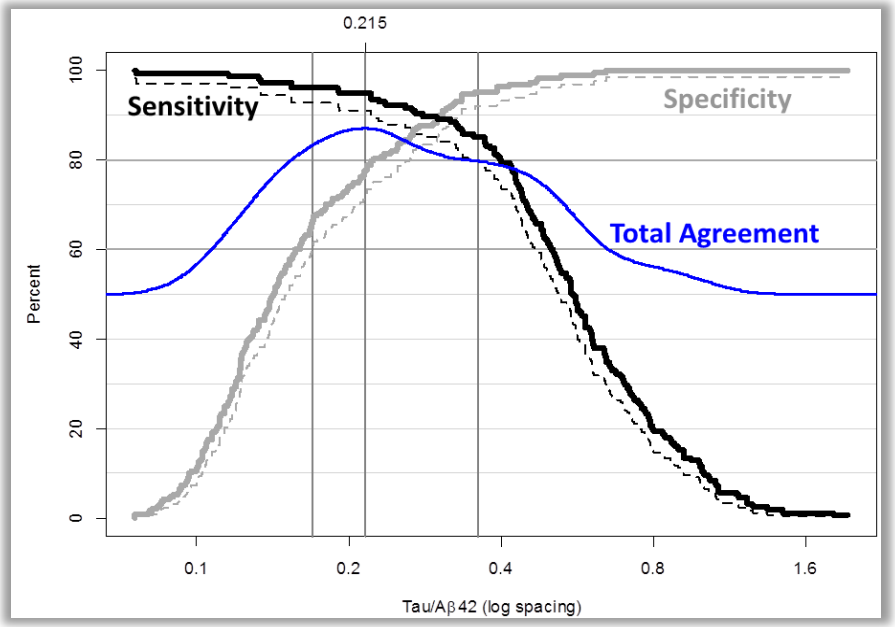
OPTION FOR DETECTING BRAIN AMYLOID DEPOSITION WHEN PET IS NOT AVAILABLE

- Higher cost of PET
- Reimbursement challenges
- Complex infrastructure (cyclotron, distribution networks, PET centers)
- Injection radioactivity – limited possibilities for repeat measures
- In some countries approval issues for use of radioactive measures when available alternatives (e.g., German BfS)

CSF TAU/AB42 SENSITIVITY & SPECIFICITY CRITERIA ACHIEVED

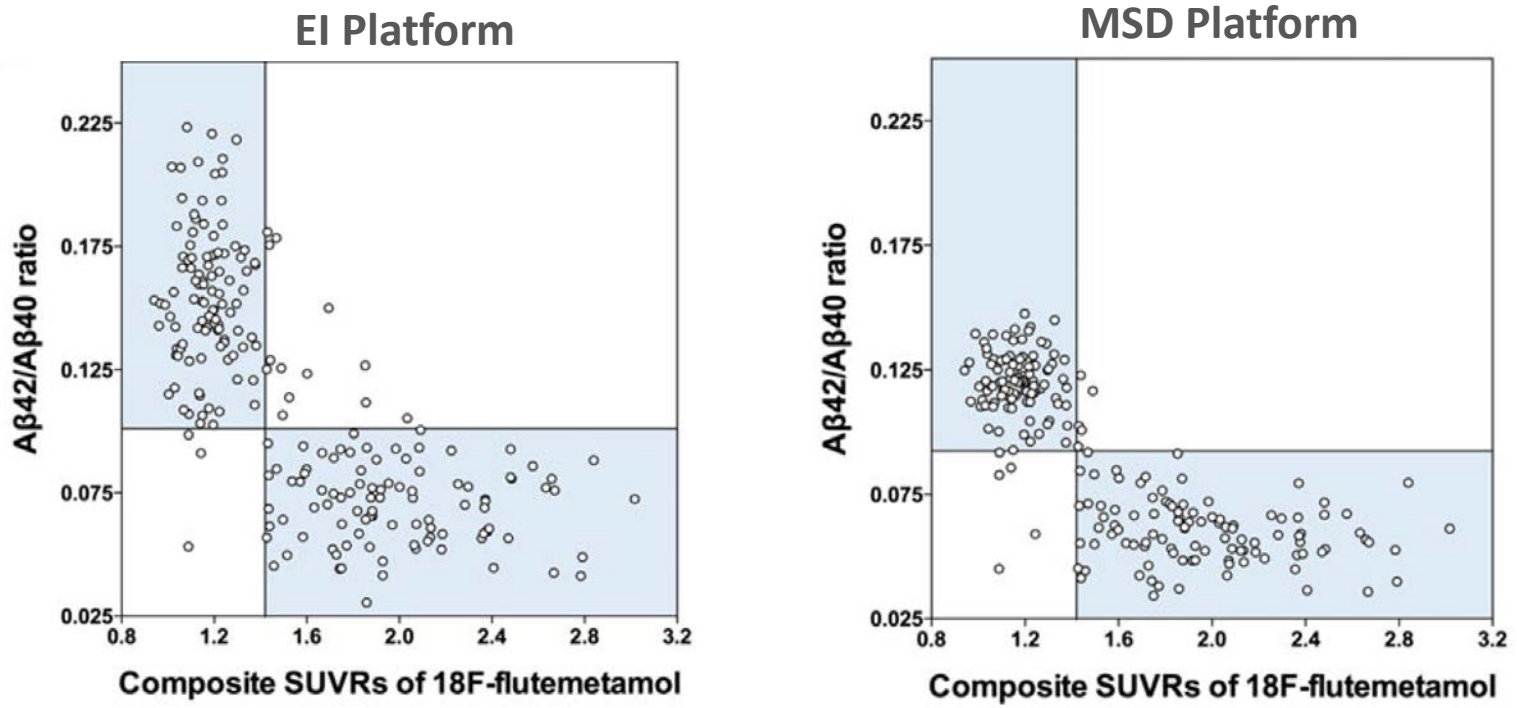
INCORPORATED PET CONCORDANCE MO, ET AL., 2016 SUBMITTED

- **Training set:** 0.215 threshold demonstrated 94.8% sensitivity, 77.7% specificity to discriminate AD from HC
  - N = 343; N = 95 with PET
  - Luminex Tau and Aβ42
- 86.9% concordance with amyloid PET visual read in a 50% PET positive population
- **Validation set:** 78.4% sensitivity & 84.9% specificity to differentiate 53 HC from 32/30 MCI/AD.



AB RATIOS FARE BETTER WITH PET CORRELATION THAN AB42 ALONE

JANELIDZE, ET AL., 2016



- Both Aβ42/40 (shown) and Aβ42/38 better predicted abnormal amyloid PET (flutemetamol / SUVR) vs CSF Aβ42. N = 215
- Subjects with subjective cognitive decline, amnestic MCI, non-amnestic MCI
- Cross studies comparisons to account for visual vs SUVR PET reads

CONCORDANCE BETWEEN AMYLOID PET VISUAL READS AND CSF TAU/AB42

CORIC, ET AL., 2015

		CSF Inclusion Criteria (Aβ42 <200 or T-tau:A42 ≥0.39)	
		+	–
Qualitative Amyloid-PET Read	+	68% (n=50) Mean CSF Aβ42 = 223 T-tau = 141	3% (n=2)
	–	10% (n=7)	19% (n=14) Mean CSF Aβ42 = 426 T-tau = 48

PET substudy sample (scans at baseline, week 24, and week 104)
- 32 Placebo
- 26 Avagacestat
- 16 Observational

Florbetapir; visual (& SUVR)
INNOBIA & MSD assays

Of the 73 patients, randomized in this PET substudy, 9 discordant cases were observed at baseline:

7 cases (10%) were amyloid-PET negative but CSF-positive and 2 cases (3%) were amyloid-PET positive but CSF-negative.

CEREBROSPINAL FLUID (CSF) BIOMARKER – OBJECTIVE

PROPOSED CONTEXT-OF-USE

Qualify baseline CSF proteins including, but not limited to $A\beta_{42}$ as concordant to amyloid PET for detecting amyloid pathology in the brain of adult patients with cognitive impairment who are being evaluated for potential inclusion in Alzheimer's dementia trials

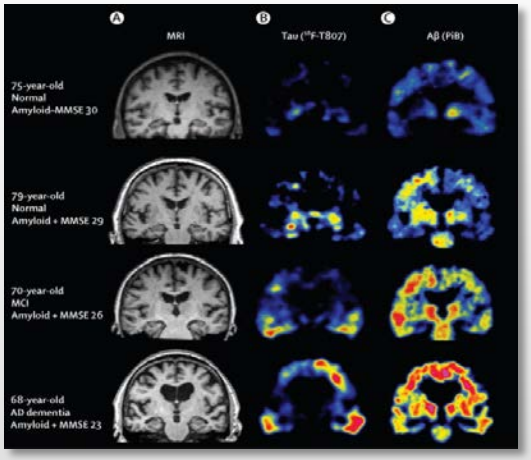
PROPOSED BIOMARKERS

Measures of CSF analytes demonstrating concordance to Amyloid PET to verify presence of amyloid in the brain

TARGET POPULATION FOR USE

Adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline

Focus on analytes that replicate a combined Amyloid PET assessments



CONTEXT-OF-USE

Additional points to consider

Qualify baseline CSF proteins including, but not limited to $A\beta_{42}$ as concordant to amyloid PET for detecting amyloid pathology in the brain of adult patients with cognitive impairment who are being evaluated for potential inclusion in Alzheimer's dementia trials

$A\beta_{42}$: 1-42, X-42, other

...with cognitive impairment... does this need to be stated though in amyloid PET labels…

…MCI or Alzheimer's dementia trials… is it enough to say 'AD trials'?

DATASETS, ANALYSIS PARAMETERS AND SUCCESS CRITERIA TO SUPPORT BIOMARKER QUALIFICATION

Are FDA-approved amyloid PET ligands a 'gold standard' for detection of brain amyloid?

- **If yes**, is brain amyloid PET & CSF analyte concordance a relevant approach to consider CSF an alternate diagnostic marker for brain amyloid?
  - What level of concordance?
  - Similar degree of positive agreement and negative agreement?
- **If no**, would a CSF x amyloid histology study be required to support CSF as an alternative diagnostic marker for brain amyloid?

Intended use population: Adult patients with cognitive impairment who are being evaluated for AD and/or other causes of cognitive decline

- Would appropriate data set include: healthy controls, prodromal/early MCI, mild/moderate AD?
- What balance of each?

RELEVANT DATASETS

Identify CSF studies either in the public domain/within companies that can support CSF/PET correlation revised COU

- ✓ **Completed literature review including observational or clinical studies**
- **Define assay validation parameters required to include studies as part of 'gold standard' examples to the FDA**
  - Alternatively, review available validation reports for completeness
  - Deposit validation reports/manuscripts at SharePoint site
  - Does CAMD need to see validation reports? **YES**
- **Obtain raw CSF analyte and PET imaging data**
  - Proper consenting
  - Roche, BMS, Merck & Co.,Inc., Janelidze et al., others??
  - Continue working with BMS to access patient-level data relevant to both COU (prognostic and PET concordance).
  - Data Contribution Agreement template from C-Path/CAMD

Merck Lumines 42
ınd tau assays 201

Roche 42assay
2015

Luminex

FDA RESPONSES TO CAMD'S MAY 28, 2014 ALZHEIMER'S DISEASE CSF BIOMARKER QUALIFICATION SUBMISSION (CONT.) JULY 31, 2014

PPSB ADNI 3 DD

Assay Technical Considerations

- Noted technical limitations of "first generation" assays including:
  - Matrix interference
  - Lack of dilutional linearity
  - High imprecision when used at different locations
  - Absence of a reference method or reference calibrator
  - Advised: **Reference method** for standardization for validating the accuracy and precision of each assay across time and across sites, the mean predicted concentrations (i.e., expected results) should demonstrate "acceptable limits of variation"

FDA RESPONSES TO CAMD'S MAY 28, 2014 ALZHEIMER'S DISEASE CSF BIOMARKER QUALIFICATION SUBMISSION (CONT.) JULY 31, 2014 (continued)

- Recommended determination of:
  - Linearity for reportable range
  - Define high dose hook effect
  - Carry-over to rule out over estimation
  - Cross-contamination under recommended use
  - Precision/reproducibility study (e.g., multiple lots)
  - For automated assays, evaluate instrument-to-instrument variability
- Requested we explain how to bridge clinical data from the "first generation" assay to an analytically validated "second generation" assay

CEREBROSPINAL FLUID (CSF) BIOMARKER – 2016 PROGRESS

Milestone	Timeline
Refocus and refine Context-of-Use	2Q – 3Q 2016
Description of available data sets and publications	3Q 2016
Publication in press: **Cerebrospinal Fluid Biomarkers for Alzheimer's Disease: A View of the Regulatory Science Qualification Landscape from the Coalition Against Major Diseases CSF Biomarker Team,** *Journal of Alzheimer's Disease*	3Q 2016
Draft plan for regulatory interactions and CPIM meeting	4Q 2016 – 1Q 2017

RISK AND MITIGATION PLANS

Risks

- Insufficient data to support existing or new COU submission
- Concordance, PPA, NPA populations studied are insufficient to meet regulatory approval
- Team unable to align on revised COU or approach (specific CSF analytes)
- Other…

Mitigations

- Identify additional datasets
  - CSF and PET measures; appropriate validated assays
  - Clinical data from HC, aMCI/prodromal/mmAD
- Restart Informal regulatory dialogue
- Other…

Thank you

www.c-path.org/camd

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AMYLOID PET LABELS

A test of exclusion; not a test of diagnosis!

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Amyvid safely and effectively. See full prescribing information for Amyvid.

Amyvid (Florbetapir F 18 Injection) for intravenous use

Initial U.S. Approval: 2012

INDICATIONS AND USAGE

Amyvid is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations (1).

Limitations of Use

- A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder (1).
- Safety and effectiveness of Amyvid have not been established for:
  - Predicting development of dementia or other neurologic condition;
  - Monitoring responses to therapies (1).

VIZAMYL (flutemetamol F 18 injection) for intravenous use

Initial U.S. Approval: 2013

----------INDICATIONS AND USAGE----------

Vizamyl is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline. A negative Vizamyl scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Vizamyl scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions, as well as older people with normal cognition. Vizamyl is an adjunct to other diagnostic evaluations (1).

Limitations of Use:

- A positive Vizamyl scan does not establish a diagnosis of AD or other cognitive disorder (1)
- Safety and effectiveness of Vizamyl have not been established for:
  - Predicting development of dementia or other neurological condition (1)
  - Monitoring responses to therapies (1)

NEURACEQ (florbetaben F 18 injection), for intravenous use

Initial U.S. Approval: 2014

---------- INDICATIONS AND USAGE ----------

Neuraceq™ is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Neuraceq scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Neuraceq scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Neuraceq is an adjunct to other diagnostic evaluations. (1).

Limitations of Use

- A positive Neuraceq scan does not establish the diagnosis of AD or any other cognitive disorder (1).
- Safety and effectiveness of Neuraceq have not been established for:
  - Predicting development of dementia or other neurologic conditions (1)
  - Monitoring responses to therapies (1).